NANOPARTICULATE MEGESTROL FORMULATIONS

INFORMATION ON RELATED APPLICATIONS

[0001] This application is a continuation-in-part of Application No. 11/093,149, filed on March 30, 2005, which is a continuation-in-part of Application No. 10/412,669 filed on April, 14, 2003, which claims the priority benefit of U.S. provisional patent Application No. 60/371,680, filed on April 12, 2002, and U.S. provisional Application No. 60/430,348, filed on December 3, 2002. In addition, this application claims the priority benefit of U.S. provisional Application No. 60/693,127, filed on June 22, 2005.

FIELD OF THE INVENTION

[0002] The present invention relates to nanoparticulate compositions comprising megestrol and preferably at least one surface stabilizer associated with the surface of the drug. The nanoparticulate megestrol particles have an effective average particle size of less than about 2000 nm. Methods of making and using the compositions are also encompassed by the invention. The invention also relates to methods of increasing appetite and/or effecting weight gin in a subject suffering from weight loss and/or decreased appetite as a result of anorexia and/or cachexia, including anorexia/cachexia due to HIV//AIDS, cancer, chemotherapy, or related conditions or treatments.

BACKGROUND OF THE INVENTION

A. Background Regarding Nanoparticulate Active Agent Compositions

[0003] Nanoparticulate active agent compositions, first described in U.S. Patent No. 5,145,684 ("the '684 patent"), are particles consisting of a poorly soluble therapeutic or diagnostic agent having adsorbed onto or associated with the surface thereof a non-crosslinked surface stabilizer. The '684 patent does not describe nanoparticulate compositions of megestrol.

[0004] Methods of making nanoparticulate active agent compositions are described, for example, in U.S. Patent Nos. 5,518,187 and 5,862,999, both for "Method of Grinding Pharmaceutical Substances;" U.S. Patent No. 5,718,388, for "Continuous Method of Grinding Pharmaceutical Substances;" and U.S. Patent No. 5,510,118 for "Process of Preparing Therapeutic Compositions Containing Nanoparticles." Nanoparticulate active agent compositions are also described, for example, in U.S. Patent Nos. 5,298,262 for "Use of Ionic Cloud Point Modifiers to Prevent Particle Aggregation During Sterilization;" 5,302,401 for "Method to Reduce Particle Size Growth During Lyophilization;" 5,318,767 for "X-Ray Contrast Compositions Useful in Medical Imaging;" 5,326,552 for "Novel Formulation For Nanoparticulate X-Ray Blood Pool Contrast Agents Using High Molecular Weight Non-ionic Surfactants;" 5,328,404 for "Method of X-Ray Imaging Using Iodinated Aromatic Propanedioates;" 5,336,507 for "Use of Charged Phospholipids to Reduce Nanoparticle Aggregation;" 5,340,564 for "Formulations Comprising Olin 10-G to Prevent Particle Aggregation and Increase Stability;" 5,346,702 for "Use of Non-Ionic Cloud Point Modifiers to Minimize Nanoparticulate Aggregation During Sterilization;" 5,349,957 for "Preparation and Magnetic Properties of Very Small Magnetic-Dextran Particles;" 5,352,459 for "Use of Purified Surface Modifiers to Prevent Particle Aggregation During Sterilization;" 5,399,363 and 5,494,683, both for "Surface Modified Anticancer Nanoparticles;" 5,401,492 for "Water Insoluble Non-Magnetic Manganese Particles as Magnetic Resonance Enhancement Agents;" 5,429,824 for "Use of Tyloxapol as a Nanoparticulate Stabilizer;" 5,447,710 for "Method for Making Nanoparticulate X-Ray Blood Pool Contrast Agents Using High Molecular Weight Non-ionic Surfactants;" 5,451,393 for "X-Ray Contrast Compositions Useful in Medical Imaging;" 5,466,440 for "Formulations of Oral Gastrointestinal Diagnostic X-Ray Contrast Agents in Combination with Pharmaceutically Acceptable Clays;" 5,470,583 for "Method of Preparing Nanoparticle Compositions Containing Charged Phospholipids to Reduce Aggregation;" 5,472,683 for "Nanoparticulate Diagnostic Mixed Carbamic Anhydrides as X-Ray Contrast Agents for Blood Pool and Lymphatic System Imaging;" 5,500,204 for "Nanoparticulate Diagnostic Dimers as X-Ray Contrast Agents for Blood Pool and Lymphatic System Imaging;"

5,518,738 for "Nanoparticulate NSAID Formulations;" 5,521,218 for "Nanoparticulate Iododipamide Derivatives for Use as X-Ray Contrast Agents;" 5,525,328 for "Nanoparticulate Diagnostic Diatrizoxy Ester X-Ray Contrast Agents for Blood Pool and Lymphatic System Imaging;" 5,543,133 for "Process of Preparing X-Ray Contrast Compositions Containing Nanoparticles;" 5,552,160 for "Surface Modified NSAID Nanoparticles;" 5,560,931 for "Formulations of Compounds as Nanoparticulate Dispersions in Digestible Oils or Fatty Acids;" 5,565,188 for "Polyalkylene Block Copolymers as Surface Modifiers for Nanoparticles;" 5,569,448 for "Sulfated Non-ionic Block Copolymer Surfactant as Stabilizer Coatings for Nanoparticle Compositions;" 5,571,536 for "Formulations of Compounds as Nanoparticulate Dispersions in Digestible Oils or Fatty Acids;" 5,573,749 for "Nanoparticulate Diagnostic Mixed Carboxylic Anydrides as X-Ray Contrast Agents for Blood Pool and Lymphatic System Imaging;" 5,573,750 for "Diagnostic Imaging X-Ray Contrast Agents;" 5,573,783 for "Redispersible Nanoparticulate Film Matrices With Protective Overcoats;" 5,580,579 for "Site-specific Adhesion Within the GI Tract Using Nanoparticles Stabilized by High Molecular Weight, Linear Poly(ethylene Oxide) Polymers;" 5,585,108 for "Formulations of Oral Gastrointestinal Therapeutic Agents in Combination with Pharmaceutically Acceptable Clays;" 5,587,143 for "Butylene Oxide-Ethylene Oxide Block Copolymers Surfactants as Stabilizer Coatings for Nanoparticulate Compositions;" 5,591,456 for "Milled Naproxen with Hydroxypropyl Cellulose as Dispersion Stabilizer;" 5,593,657 for "Novel Barium Salt Formulations Stabilized by Non-ionic and Anionic Stabilizers;" 5,622,938 for "Sugar Based Surfactant for Nanocrystals;" 5,628,981 for "Improved Formulations of Oral Gastrointestinal Diagnostic X-Ray Contrast Agents and Oral Gastrointestinal Therapeutic Agents;" 5,643,552 for "Nanoparticulate Diagnostic Mixed Carbonic Anhydrides as X-Ray Contrast Agents for Blood Pool and Lymphatic System Imaging;" 5,718,388 for "Continuous Method of Grinding Pharmaceutical Substances;" 5,718,919 for "Nanoparticles Containing the R(-)Enantiomer of Ibuprofen;" 5,747,001 for "Aerosols Containing Beclomethasone Nanoparticle Dispersions;" 5,834,025 for "Reduction of Intravenously Administered Nanoparticulate Formulation Induced Adverse Physiological Reactions;" 6,045,829 "Nanocrystalline Formulations of Human Immunodeficiency Virus

(HIV) Protease Inhibitors Using Cellulosic Surface Stabilizers;" 6,068,858 for "Methods of Making Nanocrystalline Formulations of Human Immunodeficiency Virus (HIV) Protease Inhibitors Using Cellulosic Surface Stabilizers;" 6,153,225 for "Injectable Formulations of Nanoparticulate Naproxen;" 6,165,506 for "New Solid Dose Form of Nanoparticulate Naproxen;" 6,221,400 for "Methods of Treating Mammals Using Nanocrystalline Formulations of Human Immunodeficiency Virus (HIV) Protease Inhibitors;" 6,264,922 for "Nebulized Aerosols Containing Nanoparticle Dispersions;" 6,267,989 for "Methods for Preventing Crystal Growth and Particle Aggregation in Nanoparticle Compositions;" 6,270,806 for "Use of PEG-Derivatized Lipids as Surface Stabilizers for Nanoparticulate Compositions;" 6,316,029 for "Rapidly Disintegrating Solid Oral Dosage Form," 6,375,986 for "Solid Dose Nanoparticulate Compositions Comprising a Synergistic Combination of a Polymeric Surface Stabilizer and Dioctyl Sodium Sulfosuccinate," 6,428,814 for "Bioadhesive Nanoparticulate Compositions Having Cationic Surface Stabilizers;" 6,431,478 for "Small Scale Mill;" 6,432,381 for "Methods for Targeting Drug Delivery to the Upper and/or Lower Gastrointestinal Tract," 6,592,903 for "Nanoparticulate Dispersions Comprising a Synergistic Combination of a Polymeric Surface Stabilizer and Dioctyl Sodium Sulfosuccinate," 6,582,285 for "Apparatus for sanitary wet milling;" 6,656,504 for "Nanoparticulate Compositions Comprising Amorphous Cyclosporine;" 6,742,734 for "System and Method for Milling Materials;" 6,745,962 for "Small Scale Mill and Method Thereof;" 6,811,767 for "Liquid droplet aerosols of nanoparticulate drugs;" 6,908,626 for "Compositions having a combination of immediate release and controlled release characteristics;" 6,969,529 for "Nanoparticulate compositions comprising copolymers of vinyl pyrrolidone and vinyl acetate as surface stabilizers;" and 6,976,647 for "System and Method for Milling Materials," all of which are specifically incorporated by reference.

[0005] In addition, U.S. Patent Publication No. 20020012675 A1, for "Controlled Release Nanoparticulate Compositions;" U.S. Patent Publication No. 20050276974 for "Nanoparticulate Fibrate Formulations;" U.S. Patent Publication No. 20050238725 for "Nanoparticulate compositions having a peptide as a surface stabilizer;" U.S. Patent Publication No. 20050233001 for "Nanoparticulate megestrol formulations;" U.S. Patent

Publication No. 20050147664 for "Compositions comprising antibodies and methods of using the same for targeting nanoparticulate active agent delivery;" U.S. Patent Publication No. 20050063913 for "Novel metaxalone compositions;" U.S. Patent Publication No. 20050042177 for "Novel compositions of sildenafil free base;" U.S. Patent Publication No. 20050031691 for "Gel stabilized nanoparticulate active agent compositions;" U.S. Patent Publication No. 20050019412 for " Novel glipizide compositions;" U.S. Patent Publication No. 20050004049 for "Novel griseofulvin compositions;" U.S. Patent Publication No. 20040258758 for "Nanoparticulate topiramate formulations;" U.S. Patent Publication No. 20040258757 for " Liquid dosage compositions of stable nanoparticulate active agents;" U.S. Patent Publication No. 20040229038 for "Nanoparticulate meloxicam formulations;" U.S. Patent Publication No. 20040208833 for "Novel fluticasone formulations;" U.S. Patent Publication No. 20040195413 for " Compositions and method for milling materials;" U.S. Patent Publication No. 20040156895 for "Solid dosage forms comprising pullulan;" U.S. Patent Publication No. U.S. Patent Publication No. U.S. Patent Publication No. 20040156872 for "Novel nimesulide compositions;" U.S. Patent Publication No. 20040141925 for "Novel triamcinolone compositions;" U.S. Patent Publication No. 20040115134 for "Novel nifedipine compositions;" U.S. Patent Publication No. 20040105889 for "Low viscosity liquid dosage forms;" U.S. Patent Publication No. 20040105778 for "Gamma irradiation of solid nanoparticulate active agents;" U.S. Patent Publication No. 20040101566 for "Novel benzoyl peroxide compositions;" U.S. Patent Publication No. 20040057905 for "Nanoparticulate beclomethasone dipropionate compositions;" U.S. Patent Publication No. 20040033267 for "Nanoparticulate compositions of angiogenesis inhibitors;" U.S. Patent Publication No. 20040033202 for "Nanoparticulate sterol formulations and novel sterol combinations;" U.S. Patent Publication No. 20040018242 for "Nanoparticulate nystatin formulations;" U.S. Patent Publication No. 20040015134 for "Drug delivery systems and methods;" U.S. Patent Publication No. 20030232796 for "Nanoparticulate polycosanol formulations & novel polycosanol combinations;" U.S. Patent Publication No. 20030215502 for "Fast dissolving dosage forms having reduced friability;" U.S. Patent Publication No. 20030185869 for "Nanoparticulate compositions having lysozyme

as a surface stabilizer;" U.S. Patent Publication No. 20030181411 for "Nanoparticulate compositions of mitogen-activated protein (MAP) kinase inhibitors;" U.S. Patent Publication No. 20030137067 for "Compositions having a combination of immediate release and controlled release characteristics;" U.S. Patent Publication No. 20030108616 for "Nanoparticulate compositions comprising copolymers of vinyl pyrrolidone and vinyl acetate as surface stabilizers;" U.S. Patent Publication No. 20030095928 for "Nanoparticulate insulin;" U.S. Patent Publication No. 20030087308 for "Method for high through put screening using a small scale mill or microfluidics;" U.S. Patent Publication No. 20030023203 for "Drug delivery systems & methods;" U.S. Patent Publication No. 20020179758 for "System and method for milling materials; and U.S. Patent Publication No. 20010053664 for "Apparatus for sanitary wet milling," describe nanoparticulate active agent compositions and are specifically incorporated by reference.

[0006] Amorphous small particle compositions are described, for example, in U.S. Patent Nos. 4,783,484 for "Particulate Composition and Use Thereof as Antimicrobial Agent;" 4,826,689 for "Method for Making Uniformly Sized Particles from Water-Insoluble Organic Compounds;" 4,997,454 for "Method for Making Uniformly-Sized Particles From Insoluble Compounds;" 5,741,522 for "Ultrasmall, Non-aggregated Porous Particles of Uniform Size for Entrapping Gas Bubbles Within and Methods;" and 5,776,496, for "Ultrasmall Porous Particles for Enhancing Ultrasound Back Scatter."

B. Background Regarding Megestrol

[0007] Megestrol acetate, also known as 17α-acetyloxy-6-methylpregna-4,6-diene-3,20-dione, is a synthetic progestin with progestational effects similar to those of progesterone. It is used in abortion, endometriosis, and menstrual disorders. It is also used in a variety of situations including treatment of breast cancer, contraception, and hormone replacement therapy in post-menopausal women. Megestrol acetate is also frequently prescribed as an appetite enhancer for patients in a wasting state, such as HIV wasting, cancer wasting, or anorexia. In combination with ethynyl estradiol it acts as an oral contraceptive. It is also administered to subjects after castration.

[0008] Megestrol acetate is marketed by Par Pharmaceuticals, Inc. and under the brand name Megace® by Bristol Myers Squibb Co. Typical commercial formulations are relatively large volume. For example, Par Pharmaceuticals, Inc. megestrol acetate oral suspension contains 40 mg of micronized megestrol acetate per ml, and the package insert recommends an initial adult dosage of megestrol acetate oral suspension of 800 mg/day (20 mL/day). The commercial formulations of megestrol acetate are highly viscous suspensions, which have a relatively long residence time in the mouth and any tubing. Highly viscous substances are not well accepted by patient populations, particularly patients suffering wasting and those that are intubated.

[0009] U.S. Patent No. 6,028,065 for "Flocculated Suspension of Megestrol Acetate," assigned to Pharmaceutical Resources, Inc. (Spring Valley, NY), describes oral pharmaceutical micronized megestrol acetate compositions in the form of a stable flocculated suspension in water. The compositions comprise at least one compound selected from the group consisting of polyethylene glycol, propylene glycol, glycerol, and sorbitol; and a surfactant, wherein polysorbate and polyethylene glycol are not simultaneously present. U.S. Patent No. 6,268,356, also for "Flocculated Suspension of Megestrol Acetate," and assigned to Pharmaceutical Resources, Inc., describes methods of treating a neoplastic condition comprising administering the composition of U.S. Patent No. 6,028,065.

[0010] Another company that has developed a megestrol formulation is Eurand (Milan, Italy). Eurand's formulation is a modified form of megestrol acetate having increased bioavailability. Eurand structurally modifies poorly soluble drugs to increase their bioavailability. *See* www.eurand.com. For megestrol acetate, Eurand uses its' "Biorise" process, in which a New Physical Entity (NPE) is created by physically breaking down megestrol's crystal lattice. This results in drug nanocrystals and/or amorphous drug, which are then stabilized with biologically inert carriers. Eurand uses three types of carriers: swellable microparticles, composite swellable microparticles, and cyclodextrins. *See e.g.*, http://www.eurand.com/page.php?id=39. Such a delivery system can be undesirable, as "breaking down" an active agent's crystalline structure can modify

the activity of the active agent. A drug delivery system which does not alter the structure of the active agent is preferable.

[0011] Among the progestins, megestrol acetate is one of the few that can be administered orally because of its reduced first-pass (hepatic) metabolism, compared to the parent hormone. In addition, it is claimed to be superior to 19-nor compounds as an antifertility agent because it has less effect on the endometrium and vagina. *See Stedman's Medical Dictionary,* 25th Ed., page 935 (Williams & Wilkins, MD 1990).

[0012] There is a need in the art for megestrol formulations which exhibit increased bioavailability, less variability, and/or less viscosity as compared to conventional microparticulate megestrol formulations. The present invention satisfies these needs.

SUMMARY OF THE INVENTION

[0013] The invention relates to nanoparticulate megestrol compositions. The compositions comprise megestrol and preferably at least one surface stabilizer associated with the surface of the megestrol particles. The nanoparticulate megestrol particles have an effective average particle size of less than about 2000 nm.

[0014] Another aspect of the invention is directed to pharmaceutical compositions comprising a nanoparticulate megestrol composition of the invention. The pharmaceutical compositions preferably comprise megestrol, at least one surface stabilizer, and a pharmaceutically acceptable carrier, as well as any desired excipients.

[0015] The invention encompasses megestrol acetate compositions with improved physical (viscosity) and pharmacokinetic profiles (such as less variability) over traditional forms of megestrol acetate.

[0016] This invention further discloses a method of making a nanoparticulate megestrol composition according to the invention. Such a method comprises contacting megestrol particles and at least one surface stabilizer for a time and under conditions sufficient to provide a nanoparticulate megestrol composition. The one or more surface stabilizers can be contacted with megestrol either before, during, or after size reduction of the megestrol.

[0017] The present invention is also directed to methods of treatment using the nanoparticulate compositions of the invention for conditions such as endometriosis, dysmenorrhea, hirsutism, uterine bleeding, neoplastic diseases, methods of appetite enhancement, contraception, hormone replacement therapy, and treating patients following castration. In particular, the invention relates to methods of increasing appetite and/or effecting weight gin in a subject suffering from weight loss and/or decreased appetite as a result of anorexia and/or cachexia, including anorexia/cachexia due to HIV//AIDS, cancer, chemotherapy, or related conditions or treatments. Such methods comprises administering to a subject a therapeutically effective amount of a nanoparticulate megestrol composition according to the invention.

[0018] Both the foregoing general description and the following brief description of the drawings and detailed description of the invention are exemplary and explanatory and are intended to provide further explanation of the invention as claimed. Other objects, advantages, and novel features will be readily apparent to those skilled in the art from the following detailed description of the invention.

BRIEF DESCRIPTION OF THE DRAWINGS

[0010] Figure. 1: Illustrates viscosity in units of mPa s as a function of concentration. Circles indicate the experimental values and the line illustrates the expected trend;

[0011] Figure. 2: Illustrates viscosity in units of Pa s as a function of shear rate for two commercial samples, Bristol Myers Squibb and Par Pharmaceuticals, both at an active concentration of 40 mg/mL; and

[0012] Figure 3: Shows a photograph of, from left to right, a nanoparticulate dispersion of megestrol acetate, a commercial sample of megestrol acetate marketed by Par Pharmaceuticals, and a commercial sample of megestrol acetate marketed by Bristol Myers Squibb.

[0013] Figure 4: The figure graphically shows the comparative bioavailability (via plasma concentration (ng/mL)) of several nanoparticulate megestrol

compositions (575 mg/5ml, 625 mg/5ml and 675 mg/5ml) versus a conventional megestrol acetate marketed by Bristol Myers Squibb.

[0014] Figure 5: The figure graphically shows on a natural log scale the comparative bioavailability (via plasma concentration (ng/mL)) of several nanoparticulate megestrol compositions (575 mg/5ml, 625 mg/5ml and 675 mg/5ml) versus a conventional megestrol acetate marketed by Bristol Myers Squibb.

[0015] Figs 6A&B: Contain data showing weight in Kg for each subject receiving MEGACE® OS megestrol acetate oral suspension (conventional microcrystalline megestrol acetate) over the course of 12 weeks. Also shown in the average data with standard deviations and percent change. Data may contain imputed values.

[0016] Figure 7: Contains data showing weight in Kg for each subject receiving an oral dose of a dispersion of nanoparticulate megestrol acetate over the course of 12 weeks. Also shown is the average data with standard deviations and percent change. Data may contain imputed values.

[0017] Figure 8: Contain two graphs. The first graph shows the percent change in weight from the initial baseline weight after the course of 12 weeks. The second graph depicts the average weight of the subjects over the course of 12 weeks. Both graphs contain data points for MEGACE® OS megestrol actetate oral suspension (conventional microcrystalline megestrol acetate) and for an oral dose of a dispersion of nanoparticulate megestrol acetate. Data may contain imputed values.

[0018] Figs 9A&B: Contain data regarding subject's response to the fifth BACRI question "To what extent has your appetite changed since the start of treatment? [much worse – much better]" for those patients receiving MEGACE® OS megestrol acetate oral suspension (conventional microcrystalline megestrol acetate). Also shown is

the average data with standard deviations. Data may contain imputed values.

[0019] Figs 10A&B: Contain data regarding subject's response to the fifth BACRI question "To what extent has your appetite changed since the start of treatment? [much worse – much better]" for those patients receiving an oral dose of a dispersion of nanoparticulate megestrol acetate. Also shown is the average data with standard deviations. Data may contain imputed values.

[0020] Figure 11: contains a graph depicting the average weight BACRI score to the fifth question "To what extent has your appetite changed since the start of treatment? [much worse – much better]" for those patients receiving an oral dose of a dispersion of nanoparticulate megestrol acetate and those receiving MEGACE® OS megestrol actetate oral suspension (conventional microcrystalline megestrol acetate). Data may contain imputed values.

[0021] Figs 12A&B: Contain data regarding subject's response to the 24 hour recall question "How would you describe the amount of food you ate yesterday" on a scale where 1=typical, 2=considerably less, and 3=considerably more, for those patients receiving MEGACE® OS megestrol acetate oral suspension (conventional microcrystalline megestrol acetate). Also shown is the average data with standard deviations. Data may contain imputed values.

[0022] Figs 13A&B: Contain data regarding subject's response to the 24 hour recall question "How would you describe the amount of food you ate yesterday" on a scale where 1=typical, 2=considerably less, and 3=considerably more, for those patients receiving an oral dose of a dispersion of nanoparticulate megestrol acetate. Also shown is the average data with standard deviations. Data may contain imputed values.

[0023] Figs 14A&B: Contain data showing the subjects' bioimpedance data at day 1 (baseline) and week 12, as well as the change in body fat and lean muscle over the 12 weeks for those patients receiving MEGACE® OS megestrol acetate oral suspension (conventional microcrystalline megestrol acetate). Also shown is the average data with standard deviations. Data may contain imputed values.

[0024] Figs 15A&B: Contain data showing the subjects' bioimpedance data at day 1 (baseline) and week 12, as well as the change in body fat and lean muscle over the 12 weeks for those patients receiving an oral dose of a dispersion of nanoparticulate megestrol acetate. Also shown is the average data with standard deviations. Data may contain imputed values.

[0025] Figure 16: Contains a graph depicting the amounts of lean muscle and body fat the 12 weeks versus the amounts of lean muscle and body fat at day 1 for those patients receiving an oral dose of a dispersion of nanoparticulate megestrol acetate and those receiving MEGACE® OS megestrol actetate oral suspension (conventional microcrystalline megestrol acetate). Data may contain imputed values.

DETAILED DESCRIPTION OF THE INVENTION

[0015] The present invention is directed to nanoparticulate compositions comprising megestrol particles having an effective average particle size of less than about 2 microns. The compositions comprise megestrol and preferably at least one surface stabilizer associated with the surface of the drug.

[0016] As taught in the '684 patent, not every combination of surface stabilizer and active agent will result in a stable nanoparticulate composition. It was surprisingly discovered that stable nanoparticulate megestrol compositions can be made.

[0017] For example, nanoparticulate megestrol compositions with hydroxypropyl methylcellulose (HPMC) and sodium lauryl sulfate (SLS) as surface stabilizers remained stable in an electrolyte solution mimicking the physiological pH of the stomach. Nanoparticulate megestrol compositions comprising HPMC and SLS are stable for several weeks at temperatures up to 40°C with only minimal particle size growth. In addition, nanoparticulate megestrol compositions with hydroxypropylcellulose (HPC) and dioctyl sodium sulfosuccinate (DOSS) as surface stabilizers, HPMC and DOSS as surface stabilizers, polyvinylpyrrolidone (PVP) and DOSS as surface stabilizers, and Plasdone® S630 and DOSS as surface stabilizers were stable in electrolyte fluids and exhibited acceptable physical stability at 5°C for 4 weeks. (Plasdone® S630 (ISP) is a random copolymer of vinyl acetate and vinyl pyrrolidone.) Moreover, the nanoparticulate megestrol/HPMC/SLS and nanoparticulate megestrol/HPMC/DOSS compositions also exhibited acceptable physical stability at 25°C and 40°C for 4 weeks.

[0018] Advantages of the nanoparticulate megestrol compositions of the invention include, but are not limited to: (1) low viscosity liquid nanoparticulate megestrol dosage forms; (2) for liquid nanoparticulate megestrol compositions having a low viscosity - better subject compliance due to the perception of a lighter formulation which is easier to consume and digest; (3) for liquid nanoparticulate megestrol compositions having a low viscosity - ease of dispensing because one can use a cup or a syringe; (4) faster onset of action; (5) smaller doses of megestrol required to obtain the same pharmacological effect as compared to conventional microcrystalline forms of megestrol; (6) increased bioavailability as compared to conventional microcrystalline forms of megestrol; (7) substantially similar pharmacokinetic profiles of the nanoparticulate megestrol compositions when administered in the fed versus the fasted state; (8) bioequivalency of the nanoparticulate megestrol compositions when administered in the fed versus the fasted state; (9) redispersibility of the nanoparticulate megestrol particles present in the compositions of the invention following administration; (10) bioadhesive nanoparticulate megestrol compositions; (11) improved pharmacokinetic profiles, such as more rapid megestrol absorption, greater megestrol absorption, and longer megestrol dose retention in the blood following administration; (12) the nanoparticulate megestrol compositions can

be used in conjunction with other active agents; (13) the nanoparticulate megestrol compositions preferably exhibit an increased rate of dissolution as compared to conventional microcrystalline forms of megestrol; (14) improved performance characteristics for oral, intravenous, subcutaneous, or intramuscular injection, such as higher dose loading and smaller tablet or liquid dose volumes; (15) the nanoparticulate megestrol compositions are suitable for parenteral administration; (16) the nanoparticulate megestrol compositions can be sterile filtered; and (17) the nanoparticulate megestrol compositions do not require organic solvents or pH extremes.

[0019] Moreover, it has now been surprisingly shown that administration of a nanoparticulate megestrol formulation, such as nanoparticulate megestrol acetate, provides improved appetite, increased weight gain, and increased food intake in comparison to MEGACE® megestrol acetate oral suspension, which is a composition of conventional, microparticulate megestrol actetate. In particular, a trial performed in accordance with the clinical study protocol provided herein resulted in the data shown in Figures 6-16, and is described in further detail in Example 11.

[0020] To summarize the results of the study described in Example 11, subjects receiving a nanoparticulate megestrol acetate composition ("MEGACE® ES") gained an average of 5.3 kg over the course of the 12 week study, and 38% of the patients reported an increase in food intake. In contrast, patients receiving the MEGACE® OS megestrol acetate oral suspension (a conventional, microparticulate megestrol acetate composition) gained only 3.55 kg on average, and only 19% of the patients reported an increase in food intake.

[0021] The study described in Example 11 demonstrates weight gain in adult HIV-positive subjects who have weight loss associated with AIDS-related wasting (anorexia/cachexia) in the first 12 weeks of treatment with a nanoparticulate megestrol acetetate composition. The study results are significant in that they demonstrate that weight gain upon administration of a nanoparticulate megestrol formulation is not just observed with healthy patients, but it is also observed with subjects having a condition that may affect their metabolism or other factors affecting weight gain.

[0022] Accordingly, the present invention relates to a method of increasing at least one of appetite, weight gain, and food intake comprising administering an effective amount of a nanoparticulate megestrol composition, such as nanoparticulate megestrol acetate, to a subject in need thereof.

[0023] The present invention is described herein using several definitions, as set forth below and throughout the application.

[0024] "About" will be understood by persons of ordinary skill in the art and will vary to some extent on the context in which the term is used. If there are uses of the term which are not clear to persons of ordinary skill in the art given the context in which it is used, "about" will mean up to plus or minus 10% of the particular term.

[0025] As used herein with reference to stable drug particles, "stable" means that the megestrol particles do not appreciably flocculate or agglomerate due to interparticle attractive forces or otherwise increase in particle size.

[0026] "Conventional active agents or drugs" refers to non-nanoparticulate compositions of active agents or solubilized active agents or drugs. Non-nanoparticulate active agents have an effective average particle size of greater than about 2 microns.

A. Preferred Characteristics of the Nanoparticulate Megestrol Compositions of the Invention

1. Low Viscosity

[0027] Typical commercial formulations of megestrol, such as Megace®, are relatively large volume, highly viscous substances that are not well accepted by patient populations, particularly subjects suffering from wasting. "Wasting" is a condition in which a subject finds it difficult to eat because, for example, food makes the subject nauseous. A highly viscous medicine is not compatible with treating such a condition, as frequently the highly viscous substance can cause additional nausea.

[0028] Moreover, viscous solutions can be problematic in parenteral administration because these solutions require a slow syringe push and can stick to tubing. In addition, conventional formulations of poorly water-soluble active agents, such as

megestrol, tend to be unsafe for intravenous administration techniques, which are used primarily in conjunction with highly water-soluble substances.

[0029] Liquid dosage forms of the nanoparticulate megestrol compositions of the invention provide significant advantages over conventional liquid megestrol dosage forms. The low viscosity and silky texture of liquid dosage forms of the nanoparticulate megestrol compositions of the invention results in advantages in both preparation and use. These advantages include, for example: (1) better subject compliance due to the perception of a lighter formulation which is easier to consume and digest; (2) ease of dispensing because one can use a cup or a syringe; (3) potential for formulating a higher concentration of megestrol resulting in a smaller dosage volume and thus less volume for the subject to consume; and (4) easier overall formulation concerns.

[0030] Liquid megestrol dosage forms which are easier to consume are especially important when considering juvenile patients, terminally ill patients, and patients suffering from gastrointestinal tract dysfunction or other conditions where nausea and vomiting are symptoms. For example, patients suffering from cancer or AIDS-related complications are commonly hypermetabolic and, at various stages of disease, exhibit gastrointestinal dysfunction. Additionally, drugs used to treat these conditions often cause nausea and vomiting. Viscous or gritty formulations, and those that require a relatively large dosage volume, are not well tolerated by patient populations suffering from wasting associated with these diseases because the formulations can exacerbate nausea and encourage vomiting.

[0031] The viscosities of liquid dosage forms of nanoparticulate megestrol according to the invention are preferably less than about 1/200, less than about 1/175, less than about 1/150, less than about 1/125, less than about 1/100, less than about 1/75, less than about 1/50, or less than about 1/25 of existing commercial liquid oral megestrol acetate compositions, *e.g.* Megace®, at about the same concentration per ml of megestrol.

[0032] Typically the viscosity of liquid nanoparticulate megestrol dosage forms of the invention is from about 175 mPa s to about 1 mPa s, from about 150 mPa s to about 1 mPa, from about 125 mPa s to about 1 mPa s, from about 100 mPa s to about 1 mPa s, from about 75 mPa s to about 1 mPa s, from about 50 mPa s to about 1 mPa s, from about

25 mPa s to about 1 mPa s, from about 15 mPa s to about 1 mPa s, or from about 5 mPa s to about 1 mPa s. Such a viscosity is much more attractive for subject consumption and may lead to better overall subject compliance.

[0033] Viscosity is concentration and temperature dependent. Typically, a higher concentration results in a higher viscosity, while a higher temperature results in a lower viscosity. Viscosity as defined above refers to measurements taken at about 20°C. (The viscosity of water at 20°C is 1 mPa s.) The invention encompasses equivalent viscosities measured at different temperatures.

[0034] A viscosity of 1.5 mPa s for a nanoparticulate megestrol dispersion having a concentration of 30 mg/mL, measured at 20°C, was obtained by the inventors. An equivalent viscosity at 4% active agent concentration would be 1.7 mPa s. Higher and lower viscosities can be obtained by varying the temperature and concentration of megestrol.

[0035] Another important aspect of the invention is that the nanoparticulate megestrol compositions of the invention are not turbid. "Turbid," as used herein refers to the property of particulate matter that can be seen with the naked eye or that which can be felt as "gritty." The nanoparticulate megestrol compositions of the invention can be poured out of or extracted from a container as easily as water, whereas a conventional standard commercial (*i.e.,* non-nanoparticulate or solubilized) megestrol liquid dosage form exhibits notably more "sluggish" characteristics.

[0036] The liquid formulations of this invention can be formulated for dosages in any volume but preferably equivalent or smaller volumes than existing commercial formulations.

2. Fast Onset of Activity

[0037] The use of conventional formulations of megestrol is not ideal due to delayed onset of action. In contrast, the nanoparticulate megestrol compositions of the invention exhibit faster therapeutic effects.

[0038] Preferably, following administration the nanoparticulate megestrol compositions of the invention have a T_{max} of less than about 5 hours, less than about 4.5

hours, less than about 4 hours, less than about 3.5 hours, less than about 3 hours, less than about 2.75 hours, less than about 2.5 hours, less than about 2.25 hours, less than about 2 hours, less than about 1.75 hours, less than about 1.5 hours, less than about 1.25 hours, less than about 1.0 hours, less than about 50 minutes, less than about 40 minutes, less than about 30 minutes, less than about 25 minutes, less than about 20 minutes, less than about 15 minutes, or less than about 10 minutes.

3. Increased Bioavailability

[0039] The nanoparticulate megestrol compositions of the invention preferably exhibit increased bioavailability and require smaller doses as compared to prior conventional megestrol compositions administered at the same dose.

[0040] Any drug, including megestrol, can have adverse side effects. Thus, lower doses of megestrol which can achieve the same or better therapeutic effects as those observed with larger doses of conventional megestrol compositions are desired. Such lower doses can be realized with the nanoparticulate megestrol compositions of the invention because the greater bioavailability observed with the nanoparticulate megestrol compositions as compared to conventional drug formulations means that smaller doses of drug are required to obtain the desired therapeutic effect. Specifically, a once a day dose of about 375 mg/5 mL (75 mg/mL) of a nanoparticulate megestrol acetate composition is considered equivalent to an 800 mg dose of Megace®.

[0041] Administration of nanoparticulate megestrol formulations of the present invention can exhibit bioavailability, as determined by AUC0-t, in an amount of about 3000 ng hr/ml to about 15,000 ng hr/ml, wherein Cmax is about 300 ng/ml to about 1400 ng/ml, 1500 ng/ml, 1600 ng/ml, 1645 ng/ml or 1700 ng/ml in a fed human subject and AUC0-t in an amount of about 2000 ng hr/ml to about 9000 ng hr/ml, wherein Cmax is about 300 ng/ml to about 2000 ng/ml in a fasted human subject. Preferably, nanoparticulate megestrol formulations of the present invention exhibit comparable bioavailability in a range of between about 75 and about 130%, more preferably between about 80% and about 125%, of the specified therapeutic parameter (e.g., AUC0-t or Cmax).

4. The Pharmacokinetic Profiles of the Nanoparticulate Megestrol Compositions of the Invention are not Substantially Affected by the Fed or Fasted State of the Subject Ingesting the Compositions

[0042] The invention encompasses nanoparticulate megestrol compositions wherein the pharmacokinetic profile of the megestrol is not substantially affected by the fed or fasted state of a subject ingesting the composition. This means that there is no substantial difference in the quantity of megestrol absorbed or the rate of megestrol absorption when the nanoparticulate megestrol compositions are administered in the fed versus the fasted state. Thus, the invention encompasses nanoparticulate megestrol compositions that can substantially eliminate the effect of food on the pharmacokinetics of megestrol.

[0043] The difference in absorption of the nanoparticulate megestrol composition of the invention (Cmax or AUC), when administered in the fed versus the fasted state, is less than about 600%, less than about 575%, less than about 550%, less than about 525%, less than about 500%, less than about 475%, less than about 450%, less than about 425%, less than about 400%, less than about 375%, less than about 350%, less than about 325%, less than about 300%, less than about 275%, less than about 250%, less than about 225%, less than about 200%, less than about 175%, less than about 150%, less than about 125%, less than about 100%, less than about 95%, less than about 90%, less than about 85%, less than about 80%, less than about 75%, less than about 70%, less than about 65%, less than about 60%, less than about 55%, less than about 50%, less than about 45%, less than about 40%, less than about 35%, less than about 30%, less than about 25%, less than about 20%, less than about 15%, less than about 10%, less than about 5%, or less than about 3%. This is an especially important feature in treating patients with difficulty in maintaining a fed state.

[0044] In addition, preferably the difference in the rate of absorption (*i.e.*, T_{max}) of the nanoparticulate megestrol compositions of the invention, when administered in the fed versus the fasted state, is less than about 100%, less than about 90%, less than about 80%,

less than about 70%, less than about 60%, less than about 50%, less than about 40%, less than about 30%, less than about 20%, less than about 15%, less than about 10%, less than about 5%, less than about 3%, or essentially no difference.

[0045] Benefits of a dosage form which substantially eliminates the effect of food include an increase in subject convenience, thereby increasing subject compliance, as the subject does not need to ensure that they are taking a dose either with or without food.

5. Bioequivalency of Megestrol Compositions of the Invention When Administered in the Fed Versus the Fasted State

[0046] The invention also encompasses provides a nanoparticulate megestrol composition in which administration of the composition to a subject in a fasted state is bioequivalent to administration of the composition to a subject in a fed state.

[0047] In one embodiment of the invention, the invention encompasses compositions comprising a nanoparticulate megestrol, wherein administration of the composition to a subject in a fasted state is bioequivalent to administration of the composition to a subject in a fed state, in particular as defined by C_{max} and AUC guidelines given by the U.S. Food and Drug Administration and the corresponding European regulatory agency (EMEA). Under U.S. FDA guidelines, two products or methods are bioequivalent if the 90% Confidence Intervals (CI) for AUC and C_{max} are between 0.80 to 1.25 (T_{max} measurements are not relevant to bioequivalence for regulatory purposes). To show bioequivalency between two compounds or administration conditions pursuant to Europe's EMEA guidelines, the 90% CI for AUC must be between 0.80 to 1.25 and the 90% CI for C_{max} must between 0.70 to 1.43.

6. Redispersibility Profiles of the Nanoparticulate Megestrol Compositions of the Invention

[0048] An additional feature of the nanoparticulate megestrol compositions of the invention is that the compositions redisperse such that the effective average particle size of the redispersed megestrol particles is less than about 2 microns. This is significant, as if upon administration the nanoparticulate megestrol particles present in the compositions

of the invention did not redisperse to a substantially nanoparticulate particle size, then the dosage form may lose the benefits afforded by formulating megestrol into a nanoparticulate particle size.

[0049] This is because nanoparticulate megestrol compositions benefit from the small particle size of megestrol; if the nanoparticulate megestrol particles do not redisperse into the small particle sizes upon administration, then "clumps" or agglomerated megestrol particles are formed. With the formation of such agglomerated particles, the bioavailability of the dosage form may fall.

[0050] Preferably, the redispersed megestrol particles of the invention have an effective average particle size, by weight, of less than about 2 microns, less than about 1900 nm, less than about 1800 nm, less than about 1700 nm, less than about 1600 nm, less than about 1500 nm, less than about 1400 nm, less than about 1300 nm, less than about 1200 nm, less than about 1100 nm, less than about 1000 nm, less than about 900 nm, less than about 800 nm, less than about 700 nm, less than about 600 nm, less than about 500 nm, less than about 400 nm, less than about 300 nm, less than about 250 nm, less than about 200 nm, less than about 150 nm, less than about 100 nm, less than about 75 nm, or less than about 50 nm, as measured by light-scattering methods, microscopy, or other appropriate methods.

[0051] Moreover, the nanoparticulate megestrol compositions of the invention exhibit dramatic redispersion of the nanoparticulate megestrol particles upon administration to a mammal, such as a human or animal, as demonstrated by reconstitution in a biorelevant aqueous media. Such biorelevant aqueous media can be any aqueous media that exhibit the desired ionic strength and pH, which form the basis for the biorelevance of the media. The desired pH and ionic strength are those that are representative of physiological conditions found in the human body. Such biorelevant aqueous media can be, for example, aqueous electrolyte solutions or aqueous solutions of any salt, acid, or base, or a combination thereof, which exhibit the desired pH and ionic strength.

[0052] Biorelevant pH is well known in the art. For example, in the stomach, the pH ranges from slightly less than 2 (but typically greater than 1) up to 4 or 5. In the small

intestine the pH can range from 4 to 6, and in the colon it can range from 6 to 8. Biorelevant ionic strength is also well known in the art. Fasted state gastric fluid has an ionic strength of about 0.1M while fasted state intestinal fluid has an ionic strength of about 0.14. *See e.g.*, Lindahl et al., "Characterization of Fluids from the Stomach and Proximal Jejunum in Men and Women," *Pharm. Res., 14* (4): 497-502 (1997).

[0053] It is believed that the pH and ionic strength of the test solution is more critical than the specific chemical content. Accordingly, appropriate pH and ionic strength values can be obtained through numerous combinations of strong acids, strong bases, salts, single or multiple conjugate acid-base pairs (*i.e.*, weak acids and corresponding salts of that acid), monoprotic and polyprotic electrolytes, *etc.*

[0054] Representative electrolyte solutions can be, but are not limited to, HCl solutions, ranging in concentration from about 0.001 to about 0.1 M, and NaCl solutions, ranging in concentration from about 0.001 to about 0.1 M, and mixtures thereof. For example, electrolyte solutions can be, but are not limited to, about 0.1 M HCl or less, about 0.01 M HCl or less, about 0.001 M HCl or less, about 0.1 M NaCl or less, about 0.01 M NaCl or less, about 0.001 M NaCl or less, and mixtures thereof. Of these electrolyte solutions, 0.01 M HCl and/or 0.1 M NaCl, are most representative of fasted human physiological conditions, owing to the pH and ionic strength conditions of the proximal gastrointestinal tract.

[0055] Electrolyte concentrations of 0.001 M HCl, 0.01 M HCl, and 0.1 M HCl correspond to pH 3, pH 2, and pH 1, respectively. Thus, a 0.01 M HCl solution simulates typical acidic conditions found in the stomach. A solution of 0.1 M NaCl provides a reasonable approximation of the ionic strength conditions found throughout the body, including the gastrointestinal fluids, although concentrations higher than 0.1 M may be employed to simulate fed conditions within the human GI tract.

[0056] Exemplary solutions of salts, acids, bases or combinations thereof, which exhibit the desired pH and ionic strength, include but are not limited to phosphoric acid/phosphate salts + sodium, potassium and calcium salts of chloride, acetic acid/acetate salts + sodium, potassium and calcium salts of chloride, carbonic acid/bicarbonate salts +

sodium, potassium and calcium salts of chloride, and citric acid/citrate salts + sodium, potassium and calcium salts of chloride.

7. Bioadhesive Nanoparticulate Megestrol Compositions

[0057] Bioadhesive nanoparticulate megestrol compositions of the invention comprise at least one cationic surface stabilizer, which are described in more detail below. Bioadhesive formulations of megestrol exhibit exceptional bioadhesion to biological surfaces, such as mucous.

[0058] In the case of bioadhesive nanoparticulate megestrol compositions, the term "bioadhesion" is used to describe the adhesion between the nanoparticulate megestrol compositions and a biological substrate (*i.e.* gastrointestinal mucin, lung tissue, nasal mucosa, *etc.*). *See e.g.,* U.S. Patent No. 6,428,814 for "Bioadhesive Nanoparticulate Compositions Having Cationic Surface Stabilizers," which is specifically incorporated by reference.

[0059] The bioadhesive megestrol compositions of the invention are useful in any situation in which it is desirable to apply the compositions to a biological surface. The bioadhesive megestrol compositions coat the targeted surface in a continuous and uniform film which is invisible to the naked human eye.

[0060] A bioadhesive nanoparticulate megestrol composition slows the transit of the composition, and some megestrol particles would also most likely adhere to tissue other than the mucous cells and therefore give a prolonged exposure to megestrol, thereby increasing absorption and the bioavailability of the administered dosage.

8. Pharmacokinetic Profiles of the Nanoparticulate Megestrol Compositions of the Invention

[0061] The present invention also provides compositions of nanoparticulate megestrol having a desirable pharmacokinetic profile when administered to mammalian subjects. The desirable pharmacokinetic profile of the compositions comprising megestrol includes but is not limited to: (1) a C_{max} for megestrol, when assayed in the plasma of a mammalian subject following administration, that is preferably greater than

the C_{max} for a non-nanoparticulate formulation of the same megestrol, administered at the same dosage; and/or (2) an AUC for megestrol, when assayed in the plasma of a mammalian subject following administration, that is preferably greater than the AUC for a non-nanoparticulate formulation of the same megestrol, administered at the same dosage; and/or (3) a T_{max} for megestrol, when assayed in the plasma of a mammalian subject following administration, that is preferably less than the T_{max} for a non-nanoparticulate formulation of the same megestrol, administered at the same dosage. The desirable pharmacokinetic profile, as used herein, is the pharmacokinetic profile measured after the initial dose of megestrol or a salt or derivative thereof.

[0062] The desirable pharmacokinetic profile of the nanoparticulate megestrol compositions preferably comprise the parameters: (1) that the T_{max} of megestrol, when assayed in the plasma of the mammalian subject, is less than about 5 hours; and (2) a C_{max} of megestrol is greater than about 30 ng/ml. Preferably, the T_{max} parameter of the pharmacokinetic profile is not greater than about 3 hours. Most preferably, the T_{max} parameter of the pharmacokinetic profile is not greater than about 2 hours.

[0063] The desirable pharmacokinetic profile, as used herein, is the pharmacokinetic profile measured after the initial dose of megestrol. For example, in a subject receiving 40 mg of megestrol four times a day, the T_{max} and C_{max} after the initial dose must be less than about 5 hours and greater than about 30 ng/ml, respectively. The compositions can be formulated in any way as described below.

[0064] Current formulations of megestrol include oral suspensions and tablets. According to the package insert of Megace®, the pharmacokinetic profile of the oral suspension contains parameters such that the median T_{max} is 5 hours and the mean C_{max} is 753 ng/ml. Further, the T_{max} and C_{max} for the Megace® 40 mg tablet, after the initial dose, is 2.2 hours and 27.6 ng/ml, respectively. *Physicians Desk Reference*, 55th Ed., 2001. The nanoparticulate megestrol compositions of the invention simultaneously improve upon at least the T_{max} and C_{max} parameters of the pharmacokinetic profile of megestrol.

[0065] In one embodiment, a threshold blood plasma concentration of megestrol of about 700 ng/ml is attained in less than about 5 hours after administration of the formulation, and preferably not greater than about 3 hours.

[0066] A preferred nanoparticulate megestrol composition of the invention exhibits in comparative pharmacokinetic testing with a standard commercial formulation of megestrol, such as Megace® oral suspension or tablet from Bristol Myers Squibb, a T_{max} which is less than about 100%, less than about 90%, less than about 80%, less than about 70%, less than about 60%, less than about 50%, less than about 40%, less than about 30%, less than about 25%, less than about 20%, less than about 15%, or less than about 10% of the T_{max} exhibited by the standard commercial formulation of megestrol.

[0067] A preferred nanoparticulate megestrol composition of the invention exhibits in comparative pharmacokinetic testing with a standard commercial formulation of megestrol, such as Megace® oral suspension or tablet from Bristol Myers Squibb, a C_{max} which is greater than about 5%, greater than about 10%, greater than about 15%, greater than about 20%, greater than about 30%, greater than about 40%, greater than about 50%, greater than about 60%, greater than about 70%, greater than about 80%, greater than about 90%, greater than about 100%, greater than about 110%, greater than about 120%, greater than about 130%, greater than about 140%, greater than about 150%, greater than about 200%, greater than about 500% or greater than about 800% than the C_{max} exhibited by the standard commercial formulation of megestrol.

[0068] A preferred nanoparticulate megestrol composition of the invention exhibits in comparative pharmacokinetic testing with a standard commercial formulation of megestrol, such as Megace® oral suspension or tablet from Bristol Myers Squibb, an AUC which is greater than about 5%, greater than about 10%, greater than about 15%, greater than about 20%, greater than about 30%, greater than about 40%, greater than about 50%, greater than about 60%, greater than about 70%, greater than about 80%, greater than about 90%, greater than about 100%, greater than about 110%, greater than about 120%, greater than about 130%, greater than about 140%, greater than about 150%, greater than about 200%, greater than about 500% or greater than about 800% than the AUC exhibited by the standard commercial formulation of megestrol.

[0069] There is no critical upper limit of blood plasma concentration so long as the dosage amounts set out below are not significantly exceeded. A suitable dose of megestrol, administered according to the method of the invention, is typically in the range of about 1 mg/day to about 1000 mg/day, or from about 40 mg/day to about 800 mg/day. In one embodiment, a nanoparticulate megestrol composition is administered at a dose of 575 mg/day. In other embodiments, the nanoparticulate megestrol composition is administered at doses of 625 mg/day or 675 mg/day. Preferably, the therapeutically effective amount of the nanoparticulate megestrol compositions of the invention is about 1/6, 1/5, 1/4, 1/3, 1/2, 2/3, 3/4 or 5/6 of the therapeutically effective amount of existing commercial megestrol formulations.

[0070] Any standard pharmacokinetic protocol can be used to determine blood plasma concentration profile in humans following administration of a nanoparticulate megestrol composition, and thereby establish whether that composition meets the pharmacokinetic criteria set out herein. For example, a randomized single-dose crossover study can be performed using a group of healthy adult human subjects. The number of subjects should be sufficient to provide adequate control of variation in a statistical analysis, and is typically about 10 or greater, although for certain purposes a smaller group can suffice. Each subject receives by oral administration at time zero a single dose (*e.g.*, 300 mg) of a test formulation of megestrol, normally at around 8 am following an overnight fast. The subjects continue to fast and remain in an upright position for about 4 hours after administration of the megestrol formulation. Blood samples are collected from each subject prior to administration (*e.g.*, 15 minutes) and at several intervals after administration. For the present purpose it is preferred to take several samples within the first hour, and to sample less frequently thereafter. Illustratively, blood samples could be collected at 15, 30, 45, 60, and 90 minutes after administration, then every hour from 2 to 10 hours after administration. Additional blood samples may also be taken later, for example at 12 and 24 hours after administration. If the same subjects are to be used for study of a second test formulation, a period of at least 7 days should elapse before administration of the second formulation. Plasma is separated from the blood samples by centrifugation and the separated plasma is analyzed for megestrol by a validated high

performance liquid chromatography (HPLC) procedure, such as for example Garver et al., *J. Pharm. Sci. 74*(6):664-667 (1985), the entirety of which is hereby incorporated by reference. Plasma concentrations of megestrol referenced herein are intended to mean total megestrol concentrations including both free and bound megestrol.

[0071] Any formulation giving the desired pharmacokinetic profile is suitable for administration according to the present methods. Exemplary types of formulations giving such profiles are liquid dispersions and solid dose forms of nanoparticulate megestrol. Dispersions of megestrol have proven to be stable at temperatures up to 50°C. If the liquid dispersion medium is one in which the nanoparticulate megestrol has very low solubility, the nanoparticulate megestrol particles are present as suspended particles. The smaller the megestrol particles, the higher the probability that the formulation will exhibit the desired pharmacokinetic profile.

9. Combination Pharmacokinetic Profile Compositions

[0072] In yet another embodiment of the invention, a first nanoparticulate megestrol composition providing a desired pharmacokinetic profile is co-administered, sequentially administered, or combined with at least one other megestrol composition that generates a desired different pharmacokinetic profile. More than two megestrol compositions can be co-administered, sequentially administered, or combined. While the first megestrol composition has a nanoparticulate particle size, the additional one or more megestrol compositions can be nanoparticulate, solubilized, or have a conventional microparticulate particle size.

[0073] For example, a first megestrol composition can have a nanoparticulate particle size, conferring a short T_{max} and typically a higher C_{max}. This first megestrol composition can be combined, co-administered, or sequentially administered with a second composition comprising: (1) megestrol having a larger (but still nanoparticulate as defined herein) particle size, and therefore exhibiting slower absorption, a longer T_{max}, and typically a lower C_{max}; or (2) a microparticulate or solubilized megestrol composition, exhibiting a longer T_{max}, and typically a lower C_{max}.

[0074] The second, third, fourth, *etc.*, megestrol compositions can differ from the first, and from each other, for example: (1) in the effective average particle sizes of megestrol; or (2) in the dosage of megestrol. Such a combination composition can reduce the dose frequency required.

[0075] If the second megestrol composition has a nanoparticulate particle size, then preferably the megestrol particles of the second composition have at least one surface stabilizer associated with the surface of the drug particles. The one or more surface stabilizers can be the same as or different from the surface stabilizer(s) present in the first megestrol composition.

[0076] Preferably where co-administration of a "fast-acting" formulation and a "longer-lasting" formulation is desired, the two formulations are combined within a single composition, for example a dual-release composition.

10. Combination Active Agent Compositions

[0077] The invention encompasses the nanoparticulate megestrol compositions of the invention formulated or co-administered with one or more non-megestrol active agents, which are either conventional (solubilized or microparticulate) or nanoparticulate. Methods of using such combination compositions are also encompassed by the invention. The non-megestrol active agents can be present in a crystalline phase, an amorphous phase, a semi-crystalline phase, a semi-amorphous phase, or a mixture thereof.

[0078] The compound to be administered in combination with a nanoparticulate megestrol composition of the invention can be formulated separately from the nanoparticulate megestrol composition or co-formulated with the nanoparticulate megestrol composition. Where a nanoparticulate megestrol composition is co-formulated with a second active agent, the second active agent can be formulated in any suitable manner, such as immediate-release, rapid-onset, sustained-release, or dual-release form.

[0079] If the non-megestrol active agent has a nanoparticulate particle size *i.e.*, a particle size of less than about 2 microns, then preferably it will have one or more surface stabilizers associated with the surface of the active agent. In addition, if the active agent has a nanoparticulate particle size, then it is preferably poorly soluble and dispersible in at

least one liquid dispersion media. By "poorly soluble" it is meant that the active agent has a solubility in a liquid dispersion media of less than about 30 mg/mL, less than about 20 mg/mL, less than about 10 mg/mL, or less than about 1 mg/mL. Useful liquid dispersion medias include, but are not limited to, water, aqueous salt solutions, safflower oil, and solvents such as ethanol, t-butanol, hexane, and glycol.

[0080] Such non-megestrol active agents can be, for example, a therapeutic agent. A therapeutic agent can be a pharmaceutical agent, including biologics. The active agent can be selected from a variety of known classes of drugs, including, for example, amino acids, proteins, peptides, nucleotides, anti-obesity drugs, central nervous system stimulants, carotenoids, corticosteroids, elastase inhibitors, anti-fungals, oncology therapies, anti-emetics, analgesics, cardiovascular agents, anti-inflammatory agents, such as NSAIDs and COX-2 inhibitors, anthelmintics, anti-arrhythmic agents, antibiotics (including penicillins), anticoagulants, antidepressants, antidiabetic agents, antiepileptics, antihistamines, antihypertensive agents, antimuscarinic agents, antimycobacterial agents, antineoplastic agents, immunosuppressants, antithyroid agents, antiviral agents, anxiolytics, sedatives (hypnotics and neuroleptics), astringents, alpha-adrenergic receptor blocking agents, beta-adrenoceptor blocking agents, blood products and substitutes, cardiac inotropic agents, contrast media, corticosteroids, cough suppressants (expectorants and mucolytics), diagnostic agents, diagnostic imaging agents, diuretics, dopaminergics (antiparkinsonian agents), haemostatics, immunological agents, lipid regulating agents, muscle relaxants, parasympathomimetics, parathyroid calcitonin and biphosphonates, prostaglandins, radio-pharmaceuticals, sex hormones (including steroids), anti-allergic agents, stimulants and anoretics, sympathomimetics, thyroid agents, vasodilators, and xanthines.

[0081] A description of these classes of active agents and a listing of species within each class can be found in Martindale's *The Extra Pharmacopoeia,* 31st Edition (The Pharmaceutical Press, London, 1996), specifically incorporated by reference. The active agents are commercially available and/or can be prepared by techniques known in the art.

[0082] Exemplary nutraceuticals and dietary supplements are disclosed, for example, in Roberts et al., *Nutraceuticals: The Complete Encyclopedia of Supplements, Herbs, Vitamins, and Healing Foods* (American Nutraceutical Association, 2001), which is specifically incorporated by reference. Dietary supplements and nutraceuticals are also disclosed in *Physicians' Desk Reference for Nutritional Supplements*, 1st Ed. (2001) and *The Physicians' Desk Reference for Herbal Medicines,* 1st Ed. (2001), both of which are also incorporated by reference. A nutraceutical or dietary supplement, also known as a phytochemical or functional food, is generally any one of a class of dietary supplements, vitamins, minerals, herbs, or healing foods that have medical or pharmaceutical effects on the body.

[0083] Exemplary nutraceuticals or dietary supplements include, but are not limited to, lutein, folic acid, fatty acids (*e.g.*, DHA and ARA), fruit and vegetable extracts, vitamin and mineral supplements, phosphatidylserine, lipoic acid, melatonin, glucosamine/chondroitin, Aloe Vera, Guggul, glutamine, amino acids (*e.g.*, arginine, isoleucine, leucine, lysine, methionine, phenylanine, threonine, tryptophan, and valine), green tea, lycopene, whole foods, food additives, herbs, phytonutrients, antioxidants, flavonoid constituents of fruits, evening primrose oil, flax seeds, fish and marine animal oils, and probiotics. Nutraceuticals and dietary supplements also include bio-engineered foods genetically engineered to have a desired property, also known as "pharmafoods."

11. Sterile Filtered Nanoparticulate Megestrol Compositions

[0084] The nanoparticulate megestrol compositions of the invention can be sterile filtered. This obviates the need for heat sterilization, which can harm or degrade megestrol, as well as result in crystal growth and particle aggregation.

[0085] Sterile filtration can be difficult because of the required small particle size of the composition. Filtration is an effective method for sterilizing homogeneous solutions when the membrane filter pore size is less than or equal to about 0.2 microns (200 nm) because a 0.2 micron filter is sufficient to remove essentially all bacteria. Sterile filtration is normally not used to sterilize conventional suspensions of micron-

sized megestrol because the megestrol particles are too large to pass through the membrane pores.

[0086] A sterile nanoparticulate megestrol dosage form is particularly useful in treating immunocompromised patients, infants or juvenile patients, and the elderly, as these patient groups are the most susceptible to infection caused by a non-sterile liquid dosage form.

[0087] Because the nanoparticulate megestrol compositions of the invention can be sterile filtered, and because the compositions can have a very small megestrol effective average particle size, the compositions are suitable for parenteral administration.

12. Miscellaneous Benefits of the Nanoparticulate Megestrol Compositions of the Invention

[0088] The nanoparticulate megestrol compositions preferably exhibit an increased rate of dissolution as compared to conventional microcrystalline forms of megestrol. In addition, the compositions of the invention exhibit improved performance characteristics for oral, intravenous, subcutaneous, or intramuscular injection, such as higher dose loading and smaller tablet or liquid dose volumes. Moreover, the nanoparticulate megestrol compositions of the invention do not require organic solvents or pH extremes.

[0089] Another benefit of the nanoparticulate megestrol compositions of the invention is that is was surprisingly discovered that upon administration, nanoparticulate compositions of megestrol acetate reach therapeutic blood levels within one dose. This is in dramatic contrast to the current commercially available megestrol acetate composition (Megace® by Bristol Myers Squibb Co.), which requires multiple doses, administered over several days to a week, to build up to a therapeutic level of drug in the blood stream.

B. Compositions

[0090] The invention provides compositions comprising nanoparticulate megestrol particles and preferably at least one surface stabilizer. The one or more surface stabilizers are preferably associated with the surface of the megestrol particles. Surface

stabilizers useful herein preferably do not chemically react with the megestrol particles or itself. Individual molecules of the surface stabilizer are essentially free of intermolecular cross-linkages.

[0091] The present invention also includes nanoparticulate megestrol compositions together with one or more non-toxic physiologically acceptable carriers, adjuvants, or vehicles, collectively referred to as carriers. The compositions can be formulated for parenteral injection (*e.g.*, intravenous, intramuscular, or subcutaneous), oral administration in solid, liquid, or aerosol form, vaginal, nasal, rectal, ocular, local (powders, ointments or drops), buccal, intracisternal, intraperitoneal, or topical administration, and the like.

1. Megestrol Particles

[0092] As used herein the term megestrol, which is the active ingredient in the composition, is used to mean megestrol, megestrol acetate (17α-acetyloxy-6-methylpregna-4,6-diene-3,20-dione), or a salt thereof. The megestrol particles can be present in a crystalline phase, an amorphous phase, a semi-crystalline phase, a semi-amorphous phase, or a mixture thereof.

[0093] Megestrol acetate is well known in the art and is readily recognized by one of ordinary skill. Generally, megestrol is used for treating breast cancer, endometrial cancer and, less frequently, prostate cancer. Megestrol is also frequently used as an appetite stimulant for patients in a wasting state, such as HIV wasting, cancer wasting, and anorexia. Megestrol may be used for other indications where progestins are typically used, such as hormone replacement therapy in post-menopausal women and oral contraception. Further, megestrol may be used for ovarian suppression in several conditions such as endometriosis, hirsutism, dysmenorrhea, and uterine bleeding, as well as uterine cancer, cervical cancer, and renal cancer. Megestrol is also used in patients following castration.

2. Surface Stabilizers

[0094] The choice of a surface stabilizer for megestrol is non-trivial. Accordingly, the present invention is directed to the surprising discovery that nanoparticulate megestrol compositions can be made.

[0095] Combinations of more than one surface stabilizer can be used in the invention. Preferred surface stabilizers include, but are not limited to, hydroxypropyl methylcellulose, hydroxypropylcellulose, polyvinylpyrrolidone, random copolymers of vinyl pyrrolidone and vinyl acetate, sodium lauryl sulfate, dioctylsulfosuccinate or a combination thereof. . Preferred primary surface stabilizers include, but are not limited to, hydroxypropyl methylcellulose, hydroxypropylcellulose, polyvinylpyrrolidone, random copolymers of vinyl pyrrolidone and vinyl acetate, or a combination thereof. Preferred secondary surface stabilizers include, but are not limited to, sodium lauryl sulfate and dioctylsulfosuccinate.

[0096] Other surface stabilizers which can be employed in the invention include, but are not limited to, known organic and inorganic pharmaceutical excipients. Such excipients include various polymers, low molecular weight oligomers, natural products, and surfactants. Surface stabilizers include nonionic, cationic, ionic, and zwitterionic surfactants.

[0097] Representative examples of surface stabilizers include hydroxypropyl methylcellulose, hydroxypropylcellulose, polyvinylpyrrolidone, sodium lauryl sulfate, dioctylsulfosuccinate, gelatin, casein, lecithin (phosphatides), dextran, gum acacia, cholesterol, tragacanth, stearic acid, benzalkonium chloride, calcium stearate, glycerol monostearate, cetostearyl alcohol, cetomacrogol emulsifying wax, sorbitan esters, polyoxyethylene alkyl ethers (*e.g.*, macrogol ethers such as cetomacrogol 1000), polyoxyethylene castor oil derivatives, polyoxyethylene sorbitan fatty acid esters (*e.g.*, the commercially available Tweens® such as *e.g.*, Tween 20® and Tween 80® (ICI Specialty Chemicals)); polyethylene glycols (*e.g.*, Carbowaxs 3550® and 934® (Union Carbide)), polyoxyethylene stearates, colloidal silicon dioxide, phosphates, carboxymethylcellulose calcium, carboxymethylcellulose sodium, methylcellulose, hydroxyethylcellulose, hydroxypropylmethylcellulose phthalate, noncrystalline cellulose, magnesium aluminium

silicate, triethanolamine, polyvinyl alcohol (PVA), 4-(1,1,3,3-tetramethylbutyl)-phenol polymer with ethylene oxide and formaldehyde (also known as tyloxapol, superione, and triton), poloxamers (*e.g.*, Pluronics F68® and F108®, which are block copolymers of ethylene oxide and propylene oxide); poloxamines (*e.g.*, Tetronic 908®, also known as Poloxamine 908®, which is a tetrafunctional block copolymer derived from sequential addition of propylene oxide and ethylene oxide to ethylenediamine (BASF Wyandotte Corporation, Parsippany, N.J.)); Tetronic 1508® (T-1508) (BASF Wyandotte Corporation), Tritons X-200®, which is an alkyl aryl polyether sulfonate (Rohm and Haas); Crodestas F-110®, which is a mixture of sucrose stearate and sucrose distearate (Croda Inc.); p-isononylphenoxypoly-(glycidol), also known as Olin-lOG® or Surfactant 10-G® (Olin Chemicals, Stamford, CT); Crodestas SL-40® (Croda, Inc.); and SA9OHCO, which is $C_{18}H_{37}CH_2(CON(CH_3)\text{-}CH_2(CHOH)_4(CH_20H)_2$ (Eastman Kodak Co.); decanoyl-N-methylglucamide; n-decyl β-D-glucopyranoside; n-decyl β-D-maltopyranoside; n-dodecyl β-D-glucopyranoside; n-dodecyl β-D-maltoside; heptanoyl-N-methylglucamide; n-heptyl-β-D-glucopyranoside; n-heptyl β-D-thioglucoside; n-hexyl β-D-glucopyranoside; nonanoyl-N-methylglucamide; n-noyl β-D-glucopyranoside; octanoyl-N-methylglucamide; n-octyl-β-D-glucopyranoside; octyl β-D-thioglucopyranoside; PEG-phospholipid, PEG-cholesterol, PEG-cholesterol derivative, PEG-vitamin A, PEG-vitamin E, lysozyme, random copolymers of vinyl pyrrolidone and vinyl acetate, and the like.

[0098] Examples of useful cationic surface stabilizers include, but are not limited to, polymers, biopolymers, polysaccharides, cellulosics, alginates, phospholipids, and nonpolymeric compounds, such as zwitterionic stabilizers, poly-n-methylpyridinium, anthryul pyridinium chloride, cationic phospholipids, chitosan, polylysine, polyvinylimidazole, polybrene, polymethylmethacrylate trimethylammoniumbromide bromide (PMMTMABr), hexyldesyltrimethylammonium bromide (HDMAB), and polyvinylpyrrolidone-2-dimethylaminoethyl methacrylate dimethyl sulfate.

[0099] Other useful cationic stabilizers include, but are not limited to, cationic lipids, sulfonium, phosphonium, and quarternary ammonium compounds, such as stearyltrimethylammonium chloride, benzyl-di(2-chloroethyl)ethylammonium bromide,

coconut trimethyl ammonium chloride or bromide, coconut methyl dihydroxyethyl ammonium chloride or bromide, decyl triethyl ammonium chloride, decyl dimethyl hydroxyethyl ammonium chloride or bromide, C_{12-15}dimethyl hydroxyethyl ammonium chloride or bromide, coconut dimethyl hydroxyethyl ammonium chloride or bromide, myristyl trimethyl ammonium methyl sulphate, lauryl dimethyl benzyl ammonium chloride or bromide, lauryl dimethyl (ethenoxy)$_4$ ammonium chloride or bromide, N-alkyl (C_{12-18})dimethylbenzyl ammonium chloride, N-alkyl (C_{14-18})dimethyl-benzyl ammonium chloride, N-tetradecylidmethylbenzyl ammonium chloride monohydrate, dimethyl didecyl ammonium chloride, N-alkyl and (C_{12-14}) dimethyl 1-napthylmethyl ammonium chloride, trimethylammonium halide, alkyl-trimethylammonium salts and dialkyl-dimethylammonium salts, lauryl trimethyl ammonium chloride, ethoxylated alkyamidoalkyldialkylammonium salt and/or an ethoxylated trialkyl ammonium salt, dialkylbenzene dialkylammonium chloride, N-didecyldimethyl ammonium chloride, N-tetradecyldimethylbenzyl ammonium, chloride monohydrate, N-alkyl(C_{12-14}) dimethyl 1-naphthylmethyl ammonium chloride and dodecyldimethylbenzyl ammonium chloride, dialkyl benzenealkyl ammonium chloride, lauryl trimethyl ammonium chloride, alkylbenzyl methyl ammonium chloride, alkyl benzyl dimethyl ammonium bromide, C_{12}, C_{15}, C_{17} trimethyl ammonium bromides, dodecylbenzyl triethyl ammonium chloride, poly-diallyldimethylammonium chloride (DADMAC), dimethyl ammonium chlorides, alkyldimethylammonium halogenides, tricetyl methyl ammonium chloride, decyltrimethylammonium bromide, dodecyltriethylammonium bromide, tetradecyltrimethylammonium bromide, methyl trioctylammonium chloride (ALIQUAT 336™), POLYQUAT 10™, tetrabutylammonium bromide, benzyl trimethylammonium bromide, choline esters (such as choline esters of fatty acids), benzalkonium chloride, stearalkonium chloride compounds (such as stearyltrimonium chloride and Di-stearyldimonium chloride), cetyl pyridinium bromide or chloride, halide salts of quaternized polyoxyethylalkylamines, MIRAPOL™ and ALKAQUAT™ (Alkaril Chemical Company), alkyl pyridinium salts; amines, such as alkylamines, dialkylamines, alkanolamines, polyethylenepolyamines, N,N-dialkylaminoalkyl acrylates, and vinyl pyridine, amine salts, such as lauryl amine acetate, stearyl amine acetate, alkylpyridinium

salt, and alkylimidazolium salt, and amine oxides; imide azolinium salts; protonated quaternary acrylamides; methylated quaternary polymers, such as poly[diallyl dimethylammonium chloride] and poly-[N-methyl vinyl pyridinium chloride]; and cationic guar.

[00100] Such exemplary cationic surface stabilizers and other useful cationic surface stabilizers are described in J. Cross and E. Singer, *Cationic Surfactants: Analytical and Biological Evaluation* (Marcel Dekker, 1994); P. and D. Rubingh (Editor), *Cationic Surfactants: Physical Chemistry* (Marcel Dekker, 1991); and J. Richmond, *Cationic Surfactants: Organic Chemistry,* (Marcel Dekker, 1990).

[00101] Particularly preferred nonpolymeric primary stabilizers are any nonpolymeric compound, such benzalkonium chloride, a carbonium compound, a phosphonium compound, an oxonium compound, a halonium compound, a cationic organometallic compound, a quarternary phosphorous compound, a pyridinium compound, an anilinium compound, an ammonium compound, a hydroxylammonium compound, a primary ammonium compound, a secondary ammonium compound, a tertiary ammonium compound, and quarternary ammonium compounds of the formula $NR_1R_2R_3R_4^{(+)}$. For compounds of the formula $NR_1R_2R_3R_4^{(+)}$:

(i) none of R_1-R_4 are CH_3;

(ii) one of R_1-R_4 is CH_3;

(iii) three of R_1-R_4 are CH_3;

(iv) all of R_1-R_4 are CH_3;

(v) two of R_1-R_4 are CH_3, one of R_1-R_4 is $C_6H_5CH_2$, and one of R_1-R_4 is an alkyl chain of seven carbon atoms or less;

(vi) two of R_1-R_4 are CH_3, one of R_1-R_4 is $C_6H_5CH_2$, and one of R_1-R_4 is an alkyl chain of nineteen carbon atoms or more;

(vii) two of R_1-R_4 are CH_3 and one of R_1-R_4 is the group $C_6H_5(CH_2)_n$, where $n>1$;

(viii) two of R_1-R_4 are CH_3, one of R_1-R_4 is $C_6H_5CH_2$, and one of R_1-R_4 comprises at least one heteroatom;

(ix) two of R_1-R_4 are CH_3, one of R_1-R_4 is $C_6H_5CH_2$, and one of R_1-R_4 comprises at least one halogen;

(x) two of R_1-R_4 are CH_3, one of R_1-R_4 is $C_6H_5CH_2$, and one of R_1-R_4 comprises at least one cyclic fragment;

(xi) two of R_1-R_4 are CH_3 and one of R_1-R_4 is a phenyl ring; or

(xii) two of R_1-R_4 are CH_3 and two of R_1-R_4 are purely aliphatic fragments.

[00102] Such compounds include, but are not limited to, behenalkonium chloride, benzethonium chloride, cetylpyridinium chloride, behentrimonium chloride, lauralkonium chloride, cetalkonium chloride, cetrimonium bromide, cetrimonium chloride, cethylamine hydrofluoride, chlorallylmethenamine chloride (Quaternium-15), distearyldimonium chloride (Quaternium-5), dodecyl dimethyl ethylbenzyl ammonium chloride(Quaternium-14), Quaternium-22, Quaternium-26, Quaternium-18 hectorite, dimethylaminoethylchloride hydrochloride, cysteine hydrochloride, diethanolammonium POE (10) oletyl ether phosphate, diethanolammonium POE (3)oleyl ether phosphate, tallow alkonium chloride, dimethyl dioctadecylammoniumbentonite, stearalkonium chloride, domiphen bromide, denatonium benzoate, myristalkonium chloride, laurtrimonium chloride, ethylenediamine dihydrochloride, guanidine hydrochloride, pyridoxine HCl, iofetamine hydrochloride, meglumine hydrochloride, methylbenzethonium chloride, myrtrimonium bromide, oleyltrimonium chloride, polyquaternium-1, procainehydrochloride, cocobetaine, stearalkonium bentonite, stearalkoniumhectonite, stearyl trihydroxyethyl propylenediamine dihydrofluoride, tallowtrimonium chloride, and hexadecyltrimethyl ammonium bromide.

[00103] Most of these surface stabilizers are known pharmaceutical excipients and are described in detail in the *Handbook of Pharmaceutical Excipients*, published jointly by the American Pharmaceutical Association and The Pharmaceutical Society of Great Britain (The Pharmaceutical Press, 2000), specifically incorporated by reference. The surface stabilizers are commercially available and/or can be prepared by techniques known in the art.

3. Other Pharmaceutical Excipients

[00104] Pharmaceutical megestrol compositions according to the invention may also comprise one or more binding agents, filling agents, lubricating agents, suspending agents, sweeteners, flavoring agents, preservatives, buffers, wetting agents, disintegrants, effervescent agents, and other excipients. Such excipients are known in the art.

[00105] Examples of filling agents are lactose monohydrate, lactose anhydrous, and various starches; examples of binding agents are various celluloses and cross-linked polyvinylpyrrolidone, microcrystalline cellulose, such as Avicel® PH101 and Avicel® PH102, microcrystalline cellulose, and silicified microcrystalline cellulose (ProSolv SMCC™).

[00106] Suitable lubricants, including agents that act on the flowability of the powder to be compressed, are colloidal silicon dioxide, such as Aerosil® 200, talc, stearic acid, magnesium stearate, calcium stearate, and silica gel.

[0100] Examples of sweeteners are any natural or artificial sweetener, such as sucrose, xylitol, sodium saccharin, cyclamate, aspartame, and acsulfame. Examples of flavoring agents are Magnasweet® (trademark of MAFCO), bubble gum flavor, and fruit flavors, and the like.

[0101] Examples of preservatives are potassium sorbate, methylparaben, propylparaben, benzoic acid and its salts, other esters of parahydroxybenzoic acid such as butylparaben, alcohols such as ethyl or benzyl alcohol, phenolic compounds such as phenol, or quarternary compounds such as benzalkonium chloride.

[0102] Suitable diluents include pharmaceutically acceptable inert fillers, such as microcrystalline cellulose, lactose, dibasic calcium phosphate, saccharides, and/or mixtures of any of the foregoing. Examples of diluents include microcrystalline cellulose, such as Avicel® PH101 and Avicel® PH102; lactose such as lactose monohydrate, lactose anhydrous, and Pharmatose® DCL21; dibasic calcium phosphate such as Emcompress®; mannitol; starch; sorbitol; sucrose; and glucose.

[0103] Suitable disintegrants include lightly crosslinked polyvinyl pyrrolidone, corn starch, potato starch, maize starch, and modified starches, croscarmellose sodium, cross-povidone, sodium starch glycolate, and mixtures thereof.

[0104] Examples of effervescent agents are effervescent couples such as an organic acid and a carbonate or bicarbonate. Suitable organic acids include, for example, citric, tartaric, malic, fumaric, adipic, succinic, and alginic acids and anhydrides and acid salts. Suitable carbonates and bicarbonates include, for example, sodium carbonate, sodium bicarbonate, potassium carbonate, potassium bicarbonate, magnesium carbonate, sodium glycine carbonate, L-lysine carbonate, and arginine carbonate. Alternatively, only the sodium bicarbonate component of the effervescent couple may be present.

4. Nanoparticulate Megestrol or Active Agent Particle Size

[0105] As used herein, particle size is determined on the basis of the weight average particle size as measured by conventional particle size measuring techniques well known to those skilled in the art. Such techniques include, for example, sedimentation field flow fractionation, photon correlation spectroscopy, light scattering, and disk centrifugation.

[0106] The compositions of the invention comprise nanoparticulate megestrol particles which have an effective average particle size of less than about 2000 nm (*i.e.*, 2 microns). In other embodiments of the invention, the megestrol particles have an effective average particle size of less than about 1900 nm, less than about 1800 nm, less than about 1700 nm, less than about 1600 nm, less than about 1500 nm, less than about 1400 nm, less than about 1300 nm, less than about 1200 nm, less than about 1100 nm, less than about 1000 nm, less than about 900 nm, less than about 800 nm, less than about 700 nm, less than about 600 nm, less than about 500 nm, less than about 400 nm, less than about 300 nm, less than about 250 nm, less than about 200 nm, less than about 150 nm, less than about 100 nm, less than about 75 nm, or less than about 50 nm, when measured by the above techniques.

[0107] If the nanoparticulate megestrol composition additionally comprises one or more non-megestrol nanoparticulate active agents, then such active agents have an effective average particle size of less than about 2000 nm (*i.e.*, 2 microns). In other embodiments of the invention, the nanoparticulate non-megestrol active agents can have an effective average particle size of less than about 1900 nm, less than about 1800 nm, less than about 1700 nm, less than about 1600 nm, less than about 1500 nm, less than about 1400 nm, less than about 1300 nm, less than about 1200 nm, less than about 1100 nm, less than about 1000 nm, less than about 900 nm, less than about 800 nm, less than about 700 nm, less than about 600 nm, less than about 500 nm, less than about 400 nm, less than about 300 nm, less than about 250 nm, less than about 200 nm, less than about 150 nm, less than about 100 nm, less than about 75 nm, or less than about 50 nm, as measured by light-scattering methods, microscopy, or other appropriate methods.

[0108] By "an effective average particle size of less than about 2000 nm" it is meant that at least 50% of the nanoparticulate megestrol or nanoparticulate non-megestrol active agent particles have a particle size of less than about 2000 nm, by weight (or by other suitable measurement technique, such as by number, volume, etc.), when measured by the above-noted techniques. Preferably, at least about 60%, at least about 70%, at least about 80%, at least about 90%, at least about 95%, or at least about 99% of the nanoparticulate megestrol or nanoparticulate non-megestrol active agent particles have a particle size of less than the effective average, *i.e.*, less than about 2000 nm, less than about 1900 nm, less than about 1800 nm, *etc.*

[0109] If the nanoparticulate megestrol composition is combined with a conventional or microparticulate megestrol composition or non-megestrol active agent composition, then such a composition is either solubilized or has an effective average particle size of greater than about 2 microns. By "an effective average particle size of greater than about 2 microns" it is meant that at least 50% of the conventional megestrol or non-megestrol active agent particles have a particle size of greater than about 2 microns, by weight, when measured by the above-noted techniques. In other embodiments of the invention, at least about 70%, about 90%, about 95%, or about 99%

of the conventional megestrol or non-megestrol active agent particles have a particle size greater than about 2 microns.

[0110] In the present invention, the value for D50 of a nanoparticulate megestrol composition is the particle size below which 50% of the megestrol particles fall, by weight. Similarly, D90 is the particle size below which 90% of the megestrol particles fall, by weight.

5. Concentration of Nanoparticulate Megestrol and Surface Stabilizers

[0111] The relative amounts of nanoparticulate megestrol and one or more surface stabilizers can vary widely. The optimal amount of the individual components can depend, for example, the hydrophilic lipophilic balance (HLB), melting point, and the surface tension of water solutions of the stabilizer, *etc.*

[0112] The concentration of megestrol can vary from about 99.5% to about 0.001%, from about 95% to about 0.1%, or from about 90% to about 0.5%, by weight, based on the total combined dry weight of the megestrol and at least one surface stabilizer, not including other excipients.

[0113] The concentration of the at least one surface stabilizer can vary from about 0.5% to about 99.999%, from about 5.0% to about 99.9%, or from about 10% to about 99.5%, by weight, based on the total combined dry weight of the megestrol and at least one surface stabilizer, not including other excipients.

[0114] If a combination of two or more surface stabilizers is employed in the composition, the concentration of the at least one primary surface stabilizer can vary from about 0.01% to about 99.5%, from about 0.1% to about 95%, or from about 0.5% to about 90%, by weight, based on the total combined dry weight of the megestrol, at least one primary surface stabilizer, and at least one secondary surface stabilizer, not including other excipients. In addition, the concentration of the at least one secondary surface stabilizer can vary from about 0.01% to about 99.5%, from about 0.1% to about 95%, or from about 0.5% to about 90%, by weight, based on the total combined dry weight of the megestrol, at least one primary surface stabilizer, and at least one secondary surface stabilizer, not including other excipients.

C. Methods of Making Nanoparticulate Megestrol Compositions

[0115] The nanoparticulate megestrol compositions can be made using, for example, milling, homogenization, precipitation, freezing, template emulsion techniques, or any combination thereof. Exemplary methods of making nanoparticulate active agent compositions are described in the '684 patent.

[0116] Methods of making nanoparticulate compositions are also described in U.S. Patent No. 5,518,187 for "Method of Grinding Pharmaceutical Substances;" U.S. Patent No. 5,718,388 for "Continuous Method of Grinding Pharmaceutical Substances;" U.S. Patent No. 5,862,999 for "Method of Grinding Pharmaceutical Substances;" U.S. Patent No. 5,665,331 for "Co-Microprecipitation of Nanoparticulate Pharmaceutical Agents with Crystal Growth Modifiers;" U.S. Patent No. 5,662,883 for "Co-Microprecipitation of Nanoparticulate Pharmaceutical Agents with Crystal Growth Modifiers;" U.S. Patent No. 5,560,932 for "Microprecipitation of Nanoparticulate Pharmaceutical Agents;" U.S. Patent No. 5,543,133 for "Process of Preparing X-Ray Contrast Compositions Containing Nanoparticles;" U.S. Patent No. 5,534,270 for "Method of Preparing Stable Drug Nanoparticles;" U.S. Patent No. 5,510,118 for "Process of Preparing Therapeutic Compositions Containing Nanoparticles;" and U.S. Patent No. 5,470,583 for "Method of Preparing Nanoparticle Compositions Containing Charged Phospholipids to Reduce Aggregation," all of which are specifically incorporated by reference.

[0117] The resultant nanoparticulate megestrol compositions can be utilized in solid or liquid dosage formulations, such as controlled release formulations, solid dose fast melt formulations, aerosol formulations, lyophilized formulations, tablets, capsules, *etc.*

1. Milling to Obtain Nanoparticulate Megestrol Dispersions

[0118] Milling megestrol to obtain a nanoparticulate megestrol dispersion comprises dispersing megestrol particles in a liquid dispersion medium in which megestrol is poorly soluble, followed by applying mechanical means in the presence of grinding media to reduce the particle size of megestrol to the desired effective average

particle size. The dispersion medium can be, for example, water, safflower oil, ethanol, t-butanol, glycerin, polyethylene glycol (PEG), hexane, or glycol.

[0119] The megestrol particles can be reduced in size in the presence of at least one surface stabilizer. Alternatively, the megestrol particles can be contacted with one or more surface stabilizers after attrition. Other compounds, such as a diluent, can be added to the megestrol/surface stabilizer composition either before, during, or after the size reduction process. Dispersions can be manufactured continuously or in a batch mode.

2. Precipitation to Obtain Nanoparticulate Megestrol Compositions

[0120] Another method of forming the desired nanoparticulate megestrol composition is by microprecipitation. This is a method of preparing stable dispersions of poorly soluble active agents in the presence of one or more surface stabilizers and one or more colloid stability enhancing surface active agents free of any trace toxic solvents or solubilized heavy metal impurities. Such a method comprises, for example: (1) dissolving megestrol in a suitable solvent; (2) adding the formulation from step (1) to a solution comprising at least one surface stabilizer; and (3) precipitating the formulation from step (2) using an appropriate non-solvent. The method can be followed by removal of any formed salt, if present, by dialysis or diafiltration and concentration of the dispersion by conventional means.

3. Homogenization to Obtain Nanoparticulate Megestrol Compositions

[0121] Exemplary homogenization methods of preparing nanoparticulate active agent compositions are described in U.S. Patent No. 5,510,118, for "Process of Preparing Therapeutic Compositions Containing Nanoparticles."

[0122] Such a method comprises dispersing megestrol particles in a liquid dispersion medium, followed by subjecting the dispersion to homogenization to reduce the particle size of the megestrol to the desired effective average particle size. The megestrol particles can be reduced in size in the presence of at least one surface stabilizer. Alternatively, the megestrol particles can be contacted with one or more surface stabilizers either before or after attrition. Other compounds, such as a diluent, can be

added to the megestrol/surface stabilizer composition either before, during, or after the size reduction process. Dispersions can be manufactured continuously or in a batch mode.

4. Cryogenic Methodologies to Obtain Nanoparticulate Megestrol Compositions

Another method of forming the desired nanoparticulate megestrol composition is by spray freezing into liquid (SFL). This technology comprises an organic or organoaqueous solution of megestrol with stabilizers, which is injected into a cryogenic liquid, such as liquid nitrogen. The droplets of the megestrol solution freeze at a rate sufficient to minimize crystallization and particle growth, thus formulating nanostructured megestrol particles. Depending on the choice of solvent system and processing conditions, the nanoparticulate megestrol particles can have varying particle morphology. In the isolation step, the nitrogen and solvent are removed under conditions that avoid agglomeration or ripening of the megestrol particles.

As a complementary technology to SFL, ultra rapid freezing (URF) may also be used to created equivalent nanostructured megestrol particles with greatly enhanced surface area. URF comprises an organic or organoaqueous solution of megestrol with stabilizers onto a cryogenic substrate.

5. Emulsion Methodologies to Obtain Nanoparticulate Megestrol Compositions

Another method of forming the desired nanoparticulate megestrol composition is by template emulsion. Template emulsion creates nanostructured megestrol particles with controlled particle size distribution and rapid dissolution performance. The method comprises an oil-in-water emulsion that is prepared, then swelled with a non-aqueous solution comprising the megestrol and stabilizers. The particle size distribution of the megestrol particles is a direct result of the size of the emulsion droplets prior to loading with the megestrol a property which can be controlled and optimized in this process. Furthermore, through selected use of solvents and stabilizers, emulsion stability is achieved with no or suppressed Ostwald ripening. Subsequently, the solvent and water

are removed, and the stabilized nanostructured megestrol particles are recovered. Various megestrol particles morphologies can be achieved by appropriate control of processing conditions.

D. Methods of Using Nanoparticulate Megestrol Formulations of the Invention

1. Applications of the Nanoparticulate Megestrol Compositions of the Invention

[0123] The nanoparticulate megestrol compositions of the invention may be used as an appetite stimulant to treat wasting conditions or cachexia. As used herein, the term "wasting" is used to mean a condition where the patient is losing body mass as a side effect of a disease progression, a disease treatment, or other condition. Examples of conditions where wasting is prevalent include, but are not limited to, HIV or AIDS, cancer, cachexia and anorexia.

[0124] Additional conditions where the nanoparticulate megestrol compositions of the invention may be used include, but are not limited to, neoplastic diseases where the disease normally regresses or the patient's symptoms are normally reduced in response to megestrol, or any other progestin.

[0125] The nanoparticulate megestrol compositions of the invention may also be used to treat conditions such as breast cancer, endometrial cancer, uterine cancer, cervical cancer, prostate cancer, and renal cancer. As used herein, the term "cancer" is used as one of ordinary skill in the art would recognize the term. Examples of cancers include, but are not limited to, neoplasias (or neoplasms), hyperplasias, dysplasias, metaplasias, and hypertrophies. The neoplasms may be benign or malignant, and they may originate from any cell type, including but not limited to epithelial cells of various origin, muscle cells, and endothelial cells.

[0126] The present invention also provides methods of hormone replacement therapy in post-menopausal women, or in subjects after castration, comprising administering a nanoparticulate megestrol composition of the invention. Further, the compositions of the present invention may be used for ovarian suppression in several situations such as endometriosis, hirsutism, dysmenorrhea, and uterine bleeding.

[0127] The present invention also provides methods of oral contraception comprising administering a nanoparticulate megestrol composition of the invention. In one embodiment, the compositions of the invention are administered in combination with estrogen or a synthetic estrogen.

2. Dosage Forms of the Invention

[0128] The nanoparticulate megestrol compositions of the invention can be administered to a subject via any conventional means including, but not limited to, orally, rectally, ocularly, parenterally (*e.g.*, intravenous, intramuscular, or subcutaneous), intracisternally, pulmonary, intravaginally, intraperitoneally, locally (*e.g.*, powders, ointments or drops), or as a buccal or nasal spray. As used herein, the term "subject" is used to mean an animal, preferably a mammal, including a human or non-human. The terms patient and subject may be used interchangeably.

[0129] Moreover, the nanoparticulate megestrol compositions of the invention can be formulated into any suitable dosage form, including but not limited to liquid dispersions, gels, aerosols, ointments, creams, controlled release formulations, fast melt formulations, lyophilized formulations, tablets, capsules, delayed release formulations, extended release formulations, pulsatile release formulations, and mixed immediate release and controlled release formulations.

[0130] Nanoparticulate megestrol compositions suitable for parenteral injection may comprise physiologically acceptable sterile aqueous or nonaqueous solutions, dispersions, suspensions or emulsions, and sterile powders for reconstitution into sterile injectable solutions or dispersions. Examples of suitable aqueous and nonaqueous carriers, diluents, solvents, or vehicles including water, ethanol, polyols (propyleneglycol, polyethylene-glycol, glycerol, and the like), suitable mixtures thereof, vegetable oils (such as olive oil) and injectable organic esters such as ethyl oleate. Proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersions, and by the use of surfactants.

[0131] The nanoparticulate megestrol compositions may also contain adjuvants such as preserving, wetting, emulsifying, and dispensing agents. Prevention of the growth of microorganisms can be ensured by various antibacterial and antifungal agents, such as parabens, chlorobutanol, phenol, sorbic acid, and the like. It may also be desirable to include isotonic agents, such as sugars, sodium chloride, and the like. Prolonged absorption of the injectable pharmaceutical form can be brought about by the use of agents delaying absorption, such as aluminum monostearate and gelatin.

[0132] Solid dosage forms for oral administration include, but are not limited to, capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active agent is admixed with at least one of the following: (a) one or more inert excipients (or carriers), such as sodium citrate or dicalcium phosphate; (b) fillers or extenders, such as starches, lactose, sucrose, glucose, mannitol, and silicic acid; (c) binders, such as carboxymethylcellulose, alignates, gelatin, polyvinylpyrrolidone, sucrose, and acacia; (d) humectants, such as glycerol; (e) disintegrating agents, such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain complex silicates, and sodium carbonate; (f) solution retarders, such as paraffin; (g) absorption accelerators, such as quaternary ammonium compounds; (h) wetting agents, such as cetyl alcohol and glycerol monostearate; (i) adsorbents, such as kaolin and bentonite; and (j) lubricants, such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, or mixtures thereof. For capsules, tablets, and pills, the dosage forms may also comprise buffering agents.

[0133] Liquid nanoparticulate megestrol dosage forms for oral administration include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs. In addition to megestrol, the liquid dosage forms may comprise inert diluents commonly used in the art, such as water or other solvents, solubilizing agents, and emulsifiers. Exemplary emulsifiers are ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propyleneglycol, 1,3-butyleneglycol, dimethylformamide, oils, such as cottonseed oil, groundnut oil, corn germ oil, olive oil, castor oil, and sesame oil, glycerol, tetrahydrofurfuryl alcohol, polyethyleneglycols, fatty acid esters of sorbitan, or mixtures of these substances, and the like.

[0134] Besides such inert diluents, the composition can also include adjuvants, such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, and perfuming agents.

3. Dosage Quantities for the Nanoparticulate Megestrol Compositions of the Invention

[0135] The present invention provides a method of achieving therapeutically effective plasma levels of megestrol in a subject at a lower dose than the standard commercial formulations. This can permit smaller dosing volumes depending on the megestrol concentration chosen. Such a method comprises orally administering to a subject an effective amount of a nanoparticulate megestrol composition.

[0136] The nanoparticulate megestrol composition, when tested in fasting subjects in accordance with standard pharmacokinetic practice, produces a maximum blood plasma concentration profile of megestrol of greater than about 30 ng/ml in less than about 5 hours after the initial dose of the composition.

[0137] As used herein, the phrase "maximum plasma concentration" is interpreted as the maximum plasma concentration that megestrol will reach in fasting subjects.

[0138] A suitable dose of megestrol, administered according to the method of the invention, is typically in the range of about 1 mg/day to about 1000 mg/day, or from about 40 mg/day to about 800 mg/day. Preferably, the therapeutically effective amount of the megestrol of this invention is about 1/6, about 1/5, about ¼, about 1/3^{rd,} or about ½ of the therapeutically effective amount of existing commercial megestrol formulations, *e.g.*, Megace®.

[0139] "Therapeutically effective amount" as used herein with respect to a drug dosage, shall mean that dosage that provides the specific pharmacological response for which the drug is administered in a significant number of subjects in need of such treatment. It is emphasized that "therapeutically effective amount," administered to a particular subject in a particular instance will not always be effective in treating the diseases described herein, even though such dosage is deemed a "therapeutically effective amount" by those skilled in the art. It is to be further understood that drug dosages are, in

particular instances, measured as oral dosages, or with reference to drug levels as measured in blood.

[0140] One of ordinary skill will appreciate that effective amounts of megestrol can be determined empirically and can be employed in pure form or, where such forms exist, in pharmaceutically acceptable salt, ester, or prodrug form. Actual dosage levels of megestrol in the nanoparticulate compositions of the invention may be varied to obtain an amount of megestrol that is effective to obtain a desired therapeutic response for a particular composition and method of administration. The selected dosage level therefore depends upon the desired therapeutic effect, the route of administration, the potency of the administered megestrol, the desired duration of treatment, and other factors.

[0141] Dosage unit compositions may contain such amounts of such submultiples thereof as may be used to make up the daily dose. It will be understood, however, that the specific dose level for any particular patient will depend upon a variety of factors: the type and degree of the cellular or physiological response to be achieved; activity of the specific agent or composition employed; the specific agents or composition employed; the age, body weight, general health, sex, and diet of the patient; the time of administration, route of administration, and rate of excretion of the agent; the duration of the treatment; drugs used in combination or coincidental with the specific agent; and like factors well known in the medical arts.

* * * * *

[0142] The following examples are given to illustrate the present invention. It should be understood, however, that the invention is not to be limited to the specific conditions or details described in these examples. Throughout the specification, any and all references to a publicly available document, including a U.S. patent, are specifically incorporated by reference.

[0143] In the examples that follow, the value for D50 is the particle size below which 50% of the megestrol particles fall. Similarly, D90 is the particle size below which 90% of the megestrol particles fall.

[0144] The formulations in the examples that follow were also investigated using a light microscope. Here, "stable" nanoparticulate dispersions (uniform Brownian motion) were readily distinguishable from "aggregated" dispersions (relatively large, nonuniform particles without motion). Stable, as known in the art and used herein, means the particles don't substantially aggregate or ripen (increase in fundamental particle size).

Example 1

[0145] The purpose of this example was to describe preparation of nanoparticulate dispersions of megestrol acetate.

[0146] Formulations 1, 2, 3, 4 and 5, shown in Table 1, were milled under high energy milling conditions using a NanoMill® (Elan Drug Delivery, Inc.) (*see e.g.*, WO 00/72973 for "Small-Scale Mill and Method Thereof") and a Dyno®-Mill (Willy Bachofen AG).

TABLE 1

Formulation	Quantity of Megestrol	Identity and Quantity of Primary Surface Stabilizer	Identity and Quantity of Secondary Surface Stabilizer	Mean (nm)	D90 (nm)
1	5%	1% HPC-SL	0.05% DOSS	167	224
2	5%	1% HPMC	0.05% DOSS	156	215
3	5%	1% PVP	0.05% DOSS	167	226
4	5%	1% Plasdone® S630*	0.05% DOSS	164	222
5	5%	1% HPMC	0.05% SLS	148	208

* Plasdone® S630 (ISP) is a random copolymer of vinyl acetate and vinyl pyrrolidone.

[0147] Formulations 1-5 showed small, well-dispersed particles using the Horiba La-910 Laser Scattering Particle Size Distribution Analyzer (Horiba Instruments, Irvine, CA) and light microscopy. Formulations 1-5 were stable in electrolyte fluids and had acceptable physical stability at 5°C for 4 weeks. Electrolyte fluids are representative of physiological conditions found in the human body. Formulations 1, 2, 3, and 4 also exhibited acceptable stability at 25°C and 40°C for 4 weeks. Formulation 5 exhibited acceptable stability at 40°C for at least 3 weeks.

Example 2

[0148] This example compares the pharmacokinetic parameters of nanoparticulate megestrol acetate formulations of the present invention with conventional microparticulate formulations of megestrol acetate.

[0149] Twelve male beagles, at least twelve months of age, were divided into 2 groups based on whether they were fasting or being fed. The dogs were acclimated for thirteen days prior to dosing. The animals weighed approximately 11.4 to 14.3 kg at the time of dosing, and the dose was adjusted to 10 mg/kg. Water was available *ad libitum.* The animals were fasted (food only) for twelve to sixteen hours prior to dosing on day 1. On day 1, each dog was administered a formulation by gavage. Following dosing, the gavage tube was flushed with 18 ml of water. In the fed study, the animals were fed a high fat meal about 1 hour prior to dosing.

[0150] The dogs were subdivided into four groups, with each group receiving either Formulation A (nanoparticulate megestrol dispersion #1, comprising 4.0% megestrol acetate, 0.8% HPMC, and 0.4% DOSS), Formulation B (nanoparticulate megestrol dispersion #2, comprising 4.0% megestrol acetate, 0.8% HPMC, and 0.04% SLS), Formulation C (suspension of microparticulate megestrol acetate, Par Pharmaceutical, Inc., New York) or Formulation D (Megace® Oral Suspension, which is a suspension of microparticulate megestrol acetate). Each formulation was adjusted to administer a dose of 10 mg/kg of megestrol acetate to the subject.

[0151] Prior to dosing, blood samples were taken from each subject. Blood samples were then collected from each subject at 15 and 30 minutes, as well as 1, 2, 3, 4, 6, 8, 24, 48, and 72 hours after dosing and centrifuged. Plasma was then separated and diluted when necessary, and subsequently analyzed for megestrol acetate by HPLC.

[0152] Tables 2 and 3 summarize the pharmacokinetic data of the four formulations administered to fasted dogs and fed dogs, respectively.

TABLE 2
Summary of Pharmacokinetic Data in Fasted Dogs

Parameters	Formulation A n=3 (Mean ± SD)	Formulation B n=3 (Mean ± SD)	Formulation C n=3 (Mean ± SD)	Formulation D n=3 (Mean ± SD)
AUC_{0-t}	37774.23±11648.60	21857.68±10737.53	17395.95±10428.73	10094.30±1990.89
AUC_{0-inf}	49408.88±3392.80	27863.56±15279.16	6948.48±*	12007.13±1923.80
C_{max}	2209.74±351.54	1563.02±787.37	484.98±321.70	339.92±175.86
T_{max}	0.83±0.29	0.50±0.00	18.67±9.24	2.67±0.58
$t_{½}$	42.01±33.81	30.09±19.37	26.57±*	25.59±7.11
K_{el}	0.025±0.018	0.032±0.024	0.026±*	0.028±.0.007

AUC_{0-t} (ng.hr/ml) = Area under the curve from time zero to the last measurable concentration;
AUC_{0-inf} (ng.hr/ml)= Area under the curve from time zero to infinity;
C_{max} (ng/ml)= Maximum plasma concentration;
T_{max} (hr)= Time to occurrence of C_{max};
$t_{½}$ (hr)= Apparent elimination half-life;
K_{el} (1/hr)= elimination rate constant;
* n = 1.

TABLE 3
Summary of Pharmacokinetic Data in Fed Dogs

Parameters	Formulation A n=3 (Mean ± SD)	Formulation B n=3 (Mean ± SD)	Formulation C n=3 (Mean ± SD)	Formulation D n=3 (Mean ± SD)
AUC_{0-t}	48543.56±11608.55	36687.92±12016.26	27332.11±6488.79	31397.16±5823.79
AUC_{0-inf}	61734.90±4918.52	42787.74±14630.92	31720.98±5580.32	40218.66±8649.33*
C_{max}	3777.34±2489.41	2875.82±1334.32	2180.73±406.28	2577.83±665.31
T_{max}	1.67±2.02	3.00±4.33	1.00±0.00	0.83±0.29
$T_{½}$	34.35±12.10	26.67±7.80	26.16±10.88	36.60±9.62*
K_{el}	0.022±0.009	0.028±0.010	0.31±0.16	0.20±0.005

AUC_{0-t} (ng.hr/ml)= Area under the curve from time zero to the last measurable concentration;
AUC_{0-inf} (ng.hr/ml)= Area under the curve from time zero to infinity;
C_{max} (ng/ml)= Maximum plasma concentration;
T_{max} (hr)= Time to occurrence of C_{max};
$t_{½}$ (hr)= Apparent elimination half-life;
K_{el} (1/hr) = elimination rate constant;
* n = 2.

[0153] The results in the fasted dogs show that the nanoparticulate megestrol formulations (Formulations A and B) showed dramatically superior bioavailability, as

evidenced by the superior AUC and C_{max} results, as compared to the conventional microparticulate megestrol formulations (Formulations C and D). Formulation A, with a C_{max} of 2210, had a maximum concentration more than 4 ½ times that of Formulation C (485), and a maximum concentration more than 6 ½ times that of Formulation D (340). Formulation B, with a C_{max} of 1563, had a maximum concentration more than 3.2 times that of Formulation C (485), and a maximum concentration more than 4.6 times that of Formulation D (340). Also, Formulation A, with an AUC of 49,409 ng hr/mL, had an oral bioavailability more than 7 times that of Formulation C (6948 ng hr/mL) and an oral bioavailability of more than 4 times that of Formulation D (12007 ng hr/mL). Formulation B, with an AUC of 27,864 ng hr/mL, had an oral bioavailability more than 4 times that of Formulation C (6949 ng hr/mL) and an oral bioavailability more than 2 times that of Formulation D (12,007 ng hr/mL).

[0154] In addition, in the fasted dogs the nanoparticulate megestrol formulations (Formulations A and B) showed dramatically superior faster onset of action, as evidenced by the superior T_{max} results, as compared to the conventional microparticulate megestrol formulations (Formulations C and D). Formulation A, with a T_{max} of 0.83 hr, reached a maximum concentration of megestrol in less than $1/20^{th}$ the time of Formulation C (18.67 hr), and in less than $1/3^{rd}$ the time of Formulation D (2.67 hr). Formulation B, with a T_{max} of 0.50 hr, reached a maximum concentration in less than $1/37^{th}$ the time of Formulation C (18.67 hr), and in less than $1/5^{th}$ the time of Formulation D (2.67 hr).

[0155] Similarly, the results in the fed dogs show that the nanoparticulate megestrol formulations (Formulations A and B) showed dramatically superior bioavailability, as evidenced by the superior AUC and C_{max} results, as compared to the conventional microparticulate megestrol formulations (Formulations C and D). Formulation A, with a C_{max} of 3777, had a maximum concentration of about more than 1.7 times that of Formulation C (2181), and a maximum concentration of about more than 1.5 times that of Formulation D (2578). Formulation B, with a C_{max} of 2876, had a maximum concentration of about more than 1.3 times that of Formulation C (2181), and a maximum concentration of about more than 1.1 times that of Formulation D (2578).

Formulation A, with an AUC of 61,735 ng hr/mL, had an oral bioavailability of more than 1.9 times that of Formulation C (31721 ng hr/mL) and more than 1.5 times that of Formulation D (40219 ng hr/mL). Formulation B, with an AUC of 42788 ng hr/mL, had an oral bioavailability of more than 1.3 times that of Formulation C (31721 ng hr/mL) and an oral bioavailability of more than 1.1 times that of Formulation D (40218 ng hr/mL).

Example 3

[0156] This example demonstrates the physical stability of megestrol acetate dispersions at various concentrations and with the addition of sucrose, flavoring, and preservatives.

[0157] Megestrol acetate was milled under high energy milling conditions using a NanoMill™2 System (Elan Drug Delivery, Inc.) in the presence of a preservative / buffer system consisting of sodium benzoate, citric acid monohydrate, and sodium citrate dihydrate. After milling, the resulting dispersion was diluted with water, sucrose, flavoring, and additional preservative / buffer to prepare dispersions containing 3% (w/w), 5% (w/w), or 9% (w/w) megestrol acetate. The resulting formulations are shown in Table 4. The physical stability of the formulations was then monitored at 25°C, 40°C, and 50°C.

TABLE 4
Formulation Summary

	Concentrated Nanoparticle Dispersion	Diluted, Flavored Dispersions		
		Formulation E 3% Dispersion	Formulation F 5% Dispersion	Formulation G 9% Dispersion
API and Excipients	**g/kg**	**g/kg**	**g/kg**	**g/kg**
Megestrol Acetate, USP	325.000	30.000	50.000	90.000
Hydroxypropyl Methylcellulose, USP	65.000	6.000	10.000	18.000
Docusate Sodium, USP	3.250	0.300	0.500	0.900
Sodium Benzoate, USP	1.214	1.826	1.777	1.681
Sodium Citrate Dihydrate, USP	0.910	0.091	0.089	0.084
Citric Acid Monohydrate, USP	0.061	1.369	1.333	1.260
Sucrose, USP		50.000	50.000	50.000
Natural and Artificial Lemon Flavor		0.400	0.400	0.400
Artificial Lime Flavor		0.400	0.400	0.400
Purified Water, USP	604.600	909.614	885.500	837.280

API = active pharmaceutical ingredient

[0158] Particle size measurements (Table 5) were used to assess the physical stability. The results show almost no increase in the mean particle size at either 25°C or 40°C, and only a slight increase in the mean particle size at 50°C. 126 days of stability measurements were obtained for the 5% and 9% dispersions and 33 days of stability were obtained for the 3% dispersion, which was prepared at a later date.

TABLE 5
Mean particle size (nm)

	3% Dispersion			5% Dispersion			9% Dispersion		
	25°C	40°C	50°C	25°C	40°C	50°C	25°C	40°C	50°C
0 days	148	148	148	169	169	169	169	169	169
30 days				172	171	187	172	170	179
33 days	141	144	173						
126 days				171	174	188	168	175	182

Example 4

[0159] The purpose of this Example was to demonstrate the improved viscosity characteristics of the dispersions of this invention.

[0160] The viscosities of three formulations of this invention (E, F, and G as described in Example 3) and two conventional commercial formulations (Formulations C and D as described in Example 2) were determined using a rheometer (model CVO-50, Bohlin Instruments). The measurements were performed at a temperature of 20°C using a double gap (40/50) geometry.

[0161] The viscosities of the Formulations of this invention were found to be nearly Newtonian (*i.e.*, the viscosity being independent of shear rate), and were 1.5, 2.0, and 3.5 mPa s for the 30, 50, and 90 mg/mL concentrations, respectively.

[0162] The viscosity dependence on concentration is illustrated in Figure 1.

[0163] The commercial formulations C and D were shear thinning in nature. Such samples cannot be characterized by a single viscosity but rather a series of viscosities measured at different shear rates. This is most conveniently illustrated as viscosity - shear rate curves as shown in FIG. 2.

[0164] The commercial samples and the three formulations of this invention are compared in Table 6 below. Viscosities are in units of mPa s.

TABLE 6
Shear Rates of Commercial Megestrol Formulations (D and C) and the Nanoparticulate Megestrol Formulations of the Invention (E, F, & G)

Shear Rate	Commercial Samples		Formulations E, F, & G		
s^{-1}	Formulation D (mPa s)	Formulation C (mPa s)	(E) 30 mg/mL (mPa s)	(F) 50 mg/mL (mPa s)	(G) 90 mg/mL (mPa s)
0.1	4010	2860	1.5	2.0	3.5
1	929	723	"	"	"
10	215	183	"	"	"
100	49.9	46.3	"	"	"

* These samples were not measured at the 0.1 and 1 s^{-1} shear rates (the shear range was ca 2 to 100 s^{-1}) but the assessment that these exhibit Newtonian flow properties justifies the entries.

Example 5

[0165] The purpose of this Example was to visually demonstrate the difference between the viscosity characteristics of liquid megestrol formulations of the invention as compared to conventional liquid megestrol formulations.

[0166] A sample of a 50 mg/mL nanoparticulate dispersion of megestrol acetate and two conventional commercial formulations at 40 mg/mL (Formulations C and D as described in Example 2) were each placed in a vial, which was then shaken. Attached as Figure 3 is a photograph of the thee vials, which from left to right are the nanoparticulate megestrol acetate dispersion, Formulation C, and Formulation D.

[0167] The vial with the nanoparticulate dispersion shows a thin, silky, almost shear film coating the vial. In contrast, the vials containing the two commercial formulations show a gritty residue coating. Such a gritty residue is the same residue which coats a patient's mouth and throat upon administration. Such a coating is highly unpleasant, particularly for patients suffering from wasting (*i.e.*, unable to eat). Thus, Figure 3 visually demonstrates the appeal of a liquid oral nanoparticulate megestrol formulation of the invention as compared to conventional commercial liquid oral megestrol formulations.

Example 6

[0168] The purpose of this example was to prepare nanoparticulate compositions of megestrol acetate using various surface stabilizers.

[0169] 5% megestrol acetate (Par Pharmaceuticals, Inc.) was combined with 1.25% of various surface stabilizers: tyloxapol (Sterling Organics), Tween 80 (Spectrum Quality Products), Pluronic F-108 (BASF), Plasdone S-630 (ISP), hydroxypropylmethylcellulose (HPMC) (Shin Etsu), hydroxypropylcellulose (HPC-SL) (Nippon Soda Co., Ltd.), Kollidon K29/32 (polyvinylpyrrolidone) (ISP), or lysozyme (Fordras).

[0170] For each combination of megestrol acetate and surface stabilizer, the surface stabilizer was first dissolved in 7.875 g water for injection (WFI) (Abbott Laboratories, Inc.), followed by the addition of the milling media, PolyMill™-500 (Dow Chemical, Co.), and 0.42 g megestrol.

[0171] The slurries were charged into each of eight 18 cc NanoMill® (Elan Drug Delivery) chambers and milled for 30 min. Upon completion of milling the dispersions were harvested with a 26 gauge needle yielding the following particle sizes shown in Table 7.

[0172] All particle size distribution analyses were conducted on a Horiba LA-910 Laser Light Scattering Particle Size Distribution Analyzer (Horiba Instruments, Irvine, CA). RO-water was utilized as the liquid dispersing medium and a flow-through sample cell was used for all measurements. All samples were assayed in 150 cc liquid medium.

TABLE 7

Megestrol Conc.	Surface Stabilizer/Conc.	Mean Particle Size
5%	tyloxapol; 1.25%	214 nm
5%	Tween 80; 1.25%	210 nm
5%	Pluronic F-108; 1.25%	459 nm
5%	Plasdone S-630; 1.25%	292 nm
5%	HPMC; 1.25%	314 nm
5%	HPC-SL; 1.25%	623 nm
5%	PVP K29/32; 1.25%	24816 nm
5%	lysozyme; 1.25%	179 nm

[0173] The results show that tyloxapol, Tween 80, and lysozyme produced small particles without substantial aggregation. Pluronic F-108, Plasdone S-630, HPMC, HPC-SL, and K29/32 had larger particle sizes, indicating that aggregation was occurring. Thus, at the particular concentration of drug and surface stabilizer, using the described milling method, Pluronic F-108, Plasdone S-630, HPMC, HPC-SL, and K29/32 were not preferable surface stabilizers. These surface stabilizers may be useful in nanoparticulate compositions of megestrol at different drug or surface stabilizer concentrations, or when used in conjunction with another surface stabilizer.

Example 7

[0174] The purpose of this example was to prepare nanoparticulate compositions of megestrol acetate using various surface stabilizers.

[0175] Megestrol acetate (Par Pharmaceuticals, Inc.) and various surface stabilizers, as shown in Table 8, were combined and milled, followed by determination of the particle size and stability of the resulting composition. Materials were obtained as in Example 6.

[0176] All of the samples were milled using a Dyno®-Mill (Model KDL-Series, Willy Bachofen AG, Basel, Switzerland) equipped with a 150 cc stainless steel batch chamber. Cooling water (approximate temperature 5°C) was circulated through the mill and chamber during operation.

[0177] All particle size distribution analyses were conducted on a Horiba LA-910 Laser Light Scattering Particle Size Distribution Analyzer (Horiba Instruments, Irvine, CA), as described above in Example 6.

[0178] Qualitative microscopic assessments of the formulations were performed using a Leica light microscope (Type 301-371.010). Sample preparation involved diluting the product dispersions in RO-water and dispensing about 10 μL onto a glass slide. Oil immersion was utilized in conjunction with 1000x magnification.

[0179] The physical stability was assessed by storing the dispersion is 20 ml glass scintillation vials in a temperature / humidity controlled chamber at either 5°C, (25°C /

60% RH), (40°C / 75% RH), (50°C /75% RH), or 55°C. Samples were taken at varying time intervals and the particle size was analyzed.

[0180] For all formulations, the surface stabilizer(s) was first dissolved in WFI (Abbott Laboratories, Inc.) (75.0 g for Exp. Nos. 1, 2, 3, 7, and 8; 75.2 g for Exp. Nos. 4 and 9; 74.9 g for Exp. Nos. 5 and 6; 70.3 g for Exp. Nos. 10 and 11), followed by combining the surface stabilizer solution megestrol acetate and PolyMill™–500 polymeric grinding media. This mixture was then added to the appropriate milling chamber, milled for the time period shown in Table 8, followed by harvesting and vacuum filtering of the megestrol acetate dispersion.

TABLE 8

Exp. No.	Megestrol Conc.	Surface Stabilizer(s) and Conc.	Milling Time	Mean Particle Size	Stability
1	5%	1.25% lysozyme	20 min.	209 nm	The sample showed substantial aggregation after incubation in normal saline for 30 minutes as determined by optical microscopy.
2	5%	1.25% Tween 80	75 min.	157 nm	Upon storage at 5°C for 15 days the sample grew to a mean diameter of 577 nm.
3	5%	1.25% tyloxapol	2 hrs.	208 nm	Optical microscopoy revealed the presence of elongated "needle-like" crystals.
4	5%	1% Pluronic F127	2 hrs.	228 nm	Upon storage at 25°C for 5 days the sample grew to a mean diameter of 308 nm.
5	5%	1.25% HPMC 0.0625% SLS[1]	75 min.	161 nm	Upon storage at 40°C for 19 days, the sample grew to a mean diameter of 171 nm. Incubation for 30 minutes at 40°C in 0.01N HCl or normal saline resulted in particle sizes of 164 nm and 209 nm, respectively.
6	5%	1.25% HPC-SL, 0.05% SLS	60 min.	167 nm	Upon storage at 40°C for 15 days, the sample grew to a mean diameter of 194 nm. Incubation for 30 minutes at 40°C in 0.01N HCl or normal saline resulted in particle sizes of 183 nm and 179 nm, respectively.
7	5%	1.25% HPMC	45 min.	185 nm	Upon storage at 40°C for 6 days, the sample grew to a mean diameter of 31 nm. Incubation for 30 minutes at 40°C in 0.01N HCl or normal saline resulted in particle sizes of 2041 nm and 1826 nm, respectively. Optical microscopy revealed aggregation in both the saline and HCl samples.
8	5%	1.25% HPC-SL	45 min.	176 nm	Upon storage at 40°C for 6 days, the sample grew to a mean diameter of 24 nm. Incubation for 30 minutes at 40°C in 0.01N HCl or normal saline resulted in particle sizes of 873 nm and 524 nm, respectively. Optical microscopy revealed aggregation in both the saline and HCl samples.
9	5%	1% HPMC 0.05% SLS	70 min.	152 nm	Incubation for 30 minutes at 40°C in 0.01N HCl or normal saline resulted ii particle sizes of 155 nm and 539 nm, respectively. Optical microscopy confirmed that aggregation was present in the sample incubated in saline.

TABLE 8

Exp. No.	Megestrol Conc.	Surface Stabilizer(s) and Conc.	Milling Time	Mean Particle Size	Stability
10	10%	2% HPMC 0.1% DOSS[2]	70 min.	150 nm	Following harvesting the sample was diluted to 4% API by adding WFI. Upon storage at 40°C for 40 days, the sample had a mean diameter of 146 nm. Optical microscopy revealed small, well dispersed particles.
11	10%	2% HPMC 0.1% SLS	70 min.	146 nm	Upon storage at 40°C for 19 days, the sample had a mean diameter of 149 nm. Optical microscopy revealed small, well dispersed particles.
12	10%	4% lysozyme	60 min.	108 nm	Upon storage at 40°C for 9 days the sample had a mean diameter of 124 nm. Optical microscopy revealed small, well dispersed particles.

[1]Sodium lauryl sulfate (Spectrum Quality Products)

[2]Dioctyl Sodium Sulfosuccinate (Cytec)

[0181] The results shown in Table 8 indicate that the use of lysozyme (Exp. No. 1) as a surface stabilizer resulted in small well dispersed particles with a mean particle size of 209 nm, but the formulation showed aggregation when diluted into a normal saline solution. A megestrol acetate/tyloxapol sample was also stable at higher drug and stabilizer concentrations (Exp. No. 12).

[0182] Tween 80, tyloxapol, and Pluronic F127 (Exp. Nos. 2, 3, and 4) were effective primary surface stabilizers and produced well-dispersed particles without significant aggregation. Stability measurements, however, revealed rapid crystal growth for all three stabilizers. 5% megestrol acetate/1.25% Tween 80 grew from 157 nm to 577 nm after 15 days at 5°C. 5% megestrol acetate/1.25% tyloxapol showed needle-like crystals when observed under optical microscopy. 5% megestrol acetate/1.25% Pluronic F127 grew from 228 nm to 308 nm after 5 days at 25°C. Because of the rapid crystal growth observed, Tween 80, tyloxapol, and Pluronic F127 were deemed not suitable surface stabilizers at the described drug/surface stabilizer concentrations prepared under the conditions described above.

[0183] The HPC-SL formulation (Exp. No. 8) showed substantial aggregation indicating that a secondary charged stabilizer would be needed. SLS was added (Exp. No. 6) and the new formulation grew from 167 to 194 nm after storage at 40°C for 15 days and did not show any substantial aggregation upon incubation in either 0.01N HCl or normal saline. The SLS appeared effective at preventing the aggregation but the sample showed some particle size growth.

[0184] The HPMC formulation (Exp. No. 7) showed substantial aggregation indicating that a secondary charged stabilizer would be needed. SLS was added (Exp. Nos. 5 and 11), and the new formulations showed only minimal growth from 161 nm to 171 nm (Exp. No. 5), and from 146 to 149 nm (Exp. No. 11), after storage at 40°C for 19 days. In addition, the composition of Exp. No. 5 did not show any substantial aggregation upon incubation in either 0.01N HCl or normal saline. The SLS was effective at preventing the aggregation without causing significant crystal growth.

[0185] An attempt was made to reduce the concentration of the primary and secondary stabilizers (Exp. No. 9) and resulted in a post-milling mean diameter of 152

nm. Incubation for 30 minutes at 40°C in normal saline resulted in particle sizes of 539 nm. Optical microscopy confirmed that aggregation was present in the sample incubated in saline.

[0186] Docusate sodium (DOSS) was tried as a secondary stabilizer (Exp. No. 10) and resulted in well-dispersed particles with a mean diameter of 150 nm. Upon storage at 40°C for 40 days, the sample had a mean diameter of 146 nm. Optical microscopy revealed small, well-dispersed particles. DOSS seemed to result in even less particle size growth than SLS.

Example 8

[0187] The purpose of this example was to prepare nanoparticulate compositions of megestrol acetate using various surface stabilizers and further including preservatives or excipients.

[0188] The materials and methods were the same as in Example 7, except that for several of the examples different sources of megestrol acetate were used (See Table 9). In addition, for Exp. Nos. 5 , a NanoMill® milling system (Elan Drug Delivery) was used. Several different combinations of megestrol acetate, surface stabilizer(s), and one or more preservatives or excipients were prepared, following by testing the compositions for particle size and stability.

[0189] The surface stabilizer(s) and one or more preservatives were first dissolved in WFI, followed by combining the solution with megestrol acetate and the grinding media. This mixture was then added to the milling chamber and milled for the time period set forth in Table 9, below.

[0190] For several of the experiments, following milling the megestrol acetate dispersion was combined with a flavored suspension. The stability of the resultant composition was then evaluated.

[0191] The formulation details and results are shown in Table 9, below.

TABLE 9

Exp.	Megestrol Conc.	Surface Stabilizer(s) and Conc.	Preservatives/Excipients	Milling Time	Mean Particle Size	Stability
1	10%	2% HPMC 0.1% DOSS	Sodium Benzoate (0.4 g), Sodium Citrate Dihydrate (20 mg) Citric Acid Monohydrate (0.3 g)	75 min	146 nm	After milling a flavored suspension was prepared by adding sucrose (2.5 g), xanthan gum (0.113 g), glycerol (13.75 g), lemon flavor (0.1 g), WFI (18.6 g), and 20.0 g of the milled dispersion. Upon storage at 40°C for 24 days, the sample showed aggregation with a mean diameter of 837 nm. Incubation for 30 minutes at 40°C in 0.01N HCl or normal saline resulted in particle sizes of 206 nm and 3425 nm, respectively. Optical microscopy confirmed that the sample incubated in saline had aggregated.
2	25%	5% HPMC 0.05% DOSS	Sodium Benzoate (0.11 g) Citric Acid Monohydrate (0.08 g)	95 min.	See right column.	16 g of the milled drug dispersion was combined with sucrose (5 g), lime flavor (80 mg), and WFI (78.9 g). The diluted drug dispersion had a mean diameter of 192. After 6 days at 55°C the particles had a mean diameter of 10 microns, indicating substantial aggregation
3	25%	5% HPMC, 0.15% DOSS	Sodium Benzoate (0.11 g) Citric Acid Monohydrate (0.08 g)	95 min.	See right column.	16 g of the milled drug dispersion was combined with sucrose (5 g` lime flavor (80 mg), and WFI (78.9 g). The diluted drug dispersio had a mean diameter of 173 nm. After 12 days at 55°C the particle had a mean diameter of 295 nm.
4	32.5%1	6.5% HPMC 0.33% DOSS	Sodium Benzoate (13.07 g) Sodium Citrate Dihydrate (0.65 g) Citric Acid Monohydrate (9.8 g)	15.5 hrs	160 nm	Upon storage at 50°C for 44 days, the mean diameter was 190 nm.
5	32.5%	6.5% HPMC 0.33% DOSS	Sodium Benzoate (9.71 g) Sodium Citrate Dihydrate (0.49 g) Citric Acid Monohydrate (7.28 g)	12 hrs	147 nm	Upon storage at 50°C for 44 days the mean diameter was 178 nm.

[1]Pharmacia
[2]Pharmabios

[0192] In Exp. No. 1 of Table 9, a sweetened, flavored dispersion was prepared by mimicking the current commercial formulation of megestrol acetate that contains sucrose, xanthan gum, glycerol, lemon and lime flavors, and is preserved and buffered with sodium benzoate and citric acid. Upon storage at 40°C for 24 days the sample showed aggregation with a mean diameter of 837 nm. Incubation for 30 minutes at 40°C in 0.01N HCl or normal saline resulted in particle sizes of 206 nm and 3425 nm, respectively. Optical microscopy confirmed that the sample incubated in saline had aggregated. The aggregation upon storage indicated that this particular combination of drug and surface stabilizer, at the concentrations used and methodology employed to make the compositions, would not be an effective formulation.

[0193] For Exp. Nos. 4 and 5, the formulation was scaled-up in a NanoMill™-2 system to determine if the scale-up would effect the physical stability. Two different sources of megestrol acetate were tested: Pharmacia and Pharmabios. The product of Exp. No. 4 had a mean diameter of 160 nm without ultrasound. Upon storage at 50°C for 44 days the mean diameter was 190 nm. The composition of Exp. No. 5 had a post-milling mean diameter of 147 nm without ultrasound. Upon storage at 50°C for 44 days the mean diameter was 178 nm. Both sources of active agent milled effectively and showed little particle size growth even at 50°C.

* * * *

[0194] The results of Examples 6 and 7 showed that high energy milling with polymeric attrition media could be used to produce stable nanoparticulate colloidal dispersions of megestrol acetate suitable for oral administration to animals or humans. The primary stabilizer HPMC required the presence of DOSS or SLS to prevent aggregation at the concentrations of drug and stabilizer tested (other combinations of drug and HPMC concentrations may result in a stable composition without the addition of a second surface stabilizer). In general, average particle sizes of less than about 160 nm could be obtained. Tests conducted with two sources of megestrol acetate revealed that both sources milled effectively and exhibited excellent physical stability.

[0195] Based on mean particle size, physical stability, and the pre-clinical dog study, the best nanoparticulate megestrol acetate formulation for commercial development, based on the results of the data given in the examples, consisted of 32.5% megestrol acetate, 6.5% HPMC, and 0.325% DOSS (i.e., a drug:HPMC ratio of 1:5 and a drug:DOSS ratio of 1:100. The formulation milled effectively in the presence of preserved water (0.2% sodium benzoate, 0.01% sodium citrate dihydrate, and 0.15% citric acid monohydrate). Upon dilution with preserved water, flavors, and sucrose none of the dispersions showed severe aggregation, except for the dispersions containing xanthan gum (data not shown) or low levels of DOSS. The alcohol-based flavors did not effect the physical stability nor did several freeze-thaw cycles (data not shown).

Example 9

[0196] This example compares the pharmacokinetic parameters of nanoparticulate megestrol acetate formulations of the invention with a conventional microparticulate formulation of megestrol acetate. Results were obtained from a fasted study group consisting of 36 male subjects, 18 years of age or older. For a fed study group, results from 32 subjects were analyzed.

[0197] Subjects in the fasted study group and the fed study group were administered study drugs in four successive periods. Treatment A (1 x 150 mg drug as 5 ml of a 3% megestrol acetate nanoparticulate formulation) was administered in the first period. Reference Treatment B (1 x 800 mg drug as 20 ml of a 4% megestrol acetate Megace® Oral Suspension) was administered in the second period. Treatment C (1 x 250 mg drug as 5 ml of a 5% megestrol acetate nanoparticulate formulation) was administered in the third period. Treatment D (1 x 450 mg drug as 5 ml of a 9% megestrol acetate nanoparticulate formulation) was administered in the fourth period. The formulations of Treatments A, C, and D are listed in Table 10 below, with particle size information (microns) provided in Table 11.

[0198] In each period, subjects were confined from at least 10 hours prior to drug administration to after the last sample collection. In the fasted study group, no food was

consumed from at least 10 hours before dosing to at least 4 hours after dosing. In the fed study group, a high-calorie breakfast (containing about 800 to 1000 calories, approximately 50% of which were from fat) was served within 30 minutes prior to dosing; dosing occurred within 5 minutes after the breakfast was completed. A controlled meal was served to both groups after 4 hours after dosing, and standard meals were served at appropriate times thereafter. The meals in all four periods were identical. Subjects in the fasted study group were not allowed fluid intake from 1 hour before dosing to 1 hour after. Subjects in the fed study group were also not allowed fluid intake during this period except for fluids provided with the high-calorie breakfast. Water was provided *ad libitum* to both study groups at all other times.

[0199] Blood samples were obtained before dosing, at half-hourly intervals in the 6 hours following dosing, and at 7, 8, 12, 16, 20, 24, 36, 48, 72, and 96 hours after dosing. Megestrol acetate in plasma samples was then determined.

[0200] Table 12 below summarizes pharmacokinetic data for the fasted study group, and Table 13 below summarizes pharmacokinetic data for the fed study group.

[0201] Treatments A, C, and D in fasting subjects produced dose-normalized values for AUC_{0-t} and AUC_{0-inf} that were approximately twice those of Reference Treatment B. Maximum dose-normalized megestrol acetate concentrations in Treatments A, C, and D were approximately 9 to 12 times that of Reference Treatment B. The maximum megestrol acetate concentration for the 150 mg-dose of Treatment A was approximately twice that of the 800 mg-dose of reference Treatment B. Moreover, comparable values of AUC_{0-t} and AUC_{0-inf} were observed for the 450 mg-dose of Treatment D and the 800 mg-dose of Reference Treatment B.

[0202] Treatments A, C, and D in fed subjects produced dose-normalized values for AUC_{0-t} and AUC_{0-inf} that were approximately 8 to 10% greater than those of Reference Treatment B. Maximum dose-normalized megestrol acetate concentrations in Treatments A, C, and D were approximately 38 to 46% greater than that of Reference Treatment B. Megestrol acetate onset for Treatments A, C, and D was comparable to Reference Treatment B.

[0203] Nanoparticulate megestrol acetate formulations, therefore, exhibited superior oral bioavailability, relative to the Megace® Oral Suspension, in fasting and fed human subjects.

TABLE 10
Formulations for Megestrol Acetate Oral Suspension 3, 5% and 9%

Ingredients	Strengths		
	3% w/w (30 mg/mL)	5% w/w (50 mg/mL)	9% w/w (90 mg/mL)
Megestrol Acetate	3.000	5.000	9.000
Hydroxypropyl Methylcellulose	0.600	1.000	1.800
Docusate Sodium	0.030	0.050	0.090
Sodium Benzoate	0.183	0.178	0.168
Sodium Citrate Dihydrate	0.009	0.009	0.008
Citric Acid Monohydrate	0.137	0.133	0.126
Sucrose	5.000	5.000	5.000
Natural and Artificial Lemon Flavor	0.040	0.040	0.040
Artificial Lime Flavor	0.040	0.040	0.040
Purified Water	90.961	88.550	83.727
TOTAL	100.000	100.000	100.000

TABLE 11
Particle Size Data for the Megestrol Acetate Oral Suspensions*

	Strength 30mg/g			Strength 50 mg/g			Strength 90 mg/g		
	d(0.1)	d(0.5)	d(0.9)	d(0.1)	d(0.5)	d(0.9)	d(0.1)	d(0.5)	d(0.9)
Initial	0.068	0.123	0.223	0.069	0.125	0.229	0.068	0.124	0.227
ACC/1 month	0.070	0.129	0.237	0.070	0.127	0.231	0.070	0.127	0.230
ACC/2 months	0.070	0.127	0.231	0.070	0.127	0.233	0.073	0.126	0.221
ACC/3 months	0.070	0.129	0.237	0.070	0.128	0.235	0.070	0.128	0.234
RT 3 months	0.070	0.128	0.237	0.073	0.128	0.224	0.067	0.121	0.223

* All particle sizes are given in microns. "d(0.1)" means distribution of smallest 10% of the particles, *i.e.*, d(0.1) 10 μm means 10% of the particles are less than 10%. Similarly, "d(0.5)" means distribution of the smallest 50% of the particles, and "d(0.9)" means distribution of the smallest 90% of the particles. Thus, d(0.9) means that 90% of the particles are less than XX μm.

TABLE 12
Summary of Pharmacokinetic Data in Fasted Human Subjects*

Parameters	Treatment A (Mean ± SD)	Ref. Treatment B (Mean ± SD)	Treatment C (Mean ± SD)	Treatment D (Mean ± SD)
AUC_{0-t}	2800 ± 900	7000 ± 5000	4700 ± 1800	8500 ± 3200
AUC_{0-inf}	3100 ± 1000	9000 ± 9000	5200 ± 2100	9000 ± 4000
C_{max}	410 ± 120	190 ± 110	650 ± 200	950 ± 270
T_{max}	1.7 ± 0.9	6 ± 6	1.6 ± 1.0	1.7 ± 1.1
$t_{½}$	35 ± 13	31 ± 19	34 ± 10	34 ± 12
K_{el}	0.023 ± 0.011	0.026 ± 0.009	0.022 ± 0.008	0.023 ± 0.008

AUC_{0-t} (ng.hr/ml) = Area under the curve from time zero to the last measurable concentration;
AUC_{0-inf}(ng.hr/ml)= Area under the curve from time zero to infinity;
C_{max} (ng/ml)= Maximum plasma concentration;
T_{max} (hr)= Time to occurrence of C_{max};
$t_{½}$ (hr)= Apparent elimination half-life;
K_{el} (1/hr)= Elimination rate constant;
* n = 36.

TABLE 13
Summary of Pharmacokinetic Data in Fed Human Subjects*

Parameters	Treatment A (Mean ± SD)	Ref. Treatment B (Mean ± SD)	Treatment C (Mean ± SD)	Treatment D (Mean ± SD)
AUC_{0-t}	3500 ± 1100	17000 ± 5000	5700 ± 1600	10500 ± 3000
AUC_{0-inf}	3900 ± 1300	19000 ± 6000	6300 ± 2000	12000 ± 4000
C_{max}	380 ± 140	1400 ± 400	590 ± 170	1080 ± 290
T_{max}	3.8 ± 3.5	3.9 ± 0.9	3.4 ± 1.7	3.2 ± 1.7
$t_{½}$	35 ± 12	33 ± 9	35 ± 10	38 ± 12
K_{el}	0.023 ± 0.013	0.023 ± 0.007	0.023 ± 0.009	0.021 ± 0.008

AUC_{0-t} (ng.hr/ml) = Area under the curve from time zero to the last measurable concentration;
AUC_{0-inf}(ng.hr/ml)= Area under the curve from time zero to infinity;
C_{max} (ng/ml)= Maximum plasma concentration;
T_{max} (hr)= Time to occurrence of C_{max};
$t_{½}$ (hr)= Apparent elimination half-life;
K_{el} (1/hr)= Elimination rate constant;
* n = 32.

Example 10

[0204] This example compares the pharmacokinetic parameters of a nanoparticulate megestrol acetate formulations to a conventional microparticulate formulation of megestrol acetate (Megace® by Bristol Myers Squibb Co.). Results were

obtained from a fasted study group consisting of 33 male subjects, 18 years of age or older.

[0205] The nanoparticulate megestrol acetate compositions were prepared as described in Example 10.

[0206] Subjects were administered study drugs in four successive periods. Treatment A (575 mg of nanoparticulate megestrol acetate formulation in 5 ml oral suspension) was administered in the first period. Reference Treatment B (800 mg of megestrol acetate (Megace® by Bristol Myers Squibb Co.) in 20 ml oral suspension) was administered in the second period. Treatment C (625 mg of nanoparticulate megestrol acetate formulation in 5 ml oral suspension) was administered in the third period. Treatment D (675 mg of nanoparticulate megestrol acetate formulation in 5 ml oral suspension) was administered in the fourth period.

[0207] Table 14 provides the formulations of Treatments A, C and D.

Table 14
Formulations of Nanoparticulate Megestrol Acetate Oral Suspensions

Dosage	**115 mg/mL**		**125 mg/mL**		**135 mg/mL**	
FINAL AMOUNTS	Weight (g)	Conc. (mg/mL)	Weight (g)	Conc. (mg/mL)	Weight (g)	Conc. (mg/mL)
Megestrol Acetate	37,500.0	115.00	37,500.0	125.00	37,500.0	135.00
HPMC	7,500.0	23.00	7,500.0	25.00	7,500.0	27.00
Docusate Sodium	375.0	1.15	375.0	1.25	375.0	1.35
Sodium Benzoate	530.4	1.63	481.4	1.60	439.7	1.58
Sodium Citrate Dihydrate	26.5	0.08	24.0	0.08	22.0	0.08
Citric Acid Monohydrate	397.8	1.22	361.1	1.20	329.8	1.19
Sucrose	15,473.0	47.45	14,044.0	46.81	12,826.7	46.18
Lemon Flavor	123.8	0.38	112.4	0.37	102.6	0.37
Lime Flavor	123.8	0.38	112.4	0.37	102.6	0.37
Water	277,080.1	-	251,489.7	-	229,690.5	-
TOTAL (Weight, g)	339,130.4		312,000.0	-	288,888.9	-
TOTAL (volume, L)	326.1		300.0	-	277.8	-

[0208] The nanoparticulate megestrol acetate formulations were prepared by milling a concentrated dispersion of the drug substance followed by dilution to yield the final products. Hydroxypropyl methylcellulose and docusate sodium were used as stabilizing agents. The formulations were processed in a NanoMill-10 horizontal media

mill (Netzsch USA) for 20 hours. The attrition media used was 500 μm crosslinked polystyrene (PolyMill™-500). The dispersion further comprised 0.13% sodium benzoate, 0.01% sodium citrate dihydrate, and 0.1% citric acid monohydrate. Milled dispersion was diluted to final megestrol acetate concentrations of 115 mg/mL (575 mg/5 mL), 125 mg/mL (625 mg/5 mL) and 135 mg/mL (675 mg/5 mL). The final compositions additionally contained sweetening and flavoring agents.

[0209] Particle size determinations were performed on a Malvern Mastersizer 2000 instrument. The particle size distributions of the nanoparticulate megestrol acetate compositions are provided in Table 15.

Table 15

Concentration (mg/mL)	Mean particle size (nm)	50% < (nm)	90% < (nm)
115	144	130	234
125	144	127	237
135	145	131	236

[0210] In each period, subjects were confined from at least 11 hours prior to drug administration until after the 24.0 hour post-dose sample collection. After a supervised fast of at least 10 hours, subjects were fed a high-calorie meal containing about 800 to 1000 calories (approximately 150 calories from carbohydrates and 500-600 calories from fat). The meal consisted of two eggs fried in butter, two slices of toast with butter, two strips of bacon, approximately 128 g of hash brown potatoes and 200 ml of whole milk. The meals in all four periods were identical. The meal was completed within 30 minutes, and subjects were dosed 30 minutes after starting the meal.

[0211] The suspensions of Treatments A, B, C and D were administered via Slip Tip syringe directly into the mouth and swallowed. The syringe was rinsed three (3) times with approximately 5 ml (Treatments A, C and D) or 20 ml (Treatment B) of water. Following drug administration, approximately 225 ml (Treatments A, C and D) or 180 ml (Treatment B) of water was ingested.

[0212] For each period, a total of 24 blood samples were drawn from each subject. Blood samples were collected in EDTA blood tubes prior to drug administration and 0.250, 0.500, 0.750, 1.00, 1.50, 2.00, 2.50, 3.00, 3.50, 4.00, 4.50, 5.00, 5.50, 6.00, 8.00,

12.0, 16.0, 20.0, 24.0, 36.0, 48.0, 72.0 and 96.0 hours post-dose (1 x 7 mL for each sampling time).

[0213] Table 16 below summarizes the pharmacokinetic data, while Table 17 provides the statistical comparisons of the treatments.

Table 16
Pharmacokinetic Parameters

Parameters		Test-1 (Megtestrol Acetate 575 mg/5 mL (A)) Mean	±	SD	CV (%)	Reference: (Megace 40 mg/mL (B)) Mean	±	SD	Cv (%)
AUC_{o-t}	(ng-h/mL)	13657.52	±	3900.50	28.56	16896.21	±	4942.51	29.25
AUC_{o-inf}	(ng-h/mL)	14743.33	±	4451.31	30.19	18274.06	±	5623.07	30.77
C_{max}	(ng/mL)	1420.73	±	420.79	2962	1400.66	±	350.57	25.03
T_{max}	(h)	3.75	±	1.57	41.85	3.88	±	1.02	26.38
T_{max}*	(h)	4.50	±	1.00	-	4.50	±	1.00	-
K_{el}	(h^{-1})	0.0224	±	0.0062	27.44	0.0238	±	0.0054	22.84
$T_{1/2\ el}$	(h)	32.78	±	7.47	22.80	30.53	±	6.66	21.80

Parameters		Test-2 (Megtestrol Acetate 625 mg/5 mL (C)) Mean	±	SD	CV (%)	Test-3 (Megestrol Acetate 675 mg/5 mL (D)) ±	±	SD	Cv (%)
AUC_{o-t}	(ng-h/mL)	14682.37	±	4844.60	33.00	15323.29	±	4525.94	29.54
AUC_{o-inf}	(ng-h/mL)	16081.76	±	5563.09	34.59	16738.88	±	5432.52	32.45
C_{max}	(ng/mL)	1516.79	±	389.01	25.65	1645.74	±	455.71	27.69
T_{max}	(h)	2.52	±	1.60	63.52	3.13	±	1.64	52.55
T_{max}*	(h)	2.50	±	3.50	-	3.50	±	3.00	-
K_{el}	(h^{-1})	0.0211	±	0.0055	26.21	0.0211	±	0.0054	25.64
$T_{1/2\ el}$	(h)	34.75	±	7.81	22.48	34.83	±	8.12	23.30

*Median and interquartile ranges are presented.

AUC_{0-t} (ng.h/ml) = Area under the curve from time zero to the last measurable concentration

AUC_{0-inf} (ng.h/ml) = Area under the curve from time zero to infinity

C_{max} (ng/ml) = Maximum plasma concentration

T_{max} (h) = Time to occurrence of C_{max}

$t_{½\ el}$ (h) = elimination half-life

K_{el} (1/h) = elimination rate constant

Table 17
Treatment Comparisons

Statistical Analysis	Treatment	Ratio[1]	90 % Geometric CL[2]		Intra-Subject CV
(ANOVA)	Comparisons		Lower	Upper	
AUC_{o-t}	Megestrol Actate 575 mg/5 mL (A) vs Megace 40 mg/mL (B)	81.06%	78.20%	84.03%	8.82%
	Megestrol Actate 625 mg/5 mL (C) vs Megace 40 mg/mL (B)	86.29%	83.24%	89.45%	

Table 17
Treatment Comparisons

Statistical Analysis	Treatment	Ratio[1]	90 % Geometric CL[2]		Intra-Subject CV
(ANOVA)	Comparisons		Lower	Upper	
	Megestrol Actate 675 mg/5 mL (D) vs Megace 40 mg/mL (B)	90.63%	87.43%	93.95%	
$AUC_{0\text{-}inf}$	Megestrol Actate 575 mg/5 mL (A) vs Megace 40 mg/mL (B)	80.92%	77.95%	84.00%	9.16%
	Megestrol Actate 625 mg/5 mL (C) vs Megace 40 mg/mL (B)	87.33%	84.12%	90.65%	
	Megestrol Actate 675 mg/5 mL (D) vs Megace 40 mg/mL (B)	91.31%	87.96%	94.79%	
C_{max}	Megestrol Actate 575 mg/5 mL (A) vs Megace 40 mg/mL (B)	100.62%	94.10%	107.69%	16.51%
	Megestrol Actate 625 mg/5 mL (C) vs Megace 40 mg/mL (B)	108.18%	101.17%	115.69%	
	Megestrol Actate 675 mg/5 mL (D) vs Megace 40 mg/mL (B)	116.72%	109.15%	124.82%	

[1]Calculated using least-squares means
[2]90% Geometric Confidence Interval using ln-transformed data

[0214] Tables 16 and 17 demonstrate that Treatments A, C, and D produced similar pharmakinetics as Treatment B. Figures 4 and 5 show that Treatments A, C and D produce similar concentration-time curves as Treatment B.

Example 11

[0215] This example describes a randomized, open-labeled, multicenter, multinational, pilot study comparing the weight gain effect in adult HIV-positive subjects of (1) a nanoparticulate megestrol acetate composition as compared to (2) MEGACE OS, which is a conventional, microparticulate megestrol acetate formulation.

[0216] The nanoparticulate megestrol acetate formulation contained 115 mg of nanoparticulate megestrol acetate per ml, docusate sodium and hydroxyproyl methylcellulose as surface stabilizers, alcohol, artificial lime flavor, citric acid monohydrate, natural and artificial lemon flavor, purified water, sodium benzoate, sodium citrate dihydrate, and sucrose. The megestrol acetate particles in the nanoparticulate megestrol acetate formulation had a volume weighted mean of no greater than 180 nm (this is roughly equivalent to a D50 particle size).

PROTOCOL SYNOPSIS

Name of Sponsor/Company: Par Pharmaceutical		
Name of Compound: Megestrol Acetate Oral Suspension NanoCrystal™ Dispersion (NCD) formulation	**Name of Active Ingredient:** megestrol acetate (nanocrystalline formulation)	
Title of Study: A Randomized, Open-labeled, Pilot Study Comparing Weight Gain in Adults with AIDS-related Wasting (Anorexia/Cachexia) Given Either Megestrol Acetate Oral Suspension NCD Formulation or Megestrol Acetate Oral Suspension (Megace®).		
Investigators: Multicenter (approximately 20 centers) in India, South Africa and United States		
Study Centers: TBD		
Study Period (years):		**Phase of Development:**
Date of planned first enrollment	November 2004	II
Date of planned completion	April 2005	

Objectives:

Primary: To explore weight gain in adult HIV-positive subjects who have weight loss associated with AIDS-related wasting (anorexia/cachexia) in the first 12 weeks of treatment with either megestrol acetate oral suspension NCD formulation or Megace®.

Secondary: 1) To explore changes from baseline in lean body mass, fat-free mass, appetite, and Quality-of-Life assessments at multiple time points over a 12-week period among subjects who receive megestrol acetate oral suspension NCD formulation and Megace®, 2) to assess the safety and tolerability of megestrol acetate oral suspension NCD formulation and Megace® in adult HIV-positive subjects who have weight loss associated with AIDS-related wasting and 3) explore pharmacokinetic variables in the target population.

Methodology: This is a randomized, open-labeled, multicenter, multinational, pilot study intended to explore differences in weight gain within the first 12-weeks of treatment with megestrol acetate NCD formulation or Megace® in adult men and women with AIDS-related wasting. This pilot study includes a total of 60 HIV-positive adults who have weight loss associated with AIDS-related wasting and meet the inclusion/exclusion criteria. Subjects will be centrally randomized in equal proportions to receive one of the two treatments given as oral suspensions: megestrol acetate NCD formulation 575 mg or Megace® 800 mg per day as single daily doses for 12-weeks. Subjects return to the clinic weekly for the 12 weeks on treatment and then followed by a brief clinic visit 30 days later. Study-related assessments for the study are summarized in Table 2.

Methodology: (con't) Serial assessments of pharmacokinetic variables will be assessed on the first day of treatment and at the Week 6 visit. Blood samples will be obtained after a standardized meal at the following time points (hrs post dose): Baseline (0), 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 4.0, 5.0, 6.0, 7.0, 8.0, 12.0, and 24.0 hours. Trough levels of study drug will be collected at Day 3 (±1 day) after beginning treatment and at all other clinic visits prior to the time of the daily dose.
Number of Subjects (Planned and Analyzed): Total of 60 subjects enrolled to yield a total of 40 evaluable, HIV-positive adult subjects (30 enrolled per treatment group).
Diagnosis and Main Criteria for Inclusion: Adult men and women with HIV infection between the ages of 18 and 70 years of age who have an unintentional weight loss resulting in 10% less than the lower limit of Ideal Body Weight for frame size (as defined in Metropolitan Height and Weight Tables or other standardized tables appropriate for the locale) or a recent history of unintentional weight loss of 10% from the subjects baseline. Weight losses must be clinically associated with AIDS-related wasting. Women of childbearing potential may not be pregnant or nursing and must agree to use effective contraception for the duration of the study and for two weeks after the last dose. Subjects must be capable of and willing to return to the clinic regularly for study visits; must be willing to abstain from any illegal or recreational drug substances for the duration of the trial; must abstain from taking any other medications or substances known to affect appetite or weight gain (eg, steroids [other than those inhaled for treatment of asthmatic conditions], nutritional supplements, dronabinol). Subjects may have none of the following criteria: active AIDS-defining illness or other uncontrolled or clinically significant medical problems or laboratory abnormalities; evidence of or history of diabetes mellitus, hypoadrenalism or adrenal insufficiency (stimulated serum cortisol of <18µg/dL) ; evidence of clinical depression identified by GRID-HAMD-17 screening assessment; recent history of significant psychiatric illness that may compromise the subject's ability to comply with the study requirements; or a history or evidence of thromboembolic events (or any first degree relative with a history of thromboembolic events).
Test Product, Dose and Mode of Administration, Batch Number: Megestrol acetate oral suspension NCD formulation with 115 mg of nanocrystalline megestrol acetate per mL for a daily dose of 575 mg per day (5 mL dose). Lot Number: 041787.
Duration of Treatment: 12-weeks
Reference Product, Dose and Mode of Administration, Batch Number: Megace® (megestrol acetate) Oral Suspension (Bristol-Myers Squibb, Princeton, NJ) contains 40 mg micronized megestrol acetate per mL. Dose: 800 mg daily. Lot Number: 4D80437.
Criteria for Evaluation: **Primary Endpoints:** Weight gain will be assessed at baseline, then weekly x12 during treatment. Serial weight measurements for each subject should be obtained using the same scale for each assessment at approximately the same time of day. Subjects should be weighed in street clothes and without shoes.

Criteria for Evaluation: (con't)

Secondary Endpoints: Lean body mass, body fat and fat-free body mass will be assessed by bioimpedance analysis at baseline, Weeks 6 and 12. Total body muscle mass will be assessed by anthropometric measurements (mid-arm, waist and hip circumferences and triceps skinfold measurement). Appetite and food intake will be assessed by completion of a 3-day food intake diary completed prior to each clinic visit and a 24-hour recall food diary at the time of the clinic visit. Quality-of-Life Assessments will be made using a validated QOL instrument, Bristol-Myers Anorexia/Cachexia Recovery Instrument (BACRI), administered weekly through week 12 and at the 30-day post treatment visit. Appetite will be assessed via a visual analogue scale included as part of the BACRI. Safety will be assessed by collection of adverse events and vital signs at each clinic visit. Physical examinations and routine clinical laboratory samples including hematology, serum chemistry, lipid profile and routine urinalysis will be assessed at baseline, Weeks 3, 6, and 12. Additional laboratory assessments may be made at the investigator's discretion. Trough levels for study drug and concomitant medication information will be collected at each clinic visit. Pharmacokinetic assessments will be obtained on the first day and at the Week 6 visit and will include C_{max} (ng/mL), AUC_{0-t} (h•ng/mL), and T_{max} (h).

Analytical Methodology: Changes and percentage changes from baseline for continuous measurements will be calculated at Weeks 1 through 6, 9, and 12. For weight gain, an "area under the curve" analysis will also be conducted to assess the overall difference in effect of the two therapies over the first 12 weeks. Adverse events will be coded using MedDRA dictionary and reported by preferred term and treatment group.

An interim analysis reporting the results of all the endpoints for the first 40 subjects is planned.

Safety: Safety will be assessed by adverse events, vital signs, periodic physical examinations and routine clinical laboratory testing. Samples for routine hematology (complete blood count with platelet count), serum chemistry (sodium, potassium, chloride, bicarbonate, BUN, albumin, glucose, creatinine, alkaline phosphatase, total bilirubin, liver function tests, and lipid panel) and routine urinalyses (dipstick) will be collected at baseline/screening, Weeks 3, 6 and 12. Pregnancy testing will be performed on all women of childbearing potential at screening/baseline (serum β-hCG) and at each clinic visit (by urine pregnancy test) through Week 12. Adrenocorticotropin (ACTH) stimulation testing, including resting cortisol levels, and hemoglobin A1C will be assessed at screening and at week 12 (or last clinic visit).

Statistical Methods: The primary goal for this pilot study is to explore the rate of weight gain during the first 12 weeks of treatment with megestrol acetate NCD formulation or Megace® oral suspensions. No formal statistical analyses are planned; only exploratory analyses will be performed. Results for each variable will be provided with appropriate summary statistics. Due to the exploratory nature of the analyses, missing individual observations will be interpolated based on prior and subsequent values. Treatment differences will be estimated and 95% confidence intervals will be provided. Analyses will be performed on an Intent-to-Treat population that will include all randomized subjects with at least one post-randomization visit. The Per-Protocol population will include all subjects who completed the study requirements with no more than one missing visit and no major protocol violations.

Safety population will include all subjects who received any study medication.

Version Date of Synopsis: 01 November 2004

Prepared by Quintiles, Inc.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

µg/dL	Micrograms per deciliter
ACTH	Adrenocorticotropin
AE(s)	Adverse event(s)
AIDS	Acquired immunodeficiency syndrome
ALT (SGPT)	Alanine aminotransferase
AST (SGOT)	Aspartate aminotransferase
AUC	Area under the plasma drug concentration-time curve
β-hCG	Beta human chorionic gonadotropin
BACRI	Bristol-Myers Anorexia/Cachexia Recovery Instrument
BIA	Bioimpedance analysis
BUN	Blood urea nitrogen
CBC	Complete blood count
CD4+	Specific T-lymphocyte decreased in patients with HIV infections
C_{max}	Peak drug concentration
CRF	Case Report Form
FFM	Fat-free mass
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
GRID-HAMD	Structure Interview Guide to assess depression in multiple functional areas
HAART	Highly-active antiretroviral therapy
HAMD	Hamilton Rating Scale for Depression
HIV	Human immunodeficiency virus
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ITT	Intent-To-Treat
IU	International unit
L	Liter
LDH	Lactic dehydrogenase
LFT	Liver function tests
MedDRA	Medical Dictionary for Regulatory Activities

mg	Milligram
NCD	NanoCrystal™ Dispersion
PK	Pharmacokinetics
PP	Per-Protocol
QOL	Quality-of-Life
RBC	Red blood cells
SAE(s)	Serious adverse event(s)
$t_{1/2}$	Apparent terminal half-life
T_{max}	Time of observed maximum concentration
VAS	Visual Analogue Scale
WBC	White blood cells

1.0 INTRODUCTION

The AIDS-related wasting (HIV-wasting) syndrome as defined by Center for Disease Control and Prevention (CDC) is an AIDS-defining illness characterized by a profound involuntary weight loss of >10% of baseline body weight plus either chronic diarrhea or chronic weakness and documented fever in the absence of a concurrent illness or condition other than HIV infection that explain these findings.[1] The nature of the weight loss is characterized by the loss of lean body mass, predominantly muscle protein.[2] Even asymptomatic patients in the early stages of the disease may have a reduction in body mass[3] and continuing losses in weight, fat-free mass, body cell mass and fat mass are significant indicators of mortality in AIDS-related wasting syndrome.[4, 5] For the purposes of this study, AIDS-related wasting will be defined as the involuntary weight loss of >10% of baseline weight in the absence of a concurrent illness or condition other than HIV infection. The additional criteria of chronic diarrhea, chronic weakness or documented fever required by the CDC definition of AIDS-related wasting need not be present to qualify for the study.

While the causative agent is unclear, the consequences of AIDS-related wasting are well documented. Tang et al [6] reported in a longitudinal study of 678 HIV-positive participants receiving highly-active antiretroviral therapy (HAART) in the Nutrition for Healthy Living study that weight loss of ≥10% either from baseline or from the previous visit was significantly associated with a four- to six-fold increase in mortality compared with maintenance of or increase in weight. Even one episode of weight loss ≥3% from baseline or ≥5% from the previous visit was predictive of mortality in this population. In Tang's study, weight loss emerged as the single strongest independent predictor of mortality over changes in fat-free mass, body cell mass or fat mass.

Despite the success in improving overall survival with the advent of HAART, AIDS-related wasting remains problematic. Wanke [7] et al reported on the results of a prospective cohort of 469 HIV-infected adults to study the impact of HIV on nutrition in patients taking HAART. In the population studied, 58% of the cohort lost >1.5 kg of weight within 6 months (between 2 study visits) despite the prevalence of HAART therapy. While no definitive cause has been established for this condition, several possible theories have been proposed including increased energy expenditure, decreased energy intake, malabsorption, inefficient use of energy, hormonal factors and cytokine effects.[8, 9, 10, 11, 12]

Current therapies for AIDS-related wasting include nutritional education and support, nutritional supplementation, hormonal therapies (testosterone and testosterone analogues, oxandrolone, nandrolone, other androgenic compounds), recombinant human growth hormone, exercise training and cytokine modulators. [13]

2.0 BACKGROUND

Megestrol acetate is a synthetic derivative of progesterone. It has slight glucocorticoid activity and a very slight degree of mineralocorticoid activity. Megestrol has no estrogenic, androgenic or anabolic activity.[14]

The precise mechanism by which megestrol acetate produces effects in anorexia and cachexia is unknown at this time. However, evidence from clinical studies indicates that the increase in body weight observed during megestrol therapy is related to the drug's appetite-stimulant or metabolic effects rather than its glucocorticoid-like effects or the production of edema. It has been suggested that megestrol and/or its metabolites may, either directly or indirectly, stimulate appetite resulting in weight gain or may alter metabolic pathways via interference with the production or action of mediators such as cachectin (a hormone that inhibits adipocyte lipogenic enzymes). [14]

Megestrol acetate (Megace®, Bristol-Myers Squibb, Princeton, NJ) oral suspension has been widely studied as a treatment for anorexia and cachexia in both cancer patients [15, 16, 17] and patients with AIDS-related wasting syndrome.[18, 19, 20] While the exact mechanism by which the megestrol acetate improves appetite and facilitates weight gain is unclear, the results of previous studies have demonstrated its efficacy in these populations. Published studies have reported weight gain and improvement in appetite after 4 and 12 weeks of treatment; however, reports of weight gain and appetite changes within the first few weeks have not been reported.

The pivotal studies for the parent compound, Megace® [18, 19] had significant patient attrition rates of approximately 25-29% of the enrolled subjects within the first 12 weeks of treatment. Reasons for the relatively significant level of attrition were not evident in the published reports. Coincidentally, the same level of attrition was noted in both the megestrol-treated and placebo groups. The comparable attrition rates may indicate patient-related factors influencing motivation to continue treatment not measured in these studies such as a lack of subjective improvement early in the treatment course. Oster et al [18] reported a summary of reasons patients discontinued treatment during the 12-week study; however, no details of the reasons for the attrition by interval were reported.

The scientific question to be explored in this study is whether or not the onset of the improved appetite, weight gain and perception of improved quality-of-life would begin sooner with megestrol acetate NCD formulation than the reference product, Megace®. The clinical relevance of this hypothesis would be if patients noticed improvement sooner after beginning treatment, this could possibly influence patient compliance to continue with treatment.

3.0 STUDY OBJECTIVES

3.1 Primary Objective

The primary objective of the study is to:

- explore weight gain in adult, HIV-positive subjects who have weight loss associated with AIDS-related wasting (anorexia/cachexia) in the first 12 weeks of treatment with either megestrol acetate oral suspension NCD formulation or Megace®.

3.2 Secondary Objectives

The secondary objectives of this study are:

- To explore changes from baseline in lean body mass, fat-free mass, total body muscle mass, appetite, and Quality-of-Life assessments at multiple time points over a 12-week period among subjects who receive megestrol acetate oral suspension NCD formulation or Megace®
- To assess the safety and tolerability of megestrol acetate oral suspension NCD formulation and Megace® in adult HIV-positive subjects who have weight loss associated with AIDS-related wasting
- To explore pharmacokinetic variables in the target population.

4.0 INVESTIGATIONAL PLAN

4.1 Study Design and Rationale for Study Design

This is a randomized, open-labeled, multicenter, multinational, pilot study intended to explore differences in weight gain within the first 12-weeks of treatment with megestrol acetate NCD formulation or Megace® in adult men and women with AIDS-related wasting. This pilot study includes a total of 60 HIV-positive adults who have weight loss associated with AIDS-related wasting and meet the inclusion/exclusion criteria. Subjects will be centrally randomized in equal proportions to receive one of the two treatments: megestrol acetate NCD formulation 575 mg or Megace® oral suspensions 800 mg per day as single doses for 12-weeks. Subjects will return to the clinic weekly for the 12 weeks on treatment and have a brief clinic visit 30 days after treatment stops.

Serial assessments of pharmacokinetic variables will be assessed on the first day of treatment and at the Week 6 visit. Blood samples will be obtained after a standardized meal at the following time points (hours post dose): Baseline (0), 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 4.0, 5.0, 6.0, 7.0, 8.0, 12.0, and 24.0 hours. Trough levels of study drug will be collected at all other clinic visits prior to the time of the daily dose.

Results from this pilot study will be used in designing the sample size, nature and number of assessments planned for the next pivotal study.

4.2 Selection of Study Population

Subjects will be recruited from sites in the United States, India and South Africa that provide care for this population. Subjects enrolled in the study must meet all of the inclusion criteria and none of the exclusion criteria. Exceptions to these criteria may only be made after agreement by Par and the Medical Monitor responsible for the conduct of the trial.

4.2.1 Inclusion Criteria

1. Adult man or woman between the ages of 18 and 70 years of age;
2. Capable of and willing to provide informed consent;
3. Evidence of HIV infection (either HIV-seropositive, $CD4^+$ T-cell count of $\leq 350/mm^3$ or other clinically accepted indicator);
4. An unintentional weight loss resulting in a weight 10% less than the lower limit of Ideal Body Weight for frame size (as defined in Metropolitan Height and Weight Tables or other standardized tables appropriate for the locale) or a recent history of unintentional weight loss of 10% from the subjects baseline;
5. Weight losses must be clinically associated with AIDS-related wasting and not related to any other disease process;
6. Women of childbearing potential must agree to use effective contraception for the duration of the study and for two weeks after the last dose;
7. Clinical laboratory values must be within normal limits or out-of-range limits must be designated as not clinically significant. The following out-of-range laboratory values may be permissible based upon individual circumstances:
    - Hemoglobin (Hgb) values should be > 9.0gm/dL; however, values between 7.0 and 8.9 gm/dL may be admitted after consultation with the study medical monitor, Hgb values < 7.0 gm/dL are exclusionary

- Liver function tests (LFT) including AST, ALT, LDH) should be < 3 times the upper limits of normal (ULN). Acceptance of LFT values 3-5x ULN should be based on clinical significance as determined by the investigator and requires notification of the Medical Monitor

8. Normal adrenal function at baseline as evidenced by basal cortisol levels (of >10µg/dL) and adrenocorticotropin (ACTH) stimulated cortisol levels (of >18µg/dL);
9. Able to read and write in the study related documents translated into the primary local language;
10. Capable of and willing to return to the clinic regularly for study visits;
11. Must be taking a stable regimen of accepted HIV anti-retroviral treatments for at least two weeks prior to study entry;
12. Capable of completing a 3-day food intake diary with instruction;
13. Willing to abstain from any illegal or recreational drug substances for the duration of the trial; and
14. Willing to abstain from taking any other medications or substances known to affect appetite or weight gain (eg, steroids [other than those inhaled for treatment of asthmatic conditions], nutritional supplements [other than vitamins or minerals], dronabinol, recombinant human growth hormone, etc.).

4.2.2 Exclusion Criteria

1. Age is less than 18 years and greater than 70 years of age;
2. Weight loss due to factors other than AIDS-related wasting;
3. Enrollment in any other clinical trial;
4. Lack of access to regular meals;
5. Women of childbearing potential may not be pregnant or nursing;
6. Clinically severe depression evidenced by a baseline score of 17 or more on the Hamilton Depression Rating Scale (GRID-HAMD-17);
7. Recent evidence of or history of significant psychiatric illness that may compromise the subject's ability to comply with the study requirements;

8. Intractable or frequent vomiting that regularly interferes with eating;
9. Clinically significant diarrhea that would interfere with absorption of foods or medications;
10. Clinically significant oral lesions or dental conditions that interfere with eating a regular diet;
11. History or evidence of thromboembolic events or any first degree relative with a history of thromboembolic events;
12. Active AIDS-defining illness or other clinically significant or uncontrolled medical problems;
13. Current evidence of or history of diabetes mellitus or hypoadrenalism or,
14. Systemic treatment with glucocorticoids within the past 12 months.

4.2.3 Removal, Replacement, or Early Withdrawals of Patients from Therapy or Assessment

4.2.3.1 Withdrawal of Subjects

A subject is free to withdraw from the study at any time for any reason without prejudice to their future medical care by the physician or at the institution. The Investigator or Sponsor may also withdraw the subject at any time in the interest of subject safety or study integrity. Any subject who develops *de novo* diabetes mellitus or adrenal insufficiency while on study will be discontinued from taking additional study drug, followed up and treated appropriately. Please refer to Section 10.4 for additional guidance in this circumstance. Additionally, Par reserves the right to terminate the study at any time. The primary reason for withdrawal of subjects must be recorded in the subject's medical record and on the withdrawal form in the Case Report Form (CRF).

The withdrawal of a subject from the study should be discussed where possible with the Medical Monitor before the subject stops medication. Final evaluations will be performed as completely as possible at the time of the subject's withdrawal (refer to Section 7.1.11). Any comments (spontaneous or elicited) or complaints made by the subject and the reason for termination, date of stopping the study medication and the total amount of study medication must be recorded in the CRF and source documents. An attempt should be made to perform a follow-up evaluation. If the site is unable to contact the subject after three phone calls and a certified letter, the subject should be considered lost to follow-up.

If a subject is withdrawn for more than one reason, each reason should be documented in the source document and the most medically significant reason should be entered on the CRF.

Subjects that are removed or withdrawn early will not be replaced.

5.0 STUDY TREATMENTS

5.1 Identity of Investigational Products

5.1.1 Megestrol Acetate Oral Suspension NCD Formulation

Megestrol acetate oral suspension NanoCrystal™ Dispersion (NCD) formulation contains megestrol acetate, a synthetic derivative of the naturally occurring steroid hormone progesterone. Megestrol acetate is a white, crystalline solid and chemically described as 17-Hydroxy-6-methylpregna-4,6-diene-3,20-dione acetate.

Megestrol acetate oral suspension NCD is supplied as a suspension containing 115 mg of nanocrystalline megestrol acetate per mL. It also contains the following inactive ingredients: alcohol (max 0.06% v/v from flavor), artificial lime flavor, citric acid monohydrate, docusate sodium, hydroxypropyl methylcellulose, natural and artificial lemon flavor, purified water, sodium benzoate, sodium citrate dihydrate, and sucrose.

5.1.2 Megace® (megestrol acetate oral suspension)

Megace® (megestrol acetate oral suspension, Bristol-Myers Squibb, Princeton NJ) is a commercially available oral suspension with micronized megestrol acetate. It contains the following inactive ingredients: alcohol (max 0.06% v/v from flavor), citric acid, lemon-lime flavor, polyethylene glycol, polysorbate 80, purified water, sodium benzoate, sodium citrate, sucrose and xanthan gum. Megace® is supplied as an oral suspension containing 40 mg of the micronized megestrol acetate per mL.

5.1.3 Chemical Structure

Figure 1: Chemical Structure of Megestrol Acetate

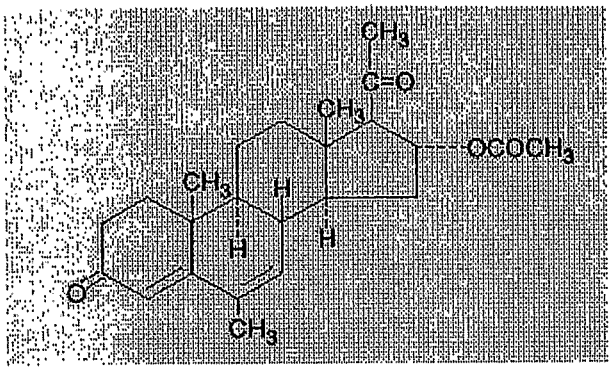


Table 1: Comparison of Characteristics of Megestrol Acetate NCD and Megace®

	Megestrol Acetate NCD	Megace®
Molecular Formula	$C_{24}H_{32}O_4$	$C_{24}H_{32}O_4$
Molecular Weight	384.51	384.51
Concentration	115 mg/mL	40 mg/mL
Bioequivalent doses	575 mg	800 mg
Batch/Lot number	041787	4D80437
Manufacturing Date	12/14/03	(see note below)

Note: No date of manufacture was available for the Megace® product; however, the expiry date provided by the manufacturer is May 2006.

Both formulations are lemon-lime flavored solutions and identical in appearance. Study medications will be dispensed in identical containers labeled only by the investigational label. An example of the investigational label is displayed in Section 5.4.

5.2 Method of Assigning Patients to Treatment Group

Subjects will be randomized by site via sealed randomized treatment cards to receive either megestrol acetate NCD formulation or Megace® in a 1:1 ratio. Treatment will be open-labeled.

5.3 Dose, Dose Schedule and Route of Administration

Megestrol acetate NCD formulation will be administered as a single daily dose of 575 mg administered as a 5 mL dose (115mg/mL concentration).

Megace® will be given according to the standard dose specified in the product labeling with a single daily dose of 800 mg megestrol acetate administered as a 20 mL dose (40mg/mL concentration).

In both treatment groups, subjects will be instructed to take one dose by mouth per day each morning for a total of 12 weeks.

5.4 Packaging, Labeling and Retention of Supplies

Single lots of each of the study medications will be used for the study.

Megace® will be obtained from a commercially available lot provided by Par Pharmaceutical and shipped to Quintiles, Inc. in its original packaging (240 mL bottles). Par Pharmaceutical will supply megestrol acetate NCD formulation to Quintiles, Inc in bottles of 150 mL. Quintiles, Inc. will re-label study medication in their original bottles with clinical labels and distribute them to the investigational sites. The clinical label will be a 2-part perforated label containing the following information: Par Pharmaceutical, protocol number, patient number, patient initials, randomization number (treatment assignment number), date dispensed, dosing instructions, cautionary statement required by Federal law, storage requirements, and lot number.

Study medications will be dispensed in bottles of 240 mL (Megace® as is commercially available) and 150 mL (NCD formulation) along with a reusable, plastic medication cup of 20 mL volume. The dosing instructions for the megestrol acetate NCD formulation will be labeled as 5 mL per dose. For the Megace®, dosing will be labeled as 20 mL per dose. Additional measuring cups will be available at the investigational sites.

The investigational product labeling will be compliant with local regulatory requirements. An example of the investigational label is shown below:

Caution: For Investigational Use Only

Study No: PAR-002 Randomization Number:_____
Subject ID number: _____ Date Dispensed: _____
Shake container well before use
Dosing Instructions: Take 5 (or 20) mL by mouth every morning
Lot Number:_____
Protect from heat and keep between 59° and 77°F (15° to 25° C)
Sponsored by: PAR Pharmaceutical, Inc., Spring Valley, NY USA

5.5 Treatment Compliance

Subjects will be asked to return the containers from the previous week at each clinic visit to determine compliance. In addition, trough blood levels for study medication will be obtained at each of the clinic visits.

5.6 Prior and Concomitant Treatments

Use of other appetite stimulating medications including any of the following must be discontinued at least 1 month prior to study entry. In addition, no other appetite-stimulating medications may be taken concurrently during the study.

This includes (but is not limited to) the following medications:

- megestrol acetate (Megace®)
- dronabinol (Marinol®)
- cyproheptadine (Periactin®)
- anabolic androgenic steroids including:

- testosterone, intramuscular (Depo-Testosterone® and others), transdermal, topical gels
- testosterone analogues (dihydrotestosterone or DHT)
- anabolic steroids including oxymetholone (Anadrol®), oxandrolone (Oxandrin®), methandrostenolone (Dianabol®)
- other androgenic compounds (dihydroepiandrosterone, androstenedione)

- recombinant human growth hormone (Serostim®)
- cytokine modulators (thalidomide, pentoxifylline)

Inhaled steroids for asthma and asthma-like conditions may be given as needed as well as short term topical steroid treatments for localized cutaneous conditions (eg, poison ivy or contact dermatitis).

Current anti-retroviral medication regimen for treatment of HIV should be well-established for at least two weeks prior to study entry. Subjects who require frequent changes in medication should be deferred until a suitable regimen of medication has been established and would be unlikely to vary considerably from baseline regimen. Medication history should be carefully collected at baseline and updated at each clinic visit.

No other investigational agents may be used concurrently during this study.

Systemic exposure to any glucocorticoids within the past 12 months prior to screening is exclusionary.

Any supplements (herbal, over-the-counter, or other) that may affect appetite in any way are specifically excluded; however, multivitamin and mineral supplements are allowed. Nutritional products intended as caloric food supplements (eg, protein-fortified drinks) are allowed.

6.0 EFFICACY AND SAFETY ANALYSIS VARIABLES

6.1 Efficacy

6.1.1 Primary Efficacy Endpoint

The primary efficacy endpoint is weight gain from baseline value. Baseline weight will be established at screening then assessed weekly for the 12 weeks of treatment and at the 30-day follow-up. Subjects will be weighed on the same scale, in street clothes and without shoes for each assessment.

6.1.2 Secondary Endpoints

Secondary endpoints include changes from baseline in:

- lean body mass, body fat and fat-free body assessed by bioimpedance analysis at Weeks 6 and 12 post treatment
- total body muscle mass assessed by anthropometric measures (mid-arm, waist and hip circumferences, triceps skinfold measurements) weekly through Week 12
- food intake will be assessed by 1) diary record of the number and time of meals during a 3-day interval beginning at baseline and prior to each clinic visit thereafter and 2) a 24-hour recall food diary obtained at each clinic visit
- appetite assessed weekly by visual analog scale (included in Quality of Life assessment described below)
- Quality-of-Life Assessments (Bristol-Myers Anorexia/Cachexia Recovery Instrument or BACRI) completed weekly from Week 1 through Week 12 and at the 30-day follow-up
- Pharmacokinetic studies conducted on Day 1 and Week 6 visits. Trough levels of study drug will be collected at Day 3 (±1 day) after beginning treatment and at each clinic visit during the treatment period thereafter

6.2 Safety

Safety endpoints include weekly assessments of: incidence and nature of adverse events, changes in vital signs, and pregnancy testing for women of childbearing potential. Routine clinical laboratory assessments (hematology, chemistry, and urinalyses) will be assessed at

baseline and Weeks 3, 6 and 12 (end of study), and physical examinations will be performed at baseline and Week 12. Hemoglobin A1C and ACTH stimulation testing will be performed at screening and Week 12 (or last visit). Additional clinical laboratory assessments may be made at the discretion of the Principal Investigator if clinically indicated.

Routine clinical laboratory samples for the sites in the United States will be processed by a centralized clinical lab and sent to the following address:

Quintiles Laboratories, Ltd.
5500 Highlands Parkway
Suite 600
Smyrna, GA 30082

Routine clinical laboratory samples for the sites in South Africa will be processed by a centralized clinical lab and sent to the following address:

Quintiles Laboratories South Africa
Pencardia 1 Ground Floor
509 Pretorius Street
Pretoria, RSA

Routine clinical laboratory samples for the sites in India will be processed by a centralized clinical lab and sent to the following address:

SRL Ranbaxy Ltd.
113, MIDC-15th Street
Andheri (East), Mumbai - 400 093
INDIA

6.3 Pharmacokinetics

Two pharmacokinetic (PK) studies will be performed on each subject; the first will be performed on the first day of treatment and the second, during the Week 6 clinic visit. The sampling times for the PK studies will be identical at each study and are described in the following sections. Pharmacokinetic assessments will include C_{max}, AUC_{0-t}, and T_{max}. Trough levels for study drug will also be assessed during each clinic visit.

6.3.1 Day 1 Pharmacokinetic Study

After eligibility has been established, subjects will be asked to come to the clinic after at least a 10-hour fast on Day 1. An indwelling venous access device will be placed to allow for

multiple blood samples and the baseline sample will be drawn. The daily dose of the assigned study medication will be administered and the time recorded. The subject will then be served a standardized breakfast. The contents of the standardized meal will vary by country and minimum requirements will be specified in the Study Procedures Manual. The schedule for the subsequent PK samples is as follows (time points refer to hours post dose):

Baseline (0), 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 4.0, 5.0, 6.0, 7.0, 8.0, 12.0, and 24.0 hours.

Subjects will be served an additional meal at approximately 4 hours after the dose of study drug and the amount of food consumed will be recorded according to the standards defined in the 3-day food intake diary. Additional details regarding these diaries are presented in the Study Procedures Manual.

6.3.2 Week 6 Pharmacokinetic Study

The second PK study will follow the same procedures as the first study with identical sampling times.

Baseline (0), 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 4.0, 5.0, 6.0, 7.0, 8.0, 12.0, and 24.0 hours.

During the PK study, the subject will be asked to record his or her food intake on the 3-day food intake diary.

6.3.3 Processing of Pharmacokinetic Samples

Samples for pharmacokinetic testing will be labeled with the unique subject identification, date and time of sample. Each sample requires 5 mL of blood collected in an EDTA K3 tube. Samples should be stored on wet ice until centrifugation, then spun within 50 minutes and the resulting plasma separated into 2 equal volumes and stored in 2 labeled cryotubes of 5 mL volume. Aliquots should be stored at approximately -20°C (nominally) or colder in a temperature-monitored freezer until shipment. Frozen samples should be stored until Par (or designee) indicates the timing of sample shipment. Samples should be sent on enough dry ice to keep samples frozen for approximately 72 hours. Samples should be sent via overnight courier to the following address:

SFBC Anapharm Inc.
2050, blvd. René-Lévesque West
Sainte-Foy (Québec), Canada, G1V 2K8
Phone: (418) 527-4000
Fax: (418) 527-3456
Attention: Mr. Louis-Philippe Beauregard, Sample Controller Coordinator

Additional details regarding handling of the PK samples are provided in Appendix D.

7.0 STUDY PROCEDURES AND SCHEDULE

Study-specific procedures including protocols for the bioimpedance analyses, and anthropometric assessments (mid-arm, waist and hip circumferences and triceps skinfold measurements) will be provided to each Investigator in an additional Study Procedures manual.

7.1 Study Schedule

The schedule of study related assessments is summarized by interval in Table 2.

7.1.1 Screening Visit

Screening assessments may satisfy the baseline requirements if the screening assessments are completed within 7 days of study entry. Pregnancy testing, however, must be completed immediately before study drug is dispensed regardless of timing of the previous pregnancy test.

The following assessments are made at screening:

- Review study procedures and obtain informed consent
- Medical history with particular attention to the review of gastrointestinal system
- Height and weight (in street clothes without shoes)
- Physical examination including vital signs (temperature, pulse, blood pressure and respirations)
- Routine clinical laboratories including:
  - hematology including complete blood count with differential, platelet count and hemoglobin A1C

- serum chemistry including sodium, potassium, chloride, bicarbonate, BUN, albumin, glucose, creatinine, alkaline phosphatase, total bilirubin, liver function tests (AST/SGOT, ALT/SGPT, LDH), and lipid panel
- routine urinalysis by dipstick (pH, specific gravity, glucose, protein, ketones, nitrites, leukocyte esterase and urobilinogen)
- beta human chorionic gonadotropin (β-hCG) for women of childbearing potential

- ACTH stimulation study with serum cortisol samples at baseline, 30 and 60 minutes post-stimulation
- Hamilton Rating Scale for Depression (GRID-HAMD-17)

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Table 2: Schedule of Study-Related Assessments:

Assessments	Screen	Baseline (Day 1)	Day 3	Weeks 1 & 2	Week 3	Weeks 4 & 5	Week 6	Weeks 7 & 8	Week 9	Weeks 10 & 11	Week 12	30-day Follow -up [a]
Informed consent	X											
Medical history	X	(X)[b]										
Height/weight	X	X[c]	X	X	X	X	X	X	X	X	X	X
Physical examination	X	(X)[b]					X				X	
Vital signs	X	(X)[b]		X	X	X	X	X	X	X	X	
Hematology labs	X	(X)[b]			X		X		(X)[d]		X	
Serum chemistry labs	X	(X)[b]			X		X		(X)[d]		X	
ACTH stimulation testing	X										X	
Hemoglobin A1C	X										X	
Routine Urinalysis	X	(X)[b]			X		X		(X)[d]		X	
Pregnancy testing	X[e]	X		X	X	X	X	X	X	X	X	
GRID-HAMD-17 screening	X[f]											
Review entry criteria		X										
Randomization		X										
Pharmacokinetic (PK) study		X[g]					X					
Trough levels for study drug [h]			X	X	X	X		X	X	X	X	
Dispense study medication [i]		X		X	X	X	X	X	X	X		
Dispense wallet ID card		X										

[a] Follow-up visit scheduled 30-days after Week 12 visit to assess weight, Quality-of-Life (BACRI) and status on any adverse events ongoing at the end of treatment.
[b] If screening visit is within 7 days of baseline, screening values may be used for baseline data. Paretheses indicate an optional or alternate time for an assessment.
[c] Height only at baseline. Weight must be obtained on the same scale every visit for a given subject dressed in street clothes and without shoes.
[d] Interim assessments of routine clinical laboratory assessments only necessary if clinically indicated.
[e] Only for women of childbearing potential: serum β-HCG at screening and urine pregnancy test thereafter at each clinic visit. All women are considered to be of childbearing potential unless they are surgically sterilized or postmenopausal (at least 12 months since last menses).
[f] Hamilton Rating Scale for Depression administered only at screening. Score of 17 or more is exclusionary.
[g] PK assessments performed on the first day of dosing and repeated at the Week 6 followup. PK sample times: pre-dose, q 30 mins for 3 hours, hourly for hours 4-8, then at 12-and 24-hours post dose. Each sample requires 5 mL blood in EDTA K3 tube.
[h] First trough level at Day 3 (±1 day), then at Week 1 visit. Subsequent trough levels prior to administration of daily dose during each clinic visit (5 mL EDTA tube).
[i] Dispense study drug amount for one week interval for Weeks 1-12.

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PCT/US2006/024349

Assessments	Screen	Baseline (Day 1)	Day 3	Weeks 1 & 2	Week 3	Weeks 4 & 5	Week 6	Weeks 7 & 8	Week 9	Weeks 10 & 11	Week 12	30-day Follow -up [a]
Dispense food intake diary [j]		X		X	X	X	X	X	X	X		
24-hour food diary recall [k]		X		X	X	X	X	X	X	X	X	
BACRI Assessment [l]			X	X	X	X	X	X	X	X	X	X
Anthropometric measurements[m]		X		X	X	X	X	X	X	X	X	
Bioimpedance analysis		X					X				X	
Adverse event assessment		X		X	X	X	X	X	X	X	X	X
Review concomitant medications		X		X	X	X	X	X	X	X	X	

[j] Food intake diary includes a 3-day qualitative record of the number and relative size of meals. Must be completed at baseline prior to Week 1 and prior to each clinic visit
[k] Baseline activities include subject training by study staff to ensure diary is completed correctly. Recall includes recall of specific foods eaten and quantities of food consumed.
[l] Bristol-Myers Anorexia/Cachexia Recovery Instrument (BACRI) includes a visual analogue scale for assessment of appetite.
[m] Includes mid-arm, waist and hip circumferences and triceps skinfold measurements.

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7.1.2 Baseline and Treatment Day (Day 1)

The following activities are to be completed after eligibility is determined and the subject agrees to enroll in the study:

- Review eligibility criteria and screening assessments
- Review informed consent is appropriately signed
- Update any screening assessments if initial screening was longer than 7 days prior to Study Day 1
- Obtain baseline weight
- Obtain urine pregnancy test for women of childbearing potential
- Obtain randomized treatment assignment.

If subject continues to be eligible, then insert indwelling venous access device for the pharmacokinetic study.

7.1.2.1 Pharmacokinetic Study

- Time 0: Baseline sample of approximately 5 mL in an EDTA K3 tube will be drawn, labeled with the unique subject identifier, date and time
- The daily dose of the assigned randomized study medication will be administered, the time recorded, and then subject will be served a standardized breakfast
- Samples for PK analysis require 5 mL in a tube containing EDTA K3 for each sample. The schedule for the subsequent PK samples are as follows (time points refer to hours post dose):

  0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 4.0, 5.0, 6.0, 7.0, 8.0, 12.0, and 24.0 hours.
- An additional meal will be served at approximately 4 hours post dose and the time of the meal will be recorded. During this meal, the subject will be instructed in the proper completion of the 3-day food intake diary
- After the conclusion of the PK study, the subject will receive the remaining study medication to take home. The 24-hour post dose sample should be obtained prior to the next day's dose

The following assessments may be collected during the conduct of the PK study:

- Anthropometric assessments (mid-arm, hip and waist circumferences and triceps skinfold measurements)
- Bioimpedance analysis
- Schedule next follow-up for Post-Treatment days 3 and 7 (Week 1)
- Dispense study medication
- Dispense wallet subject identification card and review its use
- Dispense 3-day food intake diary and review its use
- Complete 24-hour recall food diary and record findings and
- Subjects should be instructed not to take the daily dose of study before coming to the next clinic visit in order to obtain adequate trough levels. The daily dose of study medication may be taken anytime after the trough level is drawn

7.1.3 Post-treatment Day 3

- A trough level of study drug should be obtained within the first week of dosing, preferably at Day 3 (±1 day)
- Complete BACRI Quality-of-Life Assessment
- Adverse events and concomitant medications should also be assessed at this time

7.1.4 Post-treatment Weeks 1 and 2

Follow-up appointments should try to be at approximately the same time of day each week (preferably morning) if possible. All visits may vary by a 2-day window on either side of the expected date.

- Weight on same scale used for baseline; subject in street clothes and no shoes
- Vital signs (temperature, pulse, respirations and blood pressure)
- Urine pregnancy testing for women of childbearing potential prior to dispensing study drug
- Trough levels of study drug (5 mL in an EDTA K3 tube)
- Review 3-day food intake diary for accuracy, provide blank diary for following week

- Complete 24-hour recall food diary and record findings
- Complete BACRI Quality-of-Life Assessment
- Anthropometric assessments (mid-arm, waist and hip circumferences and triceps skinfold measurements)
- Return study drug dispensed from prior week, dispense study drug for following week
- Assess for adverse events or changes in concomitant medications
- Schedule next week's appointment

Unscheduled laboratory assessments may be obtained at any time to ensure the safety and well-being of the subject based upon the clinical judgment of the Principal Investigator. Abnormal laboratory values obtained as part of the routine assessments may be repeated if the Investigator judges that the results are suspect and repeat testing would be clinically indicated. However, if abnormalities persist on a subsequent assessment, the abnormality will be considered an adverse event.

7.1.5 Post-treatment Week 3

Follow-up appointments should try to be at approximately the same time of day each week (morning) if possible.

- Weight on same scale used for baseline; subject in street clothes and no shoes
- Vital signs (temperature, pulse, respirations and blood pressure)
- Routine clinical laboratory samples should be obtained in a fasting state. Samples for the following assessments should be obtained:
  - hematology including complete blood count with differential and platelet count
  - serum chemistry including sodium, potassium, chloride, bicarbonate, BUN, albumin, glucose, creatinine, alkaline phosphatase, total bilirubin, liver function tests (AST/SGOT, ALT/SGPT, LDH) and lipid panel
  - routine urinalysis by dipstick (pH, specific gravity, glucose, protein, ketones, nitrites, leukocyte esterase and urobilinogen)
- Urine pregnancy testing for women of childbearing potential prior to dispensing study drug

- Trough levels of study drug (5 mL in EDTA K3 tube)
- Return study drug dispensed from prior week, dispense study drug for following week
- Review 3-day food intake diary for accuracy, provide blank diary for following week
- Complete 24-hour recall food diary and record findings
- Complete BACRI Quality-of-Life Assessment
- Anthropometric assessments (mid-arm, waist and hip circumferences and triceps skinfold measurements)
- Assess for adverse events or changes in concomitant medications
- Schedule next week's appointment

7.1.6 Post-treatment Weeks 4 and 5

Repeat assessments under Weeks 1 and 2.

7.1.7 Post-treatment Week 6

Subjects should schedule the Week 6 visit for a morning appointment in order to obtain the baseline blood sample for the PK study in a fasting state and prior to that morning's daily dose of study medication.

- Repeat assessments under Week 3 and include the following additional assessments
- Physical examination
- Bioimpedance analysis
- Repeat Pharmacokinetic Study (same as Day 1):
  - Time 0: Baseline sample of approximately 5 mL will be drawn and added to an EDTA K3 tube, labeled with the unique subject identifier, date and time
  - The daily dose of the assigned randomized study medication will be administered, the time recorded, and then subject will be served a standardized breakfast

- Each subsequent sample for PK analysis requires 5 mL in an EDTA K3 tube. The schedule for the subsequent PK samples are as follows (time points refer to hours post dose)

  0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 4.0, 5.0, 6.0, 7.0, 8.0, 12.0, and 24.0 hours

- An additional meal will be served at approximately 4 hours post dose and the time of the meal will be recorded. During this meal, the subject will record the food consumed in the meal in the 3-day food intake diary

- After the conclusion of the PK study, the subject will receive the remaining study medication to take home. The 24-hour post dose sample should be obtained prior to the next day's dose

7.1.8 Post-treatment Weeks 7 and 8

- Repeat assessments under Weeks 1 and 2

7.1.9 Post-treatment Week 9

- Repeat assessments under Week 3
- Clinical laboratory samples may be omitted unless clinically indicated as judged by the Principal Investigator

7.1.10 Post-treatment Weeks 10 and 11

- Repeat assessments under Weeks 1 and 2

7.1.11 Post-treatment Week 12 (End-of-Study Drug Treatment Visit)

- Repeat assessments under Weeks 1 and 2
- Routine clinical laboratory samples should be obtained in a fasting state. Samples for the following assessments should be obtained

  - Hematology including complete blood count with differential, platelet count and hemoglobin A1C
  - Serum chemistry including sodium, potassium, chloride, bicarbonate, BUN, albumin, glucose, creatinine, alkaline phosphatase, total bilirubin, liver function tests (AST/SGOT, ALT/SGPT, LDH) and lipid panel
  - Routine urinalysis by dipstick (pH, specific gravity, glucose, protein, ketones, nitrites, leukocyte esterase and urobilinogen)

- Repeat ACTH stimulation testing
- Review last 3-day food diary
- Complete 24-hour recall food diary and record findings
- No dispensing of additional food diary or study drug
- Schedule 30-day follow-up

7.1.12 30-day Follow-up (End of Study Visit)

- Weight on same scale used for baseline; subject in street clothes and no shoes
- Complete BACRI Quality-of-Life Assessment
- Review status of any adverse events ongoing at the last clinic visit (Week 12) and assess for any new serious adverse events

8.0 STATISTICS

8.1 Statistical Plan

8.1.1 Primary Endpoint Analysis

The primary endpoint is change in body weight from baseline. The primary goal for this pilot study is to explore the rate of weight gain over timed intervals; therefore, only exploratory analyses will be performed. For weight gain, an "area under the curve" analysis will also be conducted to assess the overall difference in effect of the two therapies over the first 12 weeks.

Each measurement will be provided with appropriate summary statistics. Treatment differences will be estimated and 95% confidence intervals will be provided. Missing individual observations will be interpolated based on prior and subsequent values.

8.1.2 Secondary Endpoint Analysis

For analysis of secondary endpoints, each variable will be provided with appropriate summary statistics. Changes from baseline for the secondary endpoints will be explored by treatment group. Treatment differences will be estimated and 95% confidence intervals will be provided. However, because of the exploratory nature of the analyses, missing individual observations will be interpolated based on prior and subsequent values.

Safety analysis will include the incidence of adverse events coded using Medical Dictionary for Regulatory Activities (MedDRA), version 6.0 dictionary and reported by preferred term and treatment group. Descriptive statistics will be used for clinical laboratory data and vital sign data. Abnormalities in non-numeric data (eg, physical examination results) will be presented in listings.

8.1.3 Study Populations

Study populations intended for analysis will be defined as follows: Intent-to-Treat, Per-Protocol and Safety.

8.1.3.1 Intent-to-Treat

The Intent-to-Treat population will consist of all randomized subjects who were dispensed medication and had at least one post-randomization visit. Subjects will be analyzed by treatment assigned. Analyses of the primary endpoint will be performed on the Intent-to-Treat and the Per-Protocol populations

8.1.3.2 Per-Protocol

The Per-Protocol (evaluable) population will include all subjects who completed the study requirements with no more than one missing visit and no major protocol violations.

8.1.3.3 Safety Population

The Safety population will consist of all subjects who received at least one dose of study medication and will be analyzed according to actual treatment received rather than treatment assigned.

8.1.4 Planned Analyses

8.1.4.1 Patient Disposition

A detailed description of patient disposition will be provided and will include:

- A summary of data on patient discontinuation
- A summary of data on overall qualification status of all patients
- An account of all identified protocol violations

All randomized patients entered in the study will be accounted for in the summary. The number of patients who do not qualify for analysis, who die, or who discontinue before treatment begins will be specified. Patients discontinuing due to lack of treatment effect will be considered as treatment failures.

8.1.4.2 Patient Characteristics

Patient characteristics will include a summary of the following:

- Patient demographics
- Baseline disease characteristics
- Medical history
- Prior medications
- Concomitant drugs

Other patient characteristics will be summarized as deemed appropriate.

8.1.4.3 Safety Analysis

Adverse events will be coded using MedDRA, version 6.0. Frequency of AEs will be calculated for each system organ class and preferred term by treatment group. The number of patients and proportion reporting each AE will be summarized. The severity of the AE and relationship to study medication will be summarized for each system organ class and preferred term by treatment group.

Descriptive statistics (number of observations, mean, standard deviation, minimum, median and maximum values) will be calculated for clinical laboratory tests (hematology, serum chemistry and urinalysis) at applicable visits.

Vital signs (systolic and diastolic blood pressure, and pulse) and physical examination results will be summarized by treatment group using appropriate descriptive statistics. Continuous variables will be summarized using number of observations, mean, standard deviation, minimum, median, and maximum values. Categorical values will be summarized using number of observations and percentages.

Withdrawals from the study will be summarized by treatment group.

Additional details regarding the intended analyses are provided in the Statistical Analysis Plan.

8.2 Determination of Sample Size

This is an exploratory study; therefore, sample size was not contingent upon enrollment numbers required to achieve adequate statistical power.

9.0 ADVERSE EVENTS

9.1 Adverse Event Definitions

An *Adverse Event* (AE) is any untoward medical occurrence reported in a subject enrolled in clinical investigation which does not necessarily have a causal relationship with the study treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, disease or exacerbation of a pre-existing condition temporally associated with the use of a medicinal (investigational) product.) (ICH Guidance E2A: Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, October 1994)

Each AE requires a complete and thorough description including date of onset and corrective actions taken. Additionally, the intensity of the AE and its relationship to the investigational product, as well as its outcome, must be reported.

In order to avoid bias in eliciting AEs, subjects should be asked a non-leading question, such as 'How are you feeling?' It is also important to question the subject in a non-leading way about changes in their health or concomitant medication usage since their last visit. This information should be collected prior to completion of assessments at all study visits. In addition, any symptoms/conditions reported during assessments deemed to be clinically significant by the Investigator should be reported as AEs.

All AEs (related and unrelated, serious and non-serious) will be recorded for the interval beginning from the time the informed consent is signed until 30 days after the end of treatment exposure. All AEs are to be recorded on the appropriate AE pages in the Case Report Form (CRF) and in source documents. Where possible, a diagnosis rather than a list of symptoms should be recorded. If a diagnosis has not been made, then each symptom should be listed individually.

All AEs will be followed until one of the following milestones is reached: 1) the event is resolved (defined as the subject's health has returned to his/her baseline status or all variables have returned to normal); 2) the event is stabilized or designated as a chronic condition (the Investigator does not expect any further improvement or worsening of the event); or 3) the event is otherwise explained regardless of whether the subject is still participating in the study. Where appropriate, medical tests and examinations will be performed to document resolution of event(s).

9.2 Reporting Adverse Event Intensity

In general, the intensity of a particular AE is reported as the worst intensity experienced by the subject during the course of the event. However, worsening of pre-treatment events after initiation of investigational product or an increase in severity of a previously reported, post-treatment adverse event must be recorded as new AEs. For example, if a subject experiences mild hypertension at study entry (prior to dosing of investigational product) and the hypertension becomes severe and more frequent after the investigational product has been administered, a new AE of severe hypertension (with the appropriate date of onset indicating the change in severity) will be recorded on the appropriate CRF. Similarly, if an adverse event is first identified as mild and then increases in severity during the study, an additional adverse event should be recorded to document the change in severity.

The medical assessment of intensity will be determined by using the following definitions:

Mild: The AE is easily tolerated and does not interfere with usual activity.

Moderate: The AE interferes with daily activity, but the subject is still able to function.

Severe; The AE is incapacitating and the subject is unable to work or complete usual activity.

9.3 Reporting Relationships of Adverse Events to Study Drug

The Investigator must make the determination of relationship between the event and the investigational product for each AE. The Investigator should decide whether, in his or her medical judgment, there is a reasonable possibility that the event may have been caused by the investigational product. If no valid reason exists for suggesting a relationship, then the AE should be classified as 'unrelated'. Otherwise, if there is any valid reason, even if undetermined or untested, for suspecting a possible cause-and-effect relationship between the investigational product and the occurrence of the AE, then the AE should be considered "related".

Unrelated: The event can be readily explained by other factors such as the subject's underlying medical condition, concomitant therapy or accident and no obvious temporal relationship exists between the investigational product and the event.

Possibly related: There may be some temporal relationship between the event and the administration of the investigational product but there remains some ambiguity as to the cause.

Probably related: The temporal relationship between the event and the administration of the investigational product is compelling, and/or follows a known or suspected response pattern to that product, and the event cannot be explained by the subject's medical condition, other therapies or accident.

If the causal relationship between an AE and the investigational product is determined to be 'possible' or 'probable' the event will be considered related to investigational product for the purposes of expedited regulatory reporting.

9.4 Notification about Serious or Unexpected Adverse Events

A ***Serious Adverse Event*** (SAE) is any untoward medical occurrence (whether considered to be related to investigational product or not) that at any dose:

- results in death
- is life-threatening

NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it was more severe.

- requires inpatient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity
- is a congenital abnormality/birth defect

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations. Important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above should be considered for expedited reporting. These should also usually be considered serious.

All SAEs (related and unrelated) will be recorded from the time the informed consent is signed until 30 days following the end of treatment exposure. Any SAEs considered possibly or probably related to the investigational product and discovered by the Investigator at any interval after the study should be reported. All SAEs must be reported within one business day of the first awareness of the event. The Investigator must complete, sign and date the SAE pages, verify the accuracy of the information recorded on the SAE pages with the corresponding source documents, and send a copy (by fax) to the Quintiles Pharmacovigilance office using the toll-free contact numbers noted in the following table.

Quintiles Pharmacovigilance staff can be reached directly by telephone from 8:00 AM to 5:00 PM (GMT); however, faxed reports may be sent at any time.

Quintiles Pharmacovigilance Contact Information		
Country	**Fax Number**	**Telephone Number**
India	AT&T Access Code 000117 + Pause + 877-264-10 39	AT&T Access Code 000117 + Pause +877-264-10 40
South Africa	0 800 99 42 08	0 800 99 42 07
United States	1 (800) 414-8460	1 (800) 414-8451

At a minimum, the adverse event name, the name of the person making the report, the name of the suspected investigational product, and patient identifiers, and a description of the event should be provided. The Investigator's preliminary assessment of causality must be provided at the time of the initial report. Additional follow-up information, if required or available, should be faxed to Quintiles Pharmacovigilance within one business day of receipt. This should be completed on a follow up SAE form and placed with the original in the appropriate section of the CRF/study file.

The Investigator is encouraged to discuss with the Quintiles Medical Monitor any AEs for which the issue of level of reportability is unclear or questioned.

Par Pharmaceutical (or designee) is responsible for notifying the relevant regulatory authorities of serious adverse events. Additionally, some events may require immediate reporting to relevant local regulatory authorities in accordance with local requirements.

It is the Principal Investigator's responsibility to notify his or her Institutional Review Board (IRB), Independent Ethics Committee (IEC) or the relevant local regulatory authority of all SAEs that occur at his or her site. Investigators will also be notified of all unexpected, serious, drug-related events (7/15-Day Safety Reports) that occur at other sites during the study. Each site is responsible for notifying their IRB, IEC or the relevant local regulatory authority of these additional SAEs.

9.5 Notification of Adverse Events of Interest

The sponsor has identified certain adverse events of interest that should be reported to Quintiles Pharmacovigilance in the same manner and timeframe as specified in the previous

section for serious adverse event reporting. As previously noted, there have been rare occurrences of *de novo* diabetes mellitus and hypoadrenalism in the stressed and non-stressed states in subjects who have received megestrol acetate. Should the investigator observe or suspect any of these events, reports should be made promptly to the sponsor via Quintiles Pharmacovigilance following the same reporting mechanism as for SAEs.

In addition, any pregnancy identified on study should be followed to term and any fetal abnormality(s) detected reported by the same expedited reporting mechanism. Any subject who becomes pregnant on study should be discontinued from the study but followed until delivery or pregnancy termination.

10.0 EMERGENCY PROCEDURES

10.1 Emergency Sponsor Contact

In case of an Emergency, the Medical Monitor responsible for the study should be contacted. The contact information for the responsible Medical Monitor is displayed below:

Richard Levine, MD
Quintiles Medical Advisor
1801 Rockville Pike, Suite 300
Rockville, MD 20852
Office phone: (301) 272-3224
Cell phone: (301) 266-0132 (24 hours)
Fax: (301) 272-2153

Email:Richard.Levine@quintiles.com

10.2 Emergency Identification of Study Medication

This is an open-labeled study; therefore, emergency identification of study medication is not applicable.

10.3 Emergency Treatment

10.3.1 Overdosage

No serious and unexpected side effects resulted from studies involving megestrol acetate oral suspension (Megace®) administered in dosages as high as 1200 mg/day. Megestrol acetate has not been tested for dialyzability; however, due to its low solubility, it is postulated that dialysis would not be an effective means of treating overdose. [21]

10.4 Guidance for the Investigator Regarding the Possibility of Adrenal Insufficiency

The glucocorticoid activity of Megace® Oral Suspension has not been fully evaluated. Clinical cases of *de novo* diabetes mellitus, exacerbation of pre-existing diabetes mellitus, and overt Cushing's syndrome have been reported in association with the chronic use of Megace®. In addition, clinical cases of adrenal insufficiency in the stressed and non-stressed states have been observed in patients receiving or recently withdrawn from chronic Megace® therapy. Furthermore, adrenocorticotropin (ACTH) stimulation testing has revealed the frequent occurrence of asymptomatic suppression of the hypothalamic-pituitary-adrenal axis in such patients.[21] Finally, there have been reports in the literature of these events occurring in subjects within the first few weeks of Megace® therapy.[22]

Therefore, the possibility of adrenal insufficiency should be considered in the differential diagnosis when patients receiving or recently withdrawn from any form of megestrol acetate therapy (NCD or Megace®) present with symptoms and/or signs suggestive of hypoadrenalism (e.g., hypotension, nausea, vomiting, dizziness or weakness) in either the stressed or non-stressed states. Laboratory evaluation to rule out adrenal insufficiency and consideration of treatment with replacement or stress doses of a rapidly acting glucocorticoid are strongly recommended in such patients. Failure to recognize suppression of the hypothalamic-pituitary-adrenal axis may, in certain circumstances, result in death. Finally, during periods of stress or serious intercurrent illness (e.g., surgery or serious infection) in patients receiving or recently withdrawn from any form of megestrol acetate therapy, consideration should be given to the use of empiric therapy with stress doses of a rapidly acting glucocorticoid.

If, at any time during the study, a patient manifests symptoms suggestive of adrenal insufficiency, and subsequent laboratory evaluation reveals a significantly low basal serum cortisol level (<10ug/dL) and/or stimulated serum cortisol level (<18µg/dL) 30 minutes after ACTH administration, the patient should be withdrawn from the study and the study medication discontinued. These *symptomatic* patients should be treated with appropriate replacement or stress doses of glucocorticoid therapy (as should *symptomatic* patients who manifest clinical adrenal insufficiency at study termination or following withdrawal of megestrol acetate therapy). In addition, at study termination (when protocol-directed ACTH stimulation testing is scheduled to be performed), if an abnormal basal serum cortisol (typically accompanied by an abnormal stimulated serum cortisol) is observed in an *asymptomatic* patient, replacement glucocorticoid therapy should be instituted as well. In either instance described above, serial ACTH stimulation tests should then be performed at appropriate intervals. When the basal serum cortisol level exceeds 10ug/dL, daily maintenance therapy can be discontinued. However, until the stimulated serum cortisol level

exceeds 18 ug/dL, empiric therapy with stress doses of a rapid acting glucocorticoid should be provided during stress or serious intercurrent illness and the patient should carry a wallet card identifying his/her potential for adrenal insufficiency.

11.0 ETHICS

11.1 Institutional Review Board or Independent Ethics Committee

The Investigator will submit the protocol and informed consent for the Institutional Review Board or Institutional Ethics Committee (IRB/IEC) responsible for the conduct of human trials at his or her site. In addition, the Investigator agrees to provide to Par (or designee) the documentation of ethical review board (IRB/IEC) approval of the protocol and the informed consent document *before* the study may begin at the investigative site(s). Any member of the ethical review board who is directly affiliated with this study as an investigator or as site personnel must abstain from the ethical review board's vote on the approval of the protocol. The ethical review board(s) will review the protocol and any subsequent amendments to the study prior to implementation.

Minimally, the Investigator will supply the following documents to the IRB/IEC for their review and approval:

- the protocol approved by Par (or designee)
- any amendments made to the protocol after the original approval
- the current Investigator's Brochure, package labeling and any updates made to these documents during the course of the study
- informed consent document

The Investigator will forward written documentation of the IRB/IEC approval to Par (or designee) prior to shipment of any study medications.

The Investigator is also responsible for notifying the IRB/IEC in a timely manner of any serious adverse events (SAEs) reported in subjects enrolled at his or her site as well as relaying any communication from Par (or designee) to the Investigator advising the Investigator of SAEs reported at other sites.

11.2 Ethical Conduct of the Study

The Principal Investigator is expected to conduct the study in accordance with the ethical principles that have their origin in the Declaration of Helsinki and in a manner consistent with Good Clinical Practice (GCP), as well as adhering to local and federal regulatory guidelines.

11.3 Subject Information and Informed Consent

The Investigator is responsible for ensuring that the patient understands the risks and benefits of participating in the study. This includes answering any questions the patient may have throughout the study and sharing any new information that may be relevant to the patient's willingness to continue his or her participation in the trial in a timely manner.

The informed consent document will be used to explain the risks and benefits of study participation to the patient in simple terms before the patient is enrolled into the study. In addition, the informed consent documents that the patient is satisfied with his or her understanding of the risks and benefits of participating in the study and desires to participate in the study. The informed consent should also clarify the subject's right to privacy in relation to the protection of personal health information as a research subject.

The Investigator is responsible for ensuring that the informed consent given to each patient or legal representative is approved by the IRB/IEC and is specific to this study. This responsibility includes obtaining the appropriate signatures and dates on the informed consent document prior to the performance of any protocol procedures, including screening, and prior to the administration of study drug.

11.4 Protocol Amendments

Any amendment to the protocol must be approved by Par (or designee) and the responsible IRB/IEC at investigational site prior to implementing any change to the protocol.

12.0 STUDY ADMINISTRATION

12.1 Clinical Monitoring

In order to assure the quality of the data, the Principal Investigator agrees to allow representatives from Par (or designee) to periodically review study documents, audit clinical data collected during the conduct of the trial, and review source documentation and drug accountability records according to GCP guidelines. Clinical monitoring may also include regulatory authorities if indicated. Monitoring personnel, bound by professional secrecy, will not disclose any protected health information or personal medication information outside of fulfilling their responsibilities to ensuring the integrity of the data.

12.2 Data Quality Assurance

Quality assurance methods will be used to ensure the quality and integrity of the data. These methods include the following activities associated with the conduct of the study:

- provide instructional material to the study sites, as appropriate
- sponsor a start-up training session to instruct the investigators and study coordinators This session will give instruction on the protocol, the completion of the CRFs, and study procedures.
- make periodic visits to the study site
- be available for consultation and stay in contact with the study site personnel by mail, telephone, and/or fax

In addition, data quality assurance practices will include standardized practices according to the Standard Operating Procedures of the Data Management team at Quintiles, Inc. (the responsible contract research organization) including, but not limited to the following: periodic auditing of data at clinical site against source documents, double data entry (or other duplicative method of verification), periodic audits of the electronic dataset of clinical data against Case Report Forms, programmatic data checks for inconsistencies and resolution of outstanding data queries and clarifications prior to database lock.

Electronic centralized laboratory data will be stored at the central laboratory facility and transferred to the Data management team at the appropriate time.

12.3 Retention of Study Records

12.3.1 Case Report Forms

Case Report Forms (CRFs) will be supplied by Quintiles and should be handled in accordance with instructions from the Quintiles staff.

The Investigator is responsible for maintaining adequate and accurate source documents and CRFs. CRFs have been designed to record all observations and other data pertinent to the clinical investigation and should be filled out completely by the Investigator (or designate study site representative). All CRFs should be completed in a neat, legible manner to ensure accurate interpretation of the data. Black ball-point pen should be used to ensure the clarity of reproduced copies of all CRFs.

Incorrect entries should be crossed with a single line. Corrections must be made adjacent to the item to be altered, initialed and dated with the reason for the correction if necessary, by an authorized member of the investigational site team (eg, Investigator or designee). Overwriting of this information or use of liquid correcting fluid is not allowed.

The CRFs are reviewed, signed and dated by the Investigator.

Once the site monitor has verified the contents of the completed CRF pages against the source data, the duplicate pages will be collected and forwarded to Quintiles for data entry. Data queries may be raised if the data is unclear or contradictory; these queries must be addressed by the Investigator.

12.3.2 Recording, And Retention of Source Data

Source data collected during this study will include, but is not restricted to: subject's medical file, subject diaries, original laboratory reports, or any other medical records generated during the time of the study conduct.

All clinical data recorded in the CRF must also be recorded in the subject's medical notes.

The monitor (auditors, IEC/IRB or regulatory inspectors) will check the CRF entries against the source documents. The consent form will include a statement by which the subjects allow the monitor/auditor/inspector from the IEC/IRB or regulatory authority access to source data (e.g., subject's medical file, appointment books, original laboratory reports, X-rays, etc.) which substantiate information recorded in the case report forms.

As described in the ICH GCP Guidelines, 'essential documents', include CRFs, source documents, consent forms, laboratory test results, and medication inventory records. These records should be retained by the Investigator until: 1) at least 2 years after the last approval

of a marketing application in an ICH region and there are no pending or contemplated marketing applications in an ICH region or 2) at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with Par. The Investigator should obtain written permission from Par prior to the destruction of any study document.

These records will be made available at reasonable times for inspection and duplication, if required, by a properly authorized representative of the United States Food and Drug Administration in accordance with 21 CFR 312.68 or other regulatory authorities.

12.3.3 Study Drug Accountability

All study drug required for completion of this study will be provided by Par (or designee). The recipient will acknowledge receipt of the drug indicating shipment content and condition. Damaged supplies will be replaced. Accurate records of all study drugs dispensed, used and returned will be maintained.

12.4 Confidentiality

Data collected during this study may be used to support the development, registration or marketing of megestrol acetate oral suspension NCD formulation. All data collected during the study will be controlled by Par (or designee) and will abide by all relevant data protection laws and regulations according to the standards of the participating countries. After subjects have consented to take part in the study, their medical records and the data collected during the study will be reviewed by representatives of Par (or designee) to confirm that the data collected are accurate for analyzing the results. These records and resultant data may additionally be reviewed by auditors, interested commercial parties or by regulatory authorities. The subject's name, however, will not be disclosed outside the study site. Subject data, outside of the investigational site source records, will only be identified by a unique subject number.

The handling of confidential study data will be in compliance with the guidelines established by the standards of the participating countries such as the Health Insurance Portability and Accountability Act of 1996 (HIPAA), Final Rule, published August 17, 2000 for sites in the United States.

12.5 Publication Policy

All manuscripts, abstracts or other modes of presentation arising from the results of this study must be reviewed and approved in writing by Par, in advance of submission. The

review is aimed at protecting Par's pre-existing propriety information and commercial interests. Further information regarding publications shall be governed in the agreement signed between each individual center and PAR.

The Investigator will submit any proposed publication relating to or referring to the results of this study to Par for review at least sixty (60) days prior to the proposed date of submission for publication. Par will complete its review of the proposed publication within sixty (60) days of receipt and, upon Par's written request, the proposed publication will be delayed up to an additional sixty (60) days to enable Par to secure adequate intellectual property protection of confidential information that would be affected by the proposed publication. No publication of confidential information shall be made without Par's prior written consent.

No publication shall be made prior to completion of the multi-site study. If no multi-site publication has been made six (6) months after completion of this study, the Investigator may publish in accordance with the terms of the signed Investigator Agreement between the Investigator and Par. Par's written consent for the Investigator to publish data from this study will not be unreasonably withheld. The content of the publication, whether written or oral, will be given to Par to allow sufficient time for considered comment. The object of this policy to ensure consistency between data submitted to Regulatory Authorities and that appearing in publications.

13.0 SIGNATURE(S) OF INVESTIGATOR(S)

I have read this Par Pharmaceutical protocol No. PAR-002:

Title: **A Randomized, Open-labeled, Pilot Study Comparing Weight Gain in Adults with AIDS-related Wasting Given Either Megestrol Acetate NCD® Formulation Oral Suspension or Megestrol Acetate Oral Suspension (Megace®).**

I have fully discussed the objectives of this trial and the contents of this protocol with the Sponsor's (Par Pharmaceutical) representative.

I understand that the information in this protocol is confidential and should not be disclosed, other than to those directly involved in the execution or the ethical review of the study, without written authorization from Par. It is, however, permissible to provide information to a subject in order to obtain consent once IRB/IEC approval is obtained.

I agree to conduct this trial according to this protocol and to comply with its requirements, subject to ethical and safety considerations and guidelines, and to conduct the trial in accordance with ICH guidelines on GCP and with the applicable regulatory requirements.

I understand that Par may decide to suspend or prematurely terminate the trial at any time for whatever reason; such a decision will be communicated to me in writing. Conversely, should I decide to withdraw from execution of the trial I will communicate my intention immediately in writing to Par.

Investigator Signature: Date:

Name and Title of Investigator: Investigational Site:

Investigator Address:

14.0 REFERENCES

1. Centers for Disease Control and Prevention. 1993 Revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults. *MMWR* 1992;41(RR-17):1-19

2. Coodley GO, Loveless MO, Merrill TM. The HIV Wasting Syndrome; a review. *J Acquir Immune Defic Syndr.* 1994;7:681-694

3. Ott M, Lembcke B, Fischer H, Jager R, Polat H, Geier H, et la. Early changes of body composition in human immunodeficiency virus-infected patients; tetrapolar body impedance analysis indicates significant malnutrition. *Am J Clin Nutr* 1992;15-19.

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APPENDIX A: METROPOLITAN HEIGHT AND WEIGHT TABLES

TABLE 1
1999 METROPOLITAN HEIGHT AND WEIGHT TABLES FOR MEN AND WOMEN
According to Frame, Ages 25-59
WOMEN
Weight in Pounds (In Indoor Clothing)*

HEIGHT (In Shoes)+		SMALL FRAME	MEDIUM FRAME	LARGE FRAME
Feet	Inches			
4	10	102-111	109-121	118-131
4	11	103-113	111-123	120-134
5	0	104-115	113-126	122-137
5	1	106-118	115-129	125-140
5	2	108-121	118-132	128-143
5	3	111-124	121-135	131-147
5	4	114-127	124-138	134-151
5	5	117-130	127-141	137-155
5	6	120-133	130-144	140-159
5	7	123-136	133-147	143-163
5	8	126-139	136-150	146-167
5	9	129-142	139-153	149-170
5	10	132-145	142-156	152-173
5	11	135-148	145-159	155-176
6	0	138-151	148-162	158-179

Prepared by Quintiles, Inc.

TABLE 1
1999 METROPOLITAN HEIGHT AND WEIGHT TABLES FOR MEN AND WOMEN
According to Frame, Ages 25-59
MEN
Weight in Pounds (In Indoor Clothing)*

HEIGHT		SMALL	MEDIUM	LARGE
(In Shoes)+		FRAME	FRAME	FRAME
Feet	Inches			
5	2	128-134	131-141	138-150
5	3	130-136	133-143	140-153
5	4	132-138	135-145	142-156
5	5	134-140	137-148	144-160
5	6	136-142	139-151	146-164
5	7	138-145	142-154	149-168
5	8	140-148	145-157	152-172
5	9	142-151	148-160	155-176
5	10	144-154	151-163	158-180
5	11	146-157	154-166	161-184
6	0	149-160	157-170	164-188
6	1	152-164	160-174	168-192
6	2	155-168	164-178	172-197
6	3	158-172	167-182	176-202
6	4	162-176	171-187	181-207

Prepared by Quintiles, Inc.

APPENDIX B: HAMILTON DEPRESSION RATING SCALE

These questions are representative of the questions asked on the GRID-HAMD-17 Structured Interview Guide. Please refer to the GRID-HAMD-17 Structured Interview Guide in the Study Procedures for specific information regarding the assessment.

Patient's Name (or Study Identifier)_____

Date of Assessment_____

For each item, write the correct number on the line next to the item. (Only one response per item)

_____ **1. DEPRESSED MOOD** (Sadness, hopeless, helpless, worthless)

0= Absent
1= These feelings states indicated only on questioning
2= These feelings states spontaneously reported verbally
3= Communicates feeling states non-verbally-ie, through facial expression, posture, voice and tendency to weep
4= Patient reports VIRTUALLY ONLY these feeling states in his spontaneous verbal and non-verbal communication

_____ **2. FEELINGS OF GUILT**

0= Absent
1= Self reproach, feels he has let people down
2= Ideas of guilt or rumination over past errors or sinful deeds
3= Present illness is a punishment. Delusions of guilt
4= Hears accusatory or denunciatory voices or experiences threatening visual hallucinations

_____ **3. SUICIDE**

0= Absent
1= Feels life is not worth living
2= Wishes he were dead or any thoughts of possible death to self
3= Suicidal ideas or gestures
4= Attempts at suicide (any serious attempt rates 4)

_____ **4. INSOMNIA EARLY**

0= No difficulty falling asleep
1= Complains of occasional difficulty falling asleep- i.e., more than ½ hour
2= Complains of nightly difficulty falling asleep

_____ **5. INSOMNIA MIDDLE**

0= No difficulty
1= Patient complains of being restless and disturbed during the night
2= Waking during the night-any getting out of bed rates 2 (except for voiding)

6. INSOMNIA LATE

_____

0= No difficulty
1= Waking in early hours of the morning but goes back to sleep
2= Unable to fall asleep again if he gets out of bed

7. WORK AND ACTIVITIES

_____

0= No difficulty
1= Thoughts and feelings of incapacity, fatigue or weakness related to activities; work or hobbies
2= Loss of interest in activity; hobbies or work-either directly reported by patient or indirect by listlessness, indecision, and vacillation (feels he has to push self to do work or activities
3= Decrease in actual time spent in activities or decreased productivity
4= Stopped working because of present illness

8. RETARDATION: PSYCHOMOTOR (Slowness of thought and speech; impaired ability to concentrate; decreased motor activity)

_____

0= Normal speech and thought
1= Slight retardation at interview
2= Obvious retardation at interview
3= Interview difficult
4= Complete stupor

9. AGITATION

_____

0= None
1= Subjective tension and irritability
2= Worrying about minor matters
3= Apprehensive attitude apparent in face or speech
4= Fears expressed without questioning

10. ANXIETY (PSYCHOLOGICAL)

_____

0= No difficulty
1= Subjective tension and irritability
2= Worrying over minor matters
3= Apprehensive attitude apparent in face and speech
4= Fears expressed without questioning

11. ANXIETY SOMATIC: Physiological concomitants of anxiety (i.e. effects of autonomic overactivity, "butterflies", indigestion, stomach cramps, belching, diarrhea, palpitations, hyperventilation, paresthesia, sweating, flushing, tremor, headache, urinary frequency). Avoid asking about possible medication side effects (i.e., dry mouth, constipation)

_____

0= Absent
1= Mild
2= Moderate
3= Severe
4= Incapacitating

12. SOMATIC SYMPTOMS (GASTROINTESTINAL):

_____ 0= None
1= Loss of appetite but eating without encouragement from others. Food intake about normal.
2= Difficulty eating without urging from others. Marked reduction of appetite and food intake

13. SOMATIC SYMPTOMS GENERAL

_____ 0= None
1= Heaviness in limbs, back, or head. Backaches, headaches, muscle aches. Loss of energy and fatigability
2= Any clear cut symptom rates 2

14. GENITAL SYMPTOMS (symptoms such as loss of libido; impaired sexual performance; menstrual disturbances)

_____ 0= Absent
1= Mild
2= Severe

15. HYPOCHONDRIASIS

_____ 0= Not present
1= Self absorption (bodily)
2= Preoccupation with health
3= Frequent complaints, requests for help, etc.
4= Hypochondriacal delusions

16. LOSS OF WEIGHT

_____ (A. When rating by history)
0= No weight loss
1= Probably weight associated weight loss with present illness
2= Definite (according to patient) weight loss
3=Not assessed

17. INSIGHT

_____ 0= Acknowledges being depressed and ill
1= Acknowledges illness but attributes cause to bad food, climate, overwork, virus, need for rest, etc.
2= Denies being ill at all

18. DIURNAL VARIATION

A. Note whether symptoms are worse in morning or evening. If NO diurnal variation, mark none.

_____ 0= No variation
1= Worse in A.M.
2= Worse in P.M.

B. When present, mark severity of the variation. Mark "None" if NO variation

_____ 0= None
1= Mild
2= Severe

19. DEPERSONALIZATION AND DEREALIZATION (Such as: Feelings of unreality; Nihilistic ideas)

_____

0= Absent
1= Mild
2= Moderate
3= Severe
4= Incapacitating

20. PARANOID SYMPTOMS

_____

0= None
1= Suspicious
2= Ideas of reference
3= Delusions of reference and persecution

21. OBSESSIONAL AND COMPULSIVE SYMPTOMS

_____

0= Absent
1= Mild
2= Severe

Adapted from Hedlung and Viewig, The Hamilton rating scale for depression. *Journal of Operational Psychiatry*, 1979;10(2): 149-165.

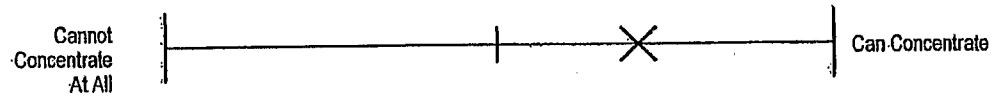
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APPENDIX C: THE BRISTOL-MYERS ANOREXIA/CACHEXIA RECOVERY INSTRUMENT (BACRI)

INSTRUCTIONS (TO BE FILLED OUT BY THE PATIENT)

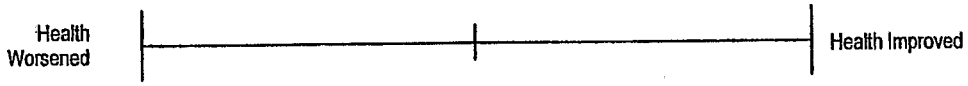
Below are several questions pertaining to your well-being. To answer a question, place an "X" on the line below each question at the point which best shows us what is happening to you **at present.** (The description "normal for me" in some cases means what was normal **prior to illness**). In some questions, if no change has occurred, mark the midpoint of the line to so signify.

Example: HOW DO YOU FEEL ABOUT YOUR ABILITY TO CONCENTRATE?



This "X" shows that you are able to concentrate fairly well.

1. Since you have begun treatment with the test drug, do you feel that any change in weight has had a significant impact on your health?



2. Are you more or less concerned about your weight now than when you started treatment?

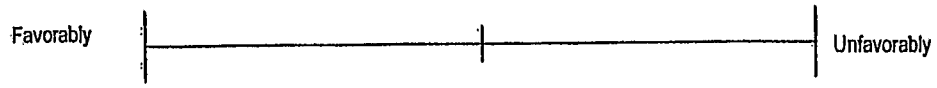


3. To what extent has your appearance changed since treatment started?

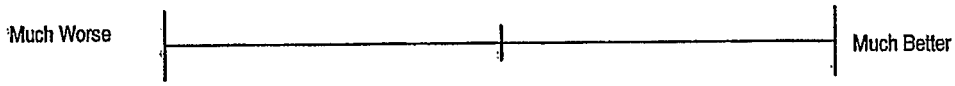


Prepared by Quintiles, Inc.

4. Based on comments from friends, coworkers and loved ones, how do you fell your appearance has changed since the start of treatment?



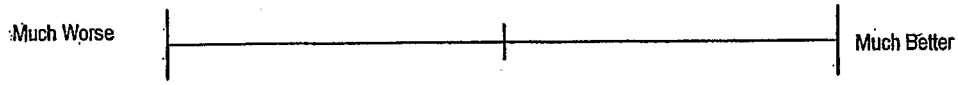
5. To what extent has your appetite changed since the start of treatment?



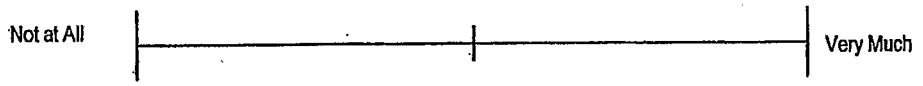
6. Do you enjoy eating more or less than before treatment began?



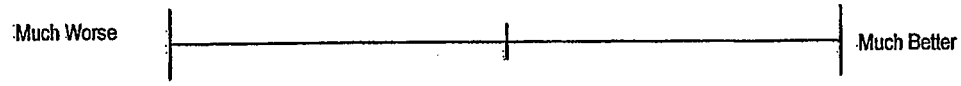
7. Since the beginning of treatment, do you feel better or worse overall?



8. Do you think this treatment has been of benefit to you?



9. Since the beginning of treatment, has your quality of life become better or worse?



Taken from: Cella DF, VonRoenn J, Lloyd S, Browder HP. The Bristol-Myers Anorexia/Cachexia Recovery Instrument (BACRI): a brief assessment of patient's subjective response to treatment for anorexia/cachexia. *Qual of Life Res.* 1995;4:221-231.

APPENDIX D: PHARMACOKINETIC SAMPLE HANDLING

The following procedures will be followed for each pharmacokinetic assessment (including trough samples).

1) Samples of 5 mL of venous blood will be collected in a sterile manner into an evacuated EDTA K3 tube for each sample.

2) Sample will be placed immediately in a container with a mixture of ice-water at a temperature of approximately 4°C until separation.

3) Samples must be centrifuged within 50 minutes of sampling time.

4) Samples must be centrifuged at 3000rpm for 10 minutes in a refrigerated centrifuge (4°C). There may be no more than 60 minutes from the beginning of centrifugation until the aliquots are separated.

5) Resulting plasma is aliquoted into at least two separate samples into propylene tubes of at least 5 mL volume with no less than 1.2 mL per aliquot. Each aliquot must be labeled with the subject identifier, date, time of draw and sample time (eg, pre-, 0.5 h, 1.0 h, etc.). The samples should be stored in separate boxes as they will be shipped to the pharmacokinetic analysis lab in 2 separate shipments. Each sample must have an identical label with the pertinent information clearly legible.

6) Aliquots should be stored as soon as possible in an upright position in a freezer of –20°C or lower. The freezer should be maintained, and monitored in case of power failure.

7) Samples for an individual subject should be retained by the investigational laboratory until the second pharmacokinetic study for that patient is completed. At that time, the investigator should send one set of samples from each of the two pharmacokinetic studies for a given subject on enough dry ice to ensure the samples remain frozen for at least 72 hours. More than one subject's samples may be shipped in a single shipment; however, no shipment should contain all of one patient's samples of any PK test date. Once the bioanalytic lab confirms receipt of the first set of samples for a given patient, then the second set of samples may be sent.

8) Samples should be sent via overnight courier on Monday or Tuesday to:

SFBC Anapharm
2050, boul Réné-Lévesque Ouest
Québec (Québec) G1V 2K8
CANADA
To the attention of: M. Louis-Phillipe Beauregard, Sample Controller Coordinator

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[0217] It will be apparent to those skilled in the art that various modifications and variations can be made in the methods and compositions of the present invention without departing from the spirit or scope of the invention. Thus, it is intended that the present invention cover the modifications and variations of this invention provided they come within the scope of the appended claims and their equivalents.

We claim:

1. A megestrol nanoparticulate composition comprising:

(a) particles of megestrol, megestrol acetate, or a salt or derivative thereof having an effective average particle size of less than about 2000 nm; and

(b) at least one surface stabilizer.

2. The composition of claim 1, wherein the megestrol, megestrol acetate, or a salt or derivative thereof is selected from the group consisting of a crystalline phase, an amorphous phase, a semi-crystalline phase, a semi-amorphous phase, and mixtures thereof.

3. The composition of claim 1 or claim 2, wherein the effective average particle size of the particles of megestrol, megestrol acetate, or a salt or derivative thereof is selected from the group consisting of less than about 1900 nm, less than about 1800 nm, less than about 1700 nm, less than about 1600 nm, less than about 1500 nm, less than about 1400 nm, less than about 1300 nm, less than about 1200 nm, less than about 1100 nm, less than about 1000 nm, less than about 900 nm, less than about 800 nm, less than about 700 nm, less than about 600 nm, less than about 500 nm, less than about 400 nm, less than about 300 nm, less than about 250 nm, less than about 200 nm, less than about 100 nm, less than about 75 nm, and less than about 50 nm.

4. The composition of any one of claims 1 to 3, wherein the composition is formulated:

(a) for administration selected from the group consisting of parental injection, oral administration in solid, liquid, or aerosol form, vaginal, nasal, rectal, otically, ocular, local, buccal, intracisternal, intraperitoneal, and topical administration;

(b) into a dosage form selected from the group consisting of liquid dispersions, gels, sachets, solutions, aerosols, ointments, tablets, capsules, creams, and mixtures thereof;

(c) into a dosage form selected from the group consisting of controlled release formulations, fast melt formulations, lyophilized formulations, delayed release formulations, extended release formulations, pulsatile release formulations, and mixed immediate release and controlled release formulations; or

(d) any combination thereof.

5. The composition of any one of claims 1 to 4, wherein the composition further comprises one or more pharmaceutically acceptable excipients, carriers, or a combination thereof.

6. The composition of any one of claims 1 to 5, wherein:

(a) the megestrol is present in an amount selected from the group consisting of from about 99.5% to about 0.001%, from about 95% to about 0.1%, and from about 90% to about 0.5%, by weight, based on the total combined weight of the megestrol and at least one surface stabilizer, not including other excipients;

(b) the at least one surface stabilizer is present in an amount selected from the group consisting of from about 0.5% to about 99.999%, from about 5.0% to about 95%, and from about 10% to about 99.5%, by weight, based on the total combined dry weight of the megestrol and at least one surface stabilizer, not including other excipients; or

(c) any combination thereof.

7. The composition of any one of claims 1 to 6, comprising at least two surface stabilizers.

8. The composition of any one of claims 1 to 7, wherein the surface stabilizer is selected from the group consisting of a nonionic surface stabilizer, an ionic surface stabilizer, an anionic surface stabilizer, a cationic surface stabilizer, and a zwitterionic surface stabilizer.

9. The composition of any one of claims 1 to 8, wherein the at least one surface stabilizer is selected from the group consisting of cetyl pyridinium chloride, gelatin, casein, phosphatides, dextran, glycerol, gum acacia, cholesterol, tragacanth, stearic acid, benzalkonium chloride, calcium stearate, glycerol monostearate, cetostearyl alcohol, cetomacrogol emulsifying wax, sorbitan esters, polyoxyethylene alkyl ethers, polyoxyethylene castor oil derivatives, polyoxyethylene sorbitan fatty acid esters, polyethylene glycols, dodecyl trimethyl ammonium bromide, polyoxyethylene stearates, colloidal silicon dioxide, phosphates, sodium dodecylsulfate, carboxymethylcellulose calcium, hydroxypropyl celluloses, hydroxypropyl methylcellulose, carboxymethylcellulose sodium, methylcellulose, hydroxyethylcellulose, hydroxypropylmethyl-cellulose phthalate, noncrystalline cellulose, magnesium aluminum silicate, triethanolamine, polyvinyl alcohol, polyvinylpyrrolidone, 4-(1,1,3,3-tetramethylbutyl)-phenol polymer with ethylene oxide and formaldehyde, poloxamers; poloxamines, a charged phospholipid, dioctylsulfosuccinate, dialkylesters of sodium sulfosuccinic acid, sodium lauryl sulfate, alkyl aryl polyether sulfonates, mixtures of sucrose stearate and sucrose distearate, p-isononylphenoxypoly-(glycidol), decanoyl-N-methylglucamide; n-decyl β-D-glucopyranoside; n-decyl β-D-maltopyranoside; n-dodecyl β-D-glucopyranoside; n-dodecyl β-D-maltoside; heptanoyl-N-methylglucamide; n-heptyl-β-D-glucopyranoside; n-heptyl β-D-thioglucoside; n-hexyl β-D-glucopyranoside; nonanoyl-N-methylglucamide; n-noyl β-D-glucopyranoside; octanoyl-N-methylglucamide; n-octyl-β-D-glucopyranoside; octyl β-D-thioglucopyranoside; lysozyme, PEG-phospholipid, PEG-cholesterol, PEG-cholesterol derivative, PEG-vitamin A, PEG-vitamin E, lysozyme, random copolymers of vinyl acetate and vinyl pyrrolidone, a cationic polymer, a cationic biopolymer, a cationic polysaccharide, a cationic cellulosic, a cationic alginate, a cationic nonpolymeric compound, a cationic phospholipid, polymethylmethacrylate trimethylammonium bromide, polyvinylpyrrolidone-2-dimethylaminoethyl methacrylate dimethyl sulfate, hexadecyltrimethyl ammonium bromide, cationic lipids, sulfonium compounds, phosphonium compounds, quarternary ammonium compounds, benzyl-di(2-chloroethyl)ethylammonium bromide, coconut trimethyl ammonium chloride, coconut trimethyl ammonium bromide, coconut methyl

dihydroxyethyl ammonium chloride, coconut methyl dihydroxyethyl ammonium bromide, decyl triethyl ammonium chloride, decyl dimethyl hydroxyethyl ammonium chloride, decyl dimethyl hydroxyethyl ammonium chloride bromide, C_{12-15}dimethyl hydroxyethyl ammonium chloride, C_{12-15}dimethyl hydroxyethyl ammonium chloride bromide, coconut dimethyl hydroxyethyl ammonium chloride, coconut dimethyl hydroxyethyl ammonium bromide, myristyl trimethyl ammonium methyl sulphate, lauryl dimethyl benzyl ammonium chloride, lauryl dimethyl benzyl ammonium bromide, lauryl dimethyl $(ethenoxy)_4$ ammonium chloride, lauryl dimethyl $(ethenoxy)_4$ ammonium bromide, N-alkyl (C_{12-18})dimethylbenzyl ammonium chloride, N-alkyl (C_{14-18})dimethyl-benzyl ammonium chloride, N-tetradecylidmethylbenzyl ammonium chloride monohydrate, dimethyl didecyl ammonium chloride, N-alkyl and (C_{12-14}) dimethyl 1-napthylmethyl ammonium chloride, trimethylammonium halide, alkyl-trimethylammonium salts, dialkyl-dimethylammonium salts, lauryl trimethyl ammonium chloride, ethoxylated alkyamidoalkyldialkylammonium salt, an ethoxylated trialkyl ammonium salt, dialkylbenzene dialkylammonium chloride, N-didecyldimethyl ammonium chloride, N-tetradecyldimethylbenzyl ammonium, chloride monohydrate, N-alkyl(C_{12-14}) dimethyl 1-naphthylmethyl ammonium chloride, dodecyldimethylbenzyl ammonium chloride, dialkyl benzenealkyl ammonium chloride, lauryl trimethyl ammonium chloride, alkylbenzyl methyl ammonium chloride, alkyl benzyl dimethyl ammonium bromide, C_{12} trimethyl ammonium bromides, C_{15} trimethyl ammonium bromides, C_{17} trimethyl ammonium bromides, dodecylbenzyl triethyl ammonium chloride, poly-diallyldimethylammonium chloride (DADMAC), dimethyl ammonium chlorides, alkyldimethylammonium halogenides, tricetyl methyl ammonium chloride, decyltrimethylammonium bromide, dodecyltriethylammonium bromide, tetradecyltrimethylammonium bromide, methyl trioctylammonium chloride, POLYQUAT 10™, tetrabutylammonium bromide, benzyl trimethylammonium bromide, choline esters, benzalkonium chloride, stearalkonium chloride compounds, cetyl pyridinium bromide, cetyl pyridinium chloride, halide salts of quaternized polyoxyethylalkylamines, MIRAPOL™, ALKAQUAT™, alkyl pyridinium salts; amines, amine salts, amine oxides, imide azolinium salts, protonated quaternary acrylamides, methylated quaternary polymers, lysozyme, and cationic guar.

10. The composition of any one of claims 1 to 9, wherein the amount of megestrol is selected from the group consisting of 3 percent by weight, 5 percent by weight, and 9 percent by weight.

11. The composition of any one of claims 1 to 10, additionally comprising at least one non-megestrol active agent.

12. The composition of claim 11, wherein the active agent is selected from the group consisting of amino acids, proteins, peptides, nucleotides, anti-obesity drugs, nutraceuticals, dietary supplements, central nervous symptom stimulants, carotenoids, corticosteroids, elastase inhibitors, anti-fungals, alkylxanthine, oncology therapies, anti-emetics, analgesics, opioids, antipyretics, cardiovascular agents, anti-inflammatory agents, anthelmintics, anti-arrhythmic agents, antibiotics, anticoagulants, antidepressants, antidiabetic agents, antiepileptics, antihistamines, antihypertensive agents, antimuscarinic agents, antimycobacterial agents, antineoplastic agents, immunosuppressants, antithyroid agents, antiviral agents, anxiolytics, sedatives, astringents, alpha-adrenergic receptor blocking agents, beta-adrenoceptor blocking agents, blood products, blood substitutes, cardiac inotropic agents, contrast media, corticosteroids, cough suppressants, diagnostic agents, diagnostic imaging agents, diuretics, dopaminergics, haemostatics, immunological agents, lipid regulating agents, muscle relaxants, parasympathomimetics, parathyroid calcitonin and biphosphonates, prostaglandins, radio- pharmaceuticals, sex hormones, anti-allergic agents, stimulants, anoretics, sympathomimetics, thyroid agents, vasodilators, vasomodulator, xanthines, Mu receptor antagonists, Kappa receptor antagonists, non-narcotic analgesics, monoamine uptake inhibitors, adenosine regulating agents, cannabinoid derivatives, Substance P antagonists, neurokinin-1 receptor antagonists, and sodium channel blockers.

13. The composition of any one of claims 1 to 12, wherein:

(a) upon administration the composition redisperses such that the megestrol

particles have a particle size selected from the group consisting of less than about 2 microns, less than about 1900 nm, less than about 1800 nm, less than about 1700 nm, less than about 1600 nm, less than about 1500 nm, less than about 1400 nm, less than about 1300 nm, less than about 1200 nm, less than about 1100 nm, less than about 1000 nm, less than about 900 nm, less than about 800 nm, less than about 700 nm, less than about 600 nm, less than about 500 nm, less than about 400 nm, less than about 300 nm, less than about 250 nm, less than about 200 nm, less than about 150 nm, less than about 100 nm, less than about 75 nm, and less than about 50 nm;

(b) the composition redisperses in a biorelevant media such that the megestrol particles have a particle size selected from the group consisting of less than about 2 microns, less than about 1900 nm, less than about 1800 nm, less than about 1700 nm, less than about 1600 nm, less than about 1500 nm, less than about 1400 nm, less than about 1300 nm, less than about 1200 nm, less than about 1100 nm, less than about 1000 nm, less than about 900 nm, less than about 800 nm, less than about 700 nm, less than about 600 nm, less than about 500 nm, less than about 400 nm, less than about 300 nm, less than about 250 nm, less than about 200 nm, less than about 150 nm, less than about 100 nm, less than about 75 nm, and less than about 50 nm; or

(c) any combination thereof.

14. The composition of any one of claims 1 to 13, wherein the composition:

(a) does not produce significantly different absorption levels (AUC) when administered under fed as compared to fasting conditions;

(b) does not produce significantly different rates of absorption (T_{max}) when administered under fed as compared to fasting conditions;

(c) does not produce a significantly different Cmax when administered under fed as compared to fasting conditions; or

(d) any combination thereof.

15. The composition of any one of claims 1 to 14, wherein:

(a) the difference in absorption of the nanoparticulate megestrol composition,

when administered in the fed versus the fasted state, is selected from the group consisting of less than about 100%, less than about 90%, less than about 80%, less than about 70%, less than about 60%, less than about 50%, less than about 40%, less than about 35%, less than about 30%, less than about 25%, less than about 20%, less than about 15%, less than about 10%, less than about 5%, and less than about 3%;

(b) the difference in the T_{max} for the nanoparticulate megestrol composition, when administered in the fed versus the fasted state, is less than about 100%, less than about 90%, less than about 80%, less than about 70%, less than about 60%, less than about 50%, less than about 40%, less than about 30%, less than about 20%, less than about 15%, less than about 10%, less than about 5%, and less than about 3%;

(c) the difference in Cmax for the nanoparticulate megestrol composition, when administered in the fed versus the fasted state, is less than about 600%, less than about 575%, less than about 550%, less than about 525%, less than about 500%, less than about 475%, less than about 450%, less than about 425%, less than about 400%, less than about 375%, less than about 350%, less than about 325%, less than about 300%, less than about 275%, less than about 250%, less than about 225%, less than about 200%, less than about 175%, less than about 150%, less than about 125%, less than about 100%, less than about 95%, less than about 90%, less than about 85%, less than about 80%, less than about 75%, less than about 70%, less than about 65%, less than about 60%, less than about 55%, less than about 50%, less than about 45%, less than about 40%, less than about 35%, less than about 30%, less than about 25%, less than about 20%, less than about 15%, less than about 10%, less than about 5%, or less than about 3%; or

(d) any combination thereof.

16. The composition of any one of claims 1 to 15, wherein following administration the composition has a T_{max} selected from the group consisting of less than about 5 hours, less than about 4.5 hours, less than about 4 hours, less than about 3.5 hours, less than about 3 hours, less than about 2.75 hours, less than about 2.5 hours, less than about 2.25 hours, less than about 2 hours, less than about 1.75 hours, less than about 1.5 hours, less than about 1.25 hours, less than about 1.0 hours, less than about 50 minutes, less than

about 40 minutes, less than about 30 minutes, less than about 25 minutes, less than about 20 minutes, less than about 15 minutes, and less than about 10 minutes.

17. The composition of any one of claims 1 to 16, wherein:

(a) the T_{max} of megestrol or a salt or derivative thereof, when assayed in the plasma of a mammalian subject following administration, is less than the T_{max} for a non-nanoparticulate composition of the same megestrol, administered at the same dosage;

(b) the C_{max} of megestrol or a salt or derivative thereof, when assayed in the plasma of a mammalian subject following administration, is greater than the C_{max} for a non-nanoparticulate composition of the same megestrol, administered at the same dosage;

(c) the AUC of megestrol or a salt or derivative thereof, when assayed in the plasma of a mammalian subject following administration, is greater than the AUC for a non-nanoparticulate composition of the same megestrol, administered at the same dosage; or

(d) any combination thereof.

18. The composition of any one of claims 1 to 17, wherein in comparative pharmacokinetic testing with a standard commercial non-nanoparticulate composition of megestrol, administered at the same dosage, the nanoparticulate composition exhibits a C_{max} selected from the group consisting of greater than about 5%, greater than about 10%, greater than about 15%, greater than about 20%, greater than about 30%, greater than about 40%, greater than about 50%, greater than about 60%, greater than about 70%, greater than about 80%, greater than about 90%, greater than about 100%, greater than about 110%, greater than about 120%, greater than about 130%, greater than about 140%, greater than about 150%, greater than about 200%, greater than about 500% and greater than about 800% than the C_{max} exhibited by the non-nanoparticulate composition of megestrol.

19. The composition of any one of claims 1 to 18, wherein the therapeutically effective amount of the megestrol is selected from the group consisting of 1/6, 1/5, ¼,

1/3rd, or ½ of the therapeutically effective amount of a standard commercial megestrol formulation.

20. The composition of any one of claims 1 to 19, wherein the composition is in a liquid oral dosage form, and:

(a) the viscosity of the composition is selected from the group consisting of less than about 1/200, less than about 1/175, less than about 1/150, less than about 1/125, less than about 1/100, less than about 1/50, and less than about 1/25 of the viscosity of a standard commercial liquid oral megestrol formulation at about the same concentration per ml of megestrol;

(b) the viscosity of the composition is selected from the group consisting of from about 175 mPa s to about 1 mPa s, from about 150 mPa s to about 1 mPa, from about 125 mPa s to about 1 mPa s, from about 100 mPa s to about 1 mPa s, from about 75 mPa s to about 1 mPa s, from about 50 mPa s to about 1 mPa s, from about 25 mPa s to about 1 mPa s, from about 15 mPa s to about 1 mPa s, and from about 5 mPa s to about 1 mPa s; or

(c) any combination thereof.

21. A method of making a nanoparticulate megestrol composition comprising contacting megestrol particles with at least one surface stabilizer for a time and under conditions sufficient to provide a nanoparticulate megestrol composition having an effective average particle size of less than about 2000 nm.

22. The method of claim 21, wherein said contacting comprising grinding, wet grinding, homogenization, precipitation, freezing, template emulsion, or a combination thereof.

23. The method of claim 21 or claim 22, wherein the effective average particle size of the nanoparticulate megestrol particles is selected from the group consisting of less than about 1900 nm, less than about 1800 nm, less than about 1700 nm, less than about 1600

nm, less than about 1500 nm, less than about 1400 nm, less than about 1300 nm, less than about 1200 nm, less than about 1100 nm, less than about 1000 nm, less than about 900 nm, less than about 800 nm, less than about 700 nm, less than about 600 nm, less than about 500 nm, less than about 400 nm, less than about 300 nm, less than about 250 nm, less than about 200 nm, less than about 100 nm, less than about 75 nm, and less than about 50 nm.

24. A method of treating a subject in need with a nanoparticulate megestrol formulation comprising administering to the subject an effective amount of a megestrol composition comprising:

(a) particles of megestrol, megestrol acetate, or a salt or derivative thereof having an effective average particle size of less than about 2000 nm; and

(b) at least one surface stabilizer,

25. The method of claim 24, wherein the condition to be treated is selected from the group consisting of neoplastic diseases, breast cancer, endometrial cancer, uterine cancer, cervical cancer, prostate cancer, renal cancer, hormone replacement therapy in post-menopausal women, endometriosis, hirsutism, dysmenorrhea, uterine bleeding, HIV wasting, cancer wasting, cachexia, anorexia, castration, and oral contraception.

26. The method of claim 24 or claim 25, wherein the condition to be treated is anorexia and/or cachexia associated with Human Immunodeficiency Virus (HIV) infection and/or Acquired Immune Deficiency Syndrome (AIDS).

27. The method of any one of claims 24 to 26, wherein the megestrol formulation is administered in the form of an oral suspension.

28. The method of ny one of claims 24 to 26, wherein a maximum blood plasma concentration of megestrol megestrol acetate, or a salt or derivative thereof:

(a) is attained in about 1 hour or less after administration of the

nanoparticulate megestrol formulation in fasting subjects;

(b) of at least about 700 ng/ml is obtained;

(c) is at least about 700 ng/ml and is attained in less than 5 hours after administration of the nanoparticulate megestrol formulation;

(d) is at least about 400 ng/ml and is attained in less than 5 hours after administration of the nanoparticulate megestrol formulation; or

(e) any combination thereof.

29. The method of any one of claims 24 to 26, wherein the megestrol formulation is administered in an amount providing:

(a) from about 1 mg/day to about 1000 mg/day of megestrol;

(b) from about 40 mg/day to about 800 mg/day of megestrol;

(c) from about 500 mg/day to about 700 mg/day of megestrol;

(d) about 575 mg/day;

(e) about 625 mg/day; or

(f) about 675 mg/day.

30. The method of any one of claims 24 to 26, wherein the effective average particle size of the particles of megestrol, megestrol acetate, or a salt or derivative thereof is selected from the group consisting of less than about 1900 nm, less than about 1800 nm, less than about 1700 nm, less than about 1600 nm, less than about 1500 nm, less than about 1400 nm, less than about 1300 nm, less than about 1200 nm, less than about 1100 nm, less than about 1000 nm, less than about 900 nm, less than about 800 nm, less than about 700 nm, less than about 600 nm, less than about 500 nm, less than about 400 nm, less than about 300 nm, less than about 250 nm, less than about 200 nm, less than about 100 nm, less than about 75 nm, and less than about 50 nm.