Date of Approval: July 31, 2014

FREEDOM OF INFORMATION SUMMARY

ORIGINAL NEW ANIMAL DRUG APPLICATION

NADA 141-348

SYNOVEX ONE FEEDLOT

Trenbolone and estradiol extended release implant

Subcutaneous extended release implant

Steers and heifers fed in confinement for slaughter

For increased rate of weight gain and improved feed efficiency for up to 200 days in steers and heifers fed in confinement for slaughter

SYNOVEX ONE GRASS

Trenbolone and estradiol extended release implant

Subcutaneous extended release implant

Pasture steers and heifers (slaughter, stocker and feeder)

For increased rate of weight gain for up to 200 days in pasture steers and heifers (slaughter, stocker and feeder)

Sponsored by:

Zoetis Inc.

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I. GENERAL INFORMATION

A. File Number

NADA 141-348

B. Sponsor

Zoetis Inc.
333 Portage St.
Kalamazoo, MI 49007

Drug Labeler Code: 054771

C. Proprietary Name

SYNOVEX ONE FEEDLOT and SYNOVEX ONE GRASS

D. Established Name

Trenbolone and estradiol extended release implant

E. Pharmacological Category

Steroid hormone

F. Dosage Form:

Subcutaneous extended release implant

G. Amount of Active Ingredient

Each pellet contains 25 mg trenbolone acetate and 3.5 mg estradiol benzoate in an extended release coating.

One SYNOVEX ONE FEEDLOT implant (eight pellets) contains 200 mg trenbolone acetate and 28 mg estradiol benzoate.

One SYNOVEX ONE GRASS implant (six pellets) contains 150 mg trenbolone acetate and 21 mg estradiol benzoate.

H. How Supplied

One pouch contains ten 10-dose cartridges (100 implants).

I. Dispensing Status

OTC

J. Dosage Regimen

SYNOVEX ONE FEEDLOT: One implant (8 pellets), containing 200 mg of trenbolone acetate and 28 mg of estradiol benzoate, is administered to each steer or heifer by subcutaneous implantation in the middle one-third of the ear.

SYNOVEX ONE GRASS: One implant (6 pellets), containing 150 mg trenbolone acetate and 21 mg of estradiol benzoate, is administered to each steer or heifer by subcutaneous implantation in the middle one-third of the ear.

K. Route of Administration

Subcutaneous implantation in the middle one-third of the ear by means of an implant gun

L. Species/Class

SYNOVEX ONE FEEDLOT: Steers and heifers fed in confinement for slaughter
SYNOVEX ONE GRASS: Pasture steers and heifers (slaughter, stocker and feeder)

M. Indication

SYNOVEX ONE FEEDLOT: For increased rate of weight gain and improved feed efficiency for up to 200 days in steers and heifers fed in confinement for slaughter

SYNOVEX ONE GRASS: For increased rate of weight gain for up to 200 days in pasture steers and heifers (slaughter, stocker and feeder)

II. EFFECTIVENESS

A. Dosage Characterization

The dosage characterization for SYNOVEX ONE FEEDLOT relied on information used for the previous approval of SYNOVEX PLUS, which contains trenbolone acetate (TBA) and estradiol benzoate (EB) in non-extended release implants (see section II.A.1. below). The ability of the SYNOVEX ONE FEEDLOT coating to extend the release of TBA and EB to up to 200 days was evaluated in an in vivo depletion study (see section II.A.2. below) and a pharmacokinetic study (see section II.A.3. below).

The dosage characterization for SYNOVEX ONE GRASS relied on a dose determination study conducted in pasture steers and heifers (see section II.A.4. below) and the in vivo depletion and pharmacokinetic studies conducted for SYNOVEX ONE FEEDLOT. The coating used for the SYNOVEX ONE GRASS implants is identical to that used for the SYNOVEX ONE FEEDLOT implants.

1. Dose determination in steers and heifers fed in confinement for slaughter

The dose of SYNOVEX ONE FEEDLOT for steers and heifers fed in confinement for slaughter consists of eight pellets (total dose of 200 mg TBA and 28 mg EB). This eight pellet dose is identical to the SYNOVEX PLUS implant approved under NADA 141-043. Adequate dose characterization of the SYNOVEX ONE FEEDLOT dose in feedlot steers is supported by three dose titration studies for SYNOVEX PLUS that were conducted in steers; similarly, dose characterization of the SYNOVEX ONE FEEDLOT dose in feedlot heifers is supported by four dose confirmation studies for SYNOVEX PLUS that were conducted in heifers.

These studies were all conducted in a "four-corners" approach and demonstrated the superior effectiveness of the combination product (200 mg TBA and 28 mg EB) when compared to its individual components or a negative control. Acceptance of the data in these studies provided the basis for the original approval of SYNOVEX PLUS for improved feed efficiency in steers fed in confinement for slaughter (approval date February 22, 1996) and supplemental approvals of increased rate of weight gain in steers (approval date March 16, 1999) and heifers (approval date September 30, 1998) fed in confinement for slaughter.

2. In vivo depletion study for dose duration characterization

   a. Title: "Depletion of Trenbolone Acetate and Estradiol Benzoate from SYNOVEX Plus Long-Acting Implants in Cattle" (Study 0738-B-US-1-98)

   b. Study Director: L.A. Kraft, Ph.D., Fort Dodge Animal Health, Princeton, NJ

      In-Life Testing Facility: Fort Dodge Animal Health, Agricultural Research Center, Princeton, NJ

      Analytical Laboratory: Fort Dodge Animal Health, Animal Health Analytical and Formulations Research, Princeton, NJ

   c. Study Design:

      (1) Objective: To determine the in vivo depletion of TBA and EB in beef cattle from the coated SYNOVEX ONE FEEDLOT implants (referred to as SYNOVEX PLUS Long-Acting during the study) compared to the previously approved uncoated SYNOVEX PLUS implants (NADA 141-043) during a 200-day period.

      (2) Study Animals: A total of 30 Hereford or Hereford crossbred steers weighing on average 620 pounds were enrolled for the study. Steers were maintained on pasture and were provided a crude protein supplement daily. Steers were supplemented with forage if necessary. Water and trace mineral/salt blocks were available ad libitum.

      (3) Experimental design: The study utilized a randomized complete block design. Animals were blocked on the basis of pretreatment body weights into six weight blocks of five animals each, and then were randomly assigned to one of five treatment groups, resulting in six animals per group.

      (4) Treatment Groups: SYNOVEX ONE FEEDLOT implants or commercial SYNOVEX PLUS implants were used. The SYNOVEX ONE FEEDLOT implants were manufactured by Oread Laboratories, Inc., Palo Alto, CA. Both SYNOVEX ONE FEEDLOT and SYNOVEX PLUS are eight-pellet implants that contain 200 mg TBA and 28 mg EB. The only difference between these two implants is that SYNOVEX ONE FEEDLOT has a coating over the implant pellets whereas the SYNOVEX PLUS implants are not coated.

      (5) Drug Administration: On Day 0, each of the 30 steers received one SYNOVEX ONE FEEDLOT implant in one ear and one SYNOVEX PLUS

implant in the contralateral ear. Implants were placed subcutaneously in the middle third of the back of the ear.

(6) Measurements and Observations: Six animals were sacrificed on each of the following collection days: Days 40, 81, 120, 160, and 200. Implants and surrounding tissue were removed ("explanted") from each ear and were analyzed for TBA and EB content using validated methods of analysis.

(7) Statistical Analysis: Linear regression of residual TBA and EB in implants across explant time points was performed to evaluate relative depletion rates of TBA and EB from SYNOVEX ONE FEEDLOT and SYNOVEX PLUS implants.

d. Results: On Day 200, mean quantities of TBA and EB remaining in SYNOVEX ONE FEEDLOT implants were 28.4 mg and 6.4 mg, respectively, and were significantly greater than the assayed quantities of TBA and EB remaining in SYNOVEX PLUS implants (Table 1).

Table 1. Mean Residual Trenbolone Acetate (TBA) or Estradiol Benzoate (EB) Concentrations (mg) Recovered from Steers Implanted with SYNOVEX ONE FEEDLOT or SYNOVEX PLUS.

Active Ingredient	Explant Day	n	Amount (mg) remaining in SYNOVEX ONE FEEDLOT explant	Amount (mg) remaining in SYNOVEX PLUS explant	Difference
TBA	-	-	201.8[1]	201.8[1]	
TBA	40	6	166.8	114.8	52.1*
TBA	81	6	136.8	50.7	83.1*
TBA	120	6	50.6	11.8	45.7*
TBA	160	6	52.0	0.0[2]	52.0*
TBA	200	6	28.4	0.0[2]	28.7*
EB	-	-	28.8[1]	28.8[1]	
EB	40	6	27.2	21.3	5.9*
EB	81	6	24.8	13.2	11.1*
EB	120	6	13.5	4.6	10.4*
EB	160	6	12.9	1.0[2]	11.8*
EB	200	6	6.4	0.2[2]	6.4*

[1] Analyzed amount of TBA or EB contained in administered dose
[2] Below the lower limit of quantitation for the assay
* The concentration of active ingredient recovered from steers implanted with SYNOVEX ONE FEEDLOT or SYNOVEX PLUS is different ($P \leq 0.05$).

The depletion rates of SYNOVEX ONE FEEDLOT and SYNOVEX PLUS implants, calculated from the slope of the regression line of depleted amounts of TBA and EB vs. days, are shown in Table 2. SYNOVEX ONE FEEDLOT had a slower ($P \leq 0.05$) depletion rate of TBA (0.9485 mg/d) than SYNOVEX PLUS (1.7138 mg/d), and SYNOVEX ONE FEEDLOT had a slower ($P \leq 0.05$) depletion rate of EB (0.1057 mg/d) than SYNOVEX PLUS (0.1689 mg/d). The slower depletion of active ingredients from the SYNOVEX ONE FEEDLOT implant extends the days of depletion to over 200 days for both TBA and EB. The ratio of TBA depletion to EB depletion is less than 10% different in the SYNOVEX ONE FEEDLOT implant (8.97) and

the SYNOVEX PLUS implant (10.15), indicating that the ratios of the two active ingredients over the release period of each implant are essentially the same. The ratio of active ingredient depletion for SYNOVEX ONE FEEDLOT and SYNOVEX PLUS depletion was less than 10% different for TBA (0.55) and EB (0.63). The similarity of these ratios provide evidence that the relative depletion rates for TBA and EB across both products are essentially equivalent.

Table 2. Depletion Rates (Slopes) and Days to Depletion of Trenbolone Acetate (TBA) and Estradiol Benzoate (EB) for SYNOVEX ONE and SYNOVEX PLUS.

Analyte	Depletion rate (mg/d) from SYNOVEX ONE FEEDLOT	Depletion rate (mg/d) from SYNOVEX PLUS	Difference
Depletion Rate, mg/d			
TBA	-0.9485	-1.7138	0.7653*
EB	-0.1057	-0.1689	0.0631*
Days to depletion			
TBA	212.8	117.8	
EB	272.3	170.5	

* The difference in depletion rates of TBA or EB from steers implanted with SYNOVEX ONE FEEDLOT or SYNOVEX PLUS is different ($P \leq 0.05$).

e. Adverse Reactions: No adverse reactions were reported in this study.

f. Conclusions: The slower depletion rates of TBA and EB from SYNOVEX ONE FEEDLOT implants compared to SYNOVEX PLUS implants demonstrate that SYNOVEX ONE FEEDLOT has active ingredients remaining at 200 days and thus supports an extended release claim such as "up to 200 days". Although this study was conducted in steers, the payout data can apply to heifers. Trenbolone acetate is a synthetic androgen, and the only source of TBA is from the implant, so it is unlikely that payout of TBA from the ear implant would differ between steers and heifers. In contrast, estradiol is present naturally in cattle. Concentrations of circulating estradiol range from 1.8 to 6.9 pg/mL in steers[1,2] and from 2.2 to 5.9 pg/mL in heifers[3,4]. Thus, similar concentrations of endogenous estradiol in steers and heifers would support similar rates of EB payout in steers and heifers. Furthermore, the clinical data from the dose confirmation effectiveness studies (see section II.B. below) substantiate the payout data from this in vivo depletion study.

References:

1. Lee, C.Y., D.M. Henricks, G.C. Skelley, and L.W. Grimes. 1990. Growth and hormonal response of intact and castrate male cattle to trenbolone acetate and estradiol. J. Anim. Sci. 68:2682-2689.
2. Hunt, D.W., D.M. Henricks, G.C. Skelley, and L.W. Grimes. 1991. Use of trenbolone acetate and estradiol in intact and castrate male cattle: effects on growth, serum hormones, and carcass characteristics. J. Anim. Sci. 69:2452-2462.

3. Henricks, D.M., R.T. Brandt, Jr., E.C. Titgemeyer, and C.T. Milton. 1997. Serum concentrations of trenbolone-17 beta and estradiol-17 beta and performance of heifers treated with trenbolone acetate, melengestrol acetate, or estradiol-17 beta. J. Anim. Sci. 75:2627-2633.

4. Moran, C., J.F. Quirke, D.J. Prendiville, S. Bourke, and J.F. Roche. 1991. The effect of estradiol, trenbolone acetate, or zeranol on growth rate, mammary development, carcass traits, and plasma estradiol concentrations of beef heifers. J. Anim. Sci. 69:4249-4258.

3. Pharmacokinetic study

   a. Title: "Depletion of Trenbolone Acetate and Estradiol Benzoate from SYNOVEX Plus Long-Acting Implants in Cattle" (Study No. 0738-B-US-2-98)

      Study Director: L.A. Kraft, PhD, Fort Dodge Animal Health, Princeton, NJ

      Analytical Laboratory Manager: S. Gray, Endocrine Physiology Laboratory, Clemson University, Clemson, SC

   b. Study Design

      (1) Objective: To determine the serum concentrations of trenbolone-17β and estradiol-17β in beef cattle implanted with the coated SYNOVEX ONE FEEDLOT implants (referred to as SYNOVEX PLUS Long-Acting during the study) compared to the currently approved uncoated SYNOVEX PLUS implants (NADA 141-043) during a 200-day period.

      (2) Study Animals: Thirty feedlot steers weighing approximately 551-771 lb were enrolled for the study. Four additional steers were used to produce incurred serum samples for quality assurance tests.

      (3) Experimental Design: The study utilized a randomized complete block design. Animals were blocked on the basis of pretreatment body weights into fifteen weight blocks of two animals each, and then were randomly assigned to one of two treatment groups, resulting in fifteen steers per group. Steers were implanted for 200 days.

      (4) Treatment Groups: SYNOVEX ONE FEEDLOT implants or commercial SYNOVEX PLUS implants were used. The SYNOVEX ONE FEEDLOT implants were manufactured by Oread Laboratories, Inc., Palo Alto, CA. Both SYNOVEX ONE FEEDLOT and SYNOVEX PLUS are eight-pellet implants that contain 200 mg TBA and 28 mg EB. The only difference between these two implants is that SYNOVEX ONE FEEDLOT has a coating over the implant pellets whereas the SYNOVEX PLUS implants are not coated.

      (5) Drug Administration: On Day 0, steers received either one SYNOVEX ONE FEEDLOT implant or one SYNOVEX PLUS implant. Implants were placed subcutaneously in the middle third of the back of the ear.

      (6) Measurements and Observations: After implantation, serum was collected on Days -2, -1, 0, 1, 4, 7, 14, 21, 28, 42, 56, 70, 91, 112,

133, 154, 175, and 200. Samples were analyzed in duplicate for the concentration of trenbolone-17β (the metabolite of TBA) and estradiol-17β (the metabolite of EB) in serum.

c. Statistical Methods: Serum concentrations of trenbolone-17β and estradiol-17β at each post-treatment day were analyzed by mixed model analysis.

d. Results

Serum concentrations of trenbolone-17β and estradiol-17β from steers treated with SYNOVEX ONE FEEDLOT or SYNOVEX PLUS implants are shown in Table 3.

Table 3. Pharmacokinetic Parameters for Serum Trenbolone-17β and Estradiol-17β in Steers Implanted with SYNOVEX ONE FEEDLOT or SYNOVEX PLUS Implants for 200 Days.

	SYNOVEX ONE FEEDLOT	SYNOVEX PLUS
Number of animals	15	15
Trenbolone-17β		
Area under the curve, pg d/mL	16603 ± 1023*	18922 ± 876
Peak concentration (C_{max}), pg/mL	317.4 ± 36.7	346.7 ± 32.5
Time to peak (T_{max}), d	55.1 ± 13.0	18.7 ± 3.9
Estradiol-17β		
Area under the curve, pg d/mL	745 ± 300	582 ± 120
Peak concentration (C_{max}), pg/mL	12.5 ± 1.8	11.3 ± 0.9
Time to peak (T_{max}), d	121.9 ± 13.6	44.1 ± 8.4

*Significantly different at $P \leq 0.10$.

e. Adverse Reactions: No adverse reactions were reported in this study.

f. Conclusions: The coating on the SYNOVEX ONE FEEDLOT implants significantly delayed the release of TBA and EB resulting in an extended release implant that lasted approximately 200 days. The maximum serum concentrations of trenbolone-17β and estradiol-17β from SYNOVEX ONE FEEDLOT were delayed, but were similar and not greater than the maximum serum concentrations from SYNOVEX PLUS.

4. Dose determination in pasture steers and heifers

a. Title: "Dose Response of Synovex Plus LA Implants on Rate of Weight Gain of Pasture Steers and Heifers" (Study 0738-B-US-1-99)

b. Investigator: Larry L. Smith, DVM, L.L. Smith Research and Development, Inc., Lodi, Wisconsin

c. Study Design:

(1) Objective: To establish the dose-response effects of SYNOVEX ONE GRASS implants (referred to as SYNOVEX PLUS LA during the study) containing different levels of the active ingredients TBA and EB on the rate of body weight gain in pasture steers and heifers.

(2) Study Animals: Steers and heifers (280 of each sex) were assigned to treatments. Animals were Continental and/or British mixed-breed beef cattle. Mean initial weights of steers and heifers were 429 and 417 lbs., respectively.

(3) Experimental design: The study was a masked, negative-controlled study that utilized a randomized complete block design within each sex. Within sexes, animals were blocked on the basis of pretreatment body weights into 70 weight blocks of four animals each, and then randomly assigned to the four treatments within each block (n = 70 animals per treatment within each sex). Within each sex, all animals were managed as a group. Animal was the experimental unit.

(4) Treatment Groups: The four treatments evaluated in each sex of cattle are shown in Table 4. Steers and heifers were implanted with 0, 2, 4, or 6 pellets of SYNOVEX ONE GRASS. Each pellet contains 25 mg TBA and 3.5 mg EB.

Table 4. Treatments Evaluated in Dose Determination Study for SYNOVEX ONE GRASS in Pasture Steers and Heifers.

Number of implanted SYNOVEX ONE GRASS pellets	Number of Steers or Heifers	Trenbolone Acetate (mg)	Estradiol Benzoate (mg)
0	70	0	0
2	70	50	7
4	70	100	14
6	70	150	21

(5) Drug Administration: Implants were placed subcutaneously in the middle third of the back of the ear in treated animals. Control animals, i.e., those assigned to receive 0 pellets, were sham implanted (implant needle inserted in ear but no implant was deposited) using identical techniques to the implanted animals.

(6) Measurements and Observations: Body weights were measured twice before treatment and averaged to obtain the initial starting weight. The final body weight was the mean of the weights measured on two consecutive days at the completion of the study. Weight gained was computed as the difference between initial body weight and final body weight. The pivotal parameter was computed for each animal as follows:

Average daily gain (ADG) = weight gain ÷ days on study

Implant sites on ears were examined on Day 42 to document animals experiencing implant site reactions and assess implant retention. Animals were observed daily during the study for abnormalities. Illnesses, injuries and medical treatments were documented and evaluated.

d. Statistical Analysis: Average daily gain data from treatment through completion of the study were statistically analyzed by mixed model

analysis. Treatment was a fixed effect and block was a random effect.

e. Results:

Average daily gain results for pasture steers and heifers implanted with 0, 2, 4, or 6 SYNOVEX ONE GRASS pellets are shown in Table 5. The evaluation period was 203 days in pasture steers and 202 days in pasture heifers. Average daily gain by steers implanted with six SYNOVEX ONE GRASS pellets was significantly greater than ADG by sham-implanted control steers or steers implanted with two or four SYNOVEX ONE GRASS pellets ($P \leq 0.05$). Average daily gain by heifers implanted with two, four or six SYNOVEX ONE GRASS pellets was greater than sham-implanted controls ($P \leq 0.05$). The ADG of heifers implanted with six SYNOVEX ONE GRASS pellets was not significantly greater than that of heifers implanted with two or four SYNOVEX ONE GRASS pellets. However, as discussed in Sections II.B., III, and IV below, the six-pellet dose for pasture heifers is effective, is safe, and will not result in a residue in excess of the established Acceptable Daily Intake (ADI) of TBA or EB. Thus, the use of the six pellet dose for heifers is permitted.

Table 5. LSMeans for Average Daily Gain (ADG) for Pasture Steers and Heifers Implanted with 0, 2, 4, or 6 SYNOVEX ONE GRASS Pellets.

	Study Duration, d	0 Pellets	2 Pellets	4 Pellets	6 Pellets
Steers, ADG (lb/d)	203	1.60 [c]	1.77 [b]	1.81 [b]	1.95 [a]
Heifers, ADG (lb/d)	202	1.38 [b]	1.47 [a]	1.48 [a]	1.54 [a]

[abc] Least square means in the same row with different superscript letters are different ($P \leq 0.05$) based on 2-sided paired t-tests.

f. Adverse Reactions: No adverse reactions were reported in this study.

g. Conclusion(s): Compared to sham-implanted controls, the six-pellet dose of SYNOVEX ONE GRASS containing 150 mg TBA and 21 mg EB significantly increased the rate of weight gain over 200 days in both pasture steers and heifers. On the basis of this study, the six-pellet dose was established for pasture steers and heifers.

B. Substantial Evidence

1. Dose confirmation studies in steers and heifers fed in confinement for slaughter

a. Title: "Effects of Synovex Plus LA Implants on Performance of Feedlot Steers" and "Effects of Synovex Plus LA Implants on Performance of Feedlot Heifers"

b. Investigators and Locations:

Table 6. Study Site Numbers, Locations, Investigators, and Slaughter Facilities.

Study Site Number, Location, and Investigator	Slaughter Facility and Distance from Study Location
0738-B-US-04-07 (steers) and 0738-B-US-08-07 (heifers) Johnson Research LLC, Parma, ID Jenifer Edmonds, DVM, PhD	Toppenish, WA 312 miles
0738-B-US-05-07 (steers) and 0738-B-US-09-07 (heifers) Agri Research Center, Inc., Canyon, TX David Bechtol, DVM	Amarillo, TX 19 miles
0738-B-US-06-07 (steers) and 0738-B-US-10-07 (heifers) Beef Cattle Research Center, Manhattan, KS James Drouillard, PhD[1]	Holcomb, KS 331 miles
0738-B-US-07-07 (steers) and 0738-B-US-11-07 (heifers) Horton Feedlot and Research Center, Wellington, CO Breck Hunsaker, DVM, PhD	Greeley, CO 43 miles

[1] Investigator address: Kansas State University, Manhattan, KS

c. Study Design:

(1) Objective: To evaluate the clinical effectiveness of SYNOVEX ONE FEEDLOT implants (referred to as SYNOVEX PLUS Long-Acting during the study) for increasing rate of weight gain and improving feed efficiency for up to 200 days in steers and heifers fed in confinement for slaughter.

(2) Study Animals: A total of 684 crossbred steers weighing on average 650 pounds were enrolled in the steer study. A total of 684 crossbred heifers weighing on average 635 pounds were enrolled in the heifer study. Steers and heifers were acquired from major cattle-producing regions of the United States and breeds were typical of the U.S. beef industry.

(3) Experimental design: The studies were conducted at four independent sites. The studies were masked, negative-controlled studies that utilized a complete randomized block design at each site. Within each study, steers or heifers were randomly assigned within blocks to one of two treatment groups. Pen was the experimental unit, with nine experimental units per treatment group. Personnel who collected study data (other than data related to drug administration and accountability) were masked to treatments.

(4) Treatment Groups: The two groups used in these studies were the treatment group (SYNOVEX ONE FEEDLOT, 200 mg TBA and 28 mg EB in an eight-pellet coated ear implant) and a negative control group (sham implant). At three sites (ID, TX, CO) each treatment group had 90 steers or heifers (ten steers or heifers per pen), and at the fourth site (KS) each treatment group had 72 steers or heifers (eight steers or heifers per pen).

(5) Drug Administration: Ears of incoming cattle were palpated for pre-existing implants 14 days before experimental administration. Any pre-existing implants were removed. Study treatment implants were placed subcutaneously in the middle third of the back of the ear in treated steers and heifers. Control steers and heifers were sham implanted (implant needle inserted in ear but no implant was deposited) using identical techniques to the implanted steers and heifers.

(6) Measurements and Observations: Individual animal weights were measured twice before treatment and averaged to obtain the initial starting weight. Interim individual animal weights were collected approximately every 35 days following treatment. At the completion of the study, individual animal weights were collected on two consecutive days and averaged to obtain the final weight. Throughout the study, feed weighbacks were recorded approximately every 14 days. Feed consumption (feed issued to a pen minus feed weighback) was recorded on a dry matter basis to calculate dry matter intake. All steers and heifers were sent to slaughter at the same time within site, when the majority of the steers or heifers were judged to have reached market condition.

Animals removed early were included in calculations based upon their last recorded body weight. For testing the claims of increased rate of weight gain and improved feed efficiency, the pivotal variables of average daily gain (ADG) and gain to feed ratio (G/F) were calculated as follows:

ADG = Total Pen Gain ÷ No. Animal Days of Pen
Total Pen Gain = Sum of Individual Animal Gains
Individual Animal Gains = (Final weight – initial weight)
No. Animal Days of Pen = Sum of Individual Animal Days

G/F = ADG ÷ dry matter intake (DMI)

To evaluate implant safety, the implant sites on ears of all steers and heifers were evaluated on Day 35 to document ear abscesses, ear inflammation, or other ear abnormalities, and the presence of an implant. In addition, all steers and heifers were observed daily during the study for abnormalities. Illnesses, injuries, and medical treatments were documented and summarized.

Steers and heifers were transported by truck to be slaughtered. At slaughter, incidence of liver abscesses and carcass data for determining USDA yield and quality grades were collected.

d. Statistical Analysis: The steer and heifer studies were analyzed separately. For each study, the primary variables, ADG and G/F, were analyzed by mixed model analysis. Treatment was a fixed effect in the model. For each study, study site, study site by treatment interaction, and blocks nested within site were random effects.

e. Pooled Results:

The mean duration of the studies was 198 days for steers and 198 days for heifers, with variation in study duration at each site as shown in Table 7.

Table 7. Critical Study Dates by Study Site for Steers and Heifers Fed in Confinement for Slaughter.

	Study start	Study end	Duration, d
Activity	Treatment and second initial weight	Second final weight	
Steers			
ID	January 30, 2008	August 18, 2008	201
TX	December 20, 2007	June 27, 2008	190
KS	April 30, 2008	November 18, 2008	202
CO	January 18, 2008	August 4, 2008	199
Heifers			
ID	January 31, 2008	August 18, 2008	200
TX	December 19, 2007	June 27, 2008	191
KS	May 1, 2008	November 18, 2008	201
CO	January 18, 2008	August 4, 2008	199

The numbers of steers and heifers enrolled, removed, or completing the studies are shown in Table 8. A total of 662 feedlot steers completed the study. Eleven control steers and 11 treated steers were removed prior to the end of the treatment period. Of these removals, nine control steers and seven treated steers were due to death. A total of 670 feedlot heifers completed the study. Six control heifers and eight treated heifers were removed prior to the end of the treatment period. Of these, three control heifers and seven treated heifers were due to death. All of the removals or deaths were for reasons unrelated to treatment, and there was no pattern of removals based on treatment group. For greater detail on health observations and reasons for animal removal, see Individual Site Details (below).

Table 8. Accountability by Study Site for Steers and Heifers Fed in Confinement for Slaughter With or Without SYNOVEX ONE FEEDLOT Implants.

	Control Enrolled [1]	Control Removed (deaths)	Control Completed	SYNOVEX ONE FEEDLOT Enrolled[1]	SYNOVEX ONE FEEDLOT Removed (deaths)	SYNOVEX ONE FEEDLOT Completed
Steers, #						
ID	90	2 (1)	88	90	1 (1)	89
TX	90	2 (2)	88	90	2 (1)	88
KS	72	2 (2)	70	72	3 (2)	69
CO	90	5 (4)	85	90	5 (3)	85
SUM	342	11 (9)	331	342	11 (7)	331
Heifers, #						
ID	90	1 (0)	89	90	1 (1)	89
TX	90	0 (0)	90	90	1 (1)	89
KS	72	3 (1)	69	72	2 (2)	70
CO	90	2 (2)	88	90	4 (3)	86
SUM	342	6 (3)	336	342	8 (7)	334

[1] Animals were enrolled in nine experimental units (pen) per site and sex.

Average daily gain and G/F results for steers and heifers are provided in Table 9. Two control steers and two treated steers were removed prior to obtaining an interim body weight. One control heifer and one treated heifer were removed prior to obtaining an interim body weight. These animals were excluded from the outcome analysis for the rate of weight gain and feed efficiency claims. In steers, both ADG ($P = 0.0023$) and G/F ($P = 0.0026$) were increased in the SYNOVEX ONE FEEDLOT group as compared to the negative control group. In heifers, both ADG ($P = 0.0027$) and G/F ($P < 0.0001$) were increased in the SYNOVEX ONE FEEDLOT group as compared to the negative control group.

Table 9. Pooled Statistical Analysis - LSMeans for Average Daily Gain (ADG), Dry Matter Intake (DMI), and Gain to Feed Ratio (G/F) of Steers and Heifers Fed in Confinement for Slaughter With or Without SYNOVEX ONE FEEDLOT Implants.

Variables	Control	SYNOVEX ONE FEEDLOT	SEM	p-value
Steers				
ADG, lb/d	3.00	3.45	0.059	0.0023
DMI, lb/d	18.48	19.35	0.415	0.0003
G/F (ADG/DMI)	0.163	0.179	0.004	0.0026
Heifers				
ADG, lb/d	2.76	3.09	0.046	0.0027
DMI, lb/d	17.60	18.41	0.416	0.0003
G/F (ADG/DMI)	0.157	0.168	0.002	< 0.0001

The carcass quality information is shown in Table 10. All cattle were inspected and passed both the ante-mortem and post-mortem inspection by USDA personnel. No animal safety concerns or treatment-related adverse conditions were observed during the study, at the end of the

study, or during the slaughter of the cattle. In both steers and heifers, there were no adverse effects of treatment on hot carcass weight, ribeye area, or USDA yield grade. Treatment with SYNOVEX ONE FEEDLOT reduced marbling scores in steers ($P < 0.0003$) and heifers ($P < 0.0310$), which resulted in a decrease in the proportion of carcasses assigned USDA Quality Grade scores of Prime or Choice, and an increase in the proportion of carcasses assigned a Quality Grade of Select or Standard in steers ($P = 0.0007$) and heifers ($P < 0.0060$).

Table 10. Pooled Statistical Analysis - LSMeans for Marbling Score and Quality Grade for Steers and Heifers Fed in Confinement for Slaughter With or Without SYNOVEX ONE FEEDLOT Implants.

Carcass Endpoint	Control	SYNOVEX ONE FEEDLOT	SEM	P-value
Steers				
Marbling score	458.7	433.5	4.8	0.0003
Quality Grade ≥ Choice, % of carcasses	73.6	60.9	N/A	0.0007
Quality Grade < Choice, % of carcasses	26.4	39.1	N/A	0.0007
Heifers				
Marbling score	483.9	450.8	13.1	0.0310
Quality Grade ≥ Choice, % of carcasses	78.7	69.1	N/A	0.0060
Quality Grade < Choice, % of carcasses	21.3	30.9	N/A	0.0060

f. Individual Site Details

Steers and heifers were given preventative treatments (USDA-licensed anti-clostridial and anti-viral vaccinations, FDA-approved parasiticides, and EPA-licensed insecticides) reflective of current industry practices. Steers and heifers were housed on dirt-floored pens (ID, TX, CO) or concrete-floored pens (KS). Water and feed was available ad libitum. Diets consisted of the following:

ID: rolled corn, earlage, dry distiller's grains, alfalfa hay, supplement, tallow, and delactosed whey
TX: flaked corn, cottonseed hulls, cottonseed meal, molasses, fat, supplement and alfalfa hay
KS: steam-flaked corn, ground alfalfa hay, corn steep liquor, and a vitamin and mineral supplement
CO: flaked corn, wet distiller's grains, alfalfa hay, vitamin and mineral supplements, corn silage, and tallow

No treatment-related adverse events were observed during the study. In steers, the 22 removals (16 of those due to death or euthanasia) were due to bloat (7), lameness or joint problems (2), pneumonia or respiratory disease (4), pulmonary hypertension and/or congestive heart failure (3), injury (2), nephritis (1), hardware disease (1), abscessed spleen (1), and inappropriate inclusion of a bull (1). In heifers, the 14 removals (10 of

those due to death or euthanasia) were due to bloat (4), lameness or joint problems (1), pneumonia or respiratory disease (1), pulmonary hypertension and/or congestive heart failure (4), injury (2), spastic paresis (1), and late-term abortion (1).

All abnormal health observations during the studies, including those that resulted in removal or death, are shown in Table 11. There were 36 control steers and 39 treated steers with abnormal health observations, and 23 control heifers and 32 treated heifers with abnormal health observations. A single animal may have had multiple observations by system. Generally, abnormal health observations were infrequent and were a result of common conditions in feedlot cattle. Some other health observations were not common conditions, but were observed with a low frequency. The most common observations included disorders of the respiratory tract (primarily pneumonia and other respiratory disease), digestive tract (primarily bloat), musculoskeletal (primarily lameness or arthritis), or other systems (congestive heart failure, conjunctivitis, skin abscess, hardware disease, nephritis, neurological symptoms, hepatopathy, internal ear disorder, or splenic abscess), or systemic disorders (primarily anorexia, lethargy, or trauma). The multiple observations of lameness and other musculoskeletal disorders at the Kansas site were likely a result of the concrete surfacing in the pens. There was no pattern of abnormal health observations based on treatment group.

Table 11. Abnormal Health Observations by Study Site for Steers (S) and Heifers (H) Fed in Confinement for Slaughter With or Without SYNOVEX ONE FEEDLOT Implants.

	ID-S	TX-S	KS-S	CO-S	SUM	ID-H	TX-H	KS-H	CO-H	SUM
Total Animals with any Abnormal Observation										
Control	1	4	16	15	36	5	2	7	9	23
SYNOVEX ONE FEEDLOT	4	4	9	22	39	5	2	6	19	32
Observations By System[1]										
Control										
Respiratory	0	1	2	8	11	4	2	0	5	11
Digestive tract	1	2	1	6	10	0	0	2	2	4
Musculoskeletal	0	0	7	0	7	0	0	5	0	5
Systemic	0	0	5	1	6	1	0	3	3	7
Other	0	1	5	2	8	0	0	1	3	4
SYNOVEX ONE FEEDLOT										
Respiratory	3	2	1	18	24	3	1	1	13	18
Digestive tract	1	0	0	1	2	1	0	1	4	6
Musculoskeletal	0	1	3	0	4	1	0	2	2	5
Systemic	1	0	2	1	4	2	0	2	1	5
Other	0	2	4	4	10	0	1	2	1	4

[1] A single animal may have had multiple observations by system

Implant site evaluations determined by palpation on Day 35 are shown in Table 12. Generally, implants were not detected in control animals, and were generally not missing in SYNOVEX ONE FEEDLOT animals. At the Colorado steer site, implants were detected in two control steers and an additional implant was found in the contralateral ear of one SYNOVEX ONE FEEDLOT steer (marked in Table 12 with an asterisk). Study records did not support that the presence of an implant in the two control steers or the one SYNOVEX ONE FEEDLOT steer had any impact on the outcome of the study. There were few reported injection site reactions and few differences between the SYNOVEX ONE FEEDLOT and control treatments. Implant reactions, when present, were described as nodules, thickening, swelling, fluid or fluid-filled, abscess or ruptured abscess, or scabs.

Table 12. Day 35 Implant Evaluation by Study Site for Steers (S) and Heifers (H) Fed in Confinement for Slaughter With or Without SYNOVEX ONE FEEDLOT Implants.

	ID-S	TX-S	KS-S	CO-S	SUM	ID-H	TX-H	KS-H	CO-H	SUM
Control										
Total Animals	90	90	72	88	340	90	90	71	90	341
Implant present	0	0	0	2*	2	0	0	0	0	0
Implant absent	90	90	72	86	338	90	90	71	90	341
Implant reaction	5	0	0	0	5	2	0	0	0	2
SYNOVEX ONE FEEDLOT										
Total Animals	90	90	72	88	340	90	90	72	89	341
Implant present	89	90	68	88*	335	88	90	70	87	335
Implant absent	1	0	4	0	5	2	0	2	2	6
Implant reaction	0	1	9	1	11	3	2	5	0	10

Average daily gain and G/F results for steers and heifers at each site are provided in Table 13.

Table 13. Initial and Final Weights, Average Daily Gain (ADG), Dry Matter Intake (DMI), and Gain to Feed Ratio (G/F) by Study Site for Steers (S) and Heifers (H) Fed in Confinement for Slaughter With or Without SYNOVEX ONE FEEDLOT Implants.

	ID-S	TX-S	KS-S	CO-S	ID-H	TX-H	KS-H	CO-H
Control								
Initial Weight, lb	700.0	661.5	572.8	684.4	679.7	627.1	552.2	686.2
Final Weight, lb	1289.8	1207.3	1184.1	1306.1	1242.9	1145.3	1102.8	1243.2
ADG, lb/d	2.95	2.89	3.03	3.12	2.82	2.71	2.71	2.78
DMI, lb/d	19.27	17.68	18.33	18.62	18.75	16.95	17.15	17.53
G/F (ADG/DMI)	0.153	0.164	0.166	0.168	0.150	0.161	0.158	0.159
SYNOVEX ONE FEEDLOT								
Initial Weight, lb	699.2	663.2	572.6	685.1	680.8	626.1	554.0	686.1
Final Weight, lb	1415.1	1286.2	1259.9	1403.3	1309.4	1186.2	1175.9	1320.0
ADG, lb/d	3.56	3.27	3.38	3.58	3.14	2.92	3.09	3.20
DMI, lb/d	20.75	18.53	19.09	18.99	19.35	17.37	18.22	18.66
G/F (ADG/DMI)	0.172	0.177	0.177	0.189	0.162	0.168	0.170	0.172

g. Adverse Reactions: Some animals exhibited mild implantation site reactions such as swelling, abscess or nodules. These reactions were observed in less than 3.2% of animals on these studies. There were no adverse effects on animal health attributable to the drug.

h. Conclusions: For steers and heifers fed in confinement for slaughter, SYNOVEX ONE FEEDLOT was effective for significantly ($P \leq 0.05$) increasing rate of weight gain and improving feed efficiency for up to 200 days over that of control animals. SYNOVEX ONE FEEDLOT reduced marbling scores and USDA quality grade, and therefore, the following statement is included on the labeling for SYNOVEX ONE FEEDLOT: *"NOTE: Studies have demonstrated that the administration of SYNOVEX ONE FEEDLOT can result in decreased marbling scores when compared to non-implanted steers and heifers."*

2. Dose confirmation study in pasture steers and heifers

a. Title: "Effects of Synovex Plus LA Implants on Performance of Steers on Pasture" and "Effects of Synovex Plus LA Implants on Performance of Heifers on Pasture"

b. Investigators and Locations:

Table 14. Study Site Numbers, Locations, and Investigators.

0738-B-US-12-08 (steers) and 0738-B-US-16-07 (heifers) Johnson Research LLC, Parma, ID Jenifer Edmonds, DVM, PhD
0738-B-US-13-08 (steers) and 0738-B-US-17-07 (heifers) L.L. Smith Research and Development Farm, Readstown, WI Larry L. Smith, DVM[1]
0738-B-US-14-08 (steers) Jason Salchow Farm, Billings, MO Thomas Yazwinski, PhD[2]
0738-B-US-18-07 (heifers) University of Arkansas, Fayetteville, AR Thomas Yazwinski, PhD[2]
0738-B-US-15-08 (steers) and 0738-B-US-19-07 (heifers) Sorensen Ranch, Wells, NV Breck Hunsaker, DVM, PhD

[1] Investigator address: L.L. Smith Research and Development, Inc., Lodi, WI
[2] Investigator address: University of Arkansas, Fayetteville, AR

c. Study Design:

(1) Objective: To evaluate the clinical effectiveness of SYNOVEX ONE GRASS implants (referred to as SYNOVEX PLUS Long-Acting during the study) for increasing rate of weight gain for up to 200 days in steers and heifers grazing pastures.

(2) Study Animals: A total of 560 steers weighing on average 518 pounds were enrolled in the steer study. A total of 560 heifers weighing on average 506 pounds were enrolled in the heifer study. Steers and

heifers were acquired from major cattle-producing regions of the United States and breeds were typical of the U.S. beef industry.

(3) Experimental design: The studies were conducted at four independent sites. The studies were masked, negative-controlled studies that utilized a complete randomized block design at each site. Animal was the experimental unit. Personnel who collected study data (other than data related to drug administration and accountability) were masked to treatments.

(4) Treatment Groups: The two groups used in these studies were the treatment group (SYNOVEX ONE GRASS, 150 mg TBA and 21 mg EB in a 6-pellet coated ear implant) and a negative control group (sham implant). Within each study and study site, 70 steers or heifers were randomly assigned to one of the two treatment groups except at the Nevada site, where 69 and 71 heifers were randomly assigned to the SYNOVEX ONE GRASS and control treatment groups, respectively.

(5) Drug Administration: Ears of incoming cattle were palpated for pre-existing implants 14 days before experimental administration. Any pre-existing implants were removed. Study treatment implants were placed subcutaneously in the middle third of the back of the ear in treated steers and heifers. Control steers and heifers were sham implanted (implant needle inserted in ear but no implant was deposited) using identical techniques to the implanted steers and heifers.

(6) Measurements and Observations: Individual animal weights were measured twice before treatment and averaged to obtain the initial starting weight. Interim individual animal weights were collected approximately every 42 days following treatment. At the completion of the study, individual animal weights were collected on two consecutive days and averaged to obtain the final weight. Weight gained was computed as the difference between final body weight and initial body weight. Animals removed early were included in average daily gain (ADG) calculations based upon their last recorded body weight. The pivotal parameter was computed for each animal as follows:

Average daily gain (ADG) = weight gain ÷ days on study

To evaluate implant safety, the implant sites on ears of all steers and heifers were evaluated on Day 42 to document ear abscesses, ear inflammation, or other ear abnormalities, and the presence of an implant. In addition, all steers and heifers were observed daily during the study for abnormalities. Illnesses, injuries, and medical treatments were documented and summarized.

d. Statistical Analysis: The steer and heifer studies were analyzed separately. For each study, the primary variable, ADG, was analyzed by mixed model analysis. Treatment was a fixed effect in the model. For each study, study site and the study site by treatment interaction were random effects.

e. Pooled Results:

The mean duration of the studies was 202 days for steers and 202 days for heifers, with variation in study duration at each site as shown in Table 15.

Table 15. Critical Study Dates by Study Site for Pasture Steers and Heifers.

	Study start	Study end	Duration, d
Activity	Treatment and second initial weight	Second final weight	
Steers			
ID	May 5, 2008	November 23, 2008	202
WI	April 30, 2008	November 18, 2008	202
MO	April 25, 2008	November 12, 2008	201
NV	May 1, 2008	November 19, 2008	202
Heifers			
ID	May 5, 2008	November 23, 2008	202
WI	April 30, 2008	November 18, 2008	202
AR	April 23, 2008	November 11, 2008	202
NV	May 1, 2008	November 19, 2008	202

The numbers of steers and heifers enrolled, removed, or completing the studies are shown in Table 16. A total of 547 pasture steers completed the study. Eight control steers and 5 treated steers were removed prior to the end of the treatment period. Of these removals, six control steers and four treated steers were due to death. A total of 556 feedlot heifers completed the study. Three control heifers and one treated heifer were removed prior to the end of the treatment period. Of these, two control heifers and zero treated heifers were due to death. All of the removals or deaths were for reasons unrelated to treatment and there was no pattern of removals based on treatment group. For greater detail on health observations and reasons for animal removal, see Individual Site Details (below).

Table 16. Accountability by Study Site for Pasture Steers and Heifers With or Without SYNOVEX ONE GRASS Implants.

	Control Enrolled	Control Removed (deaths)	Control Completed	SYNOVEX ONE GRASS Enrolled	SYNOVEX ONE GRASS Removed (deaths)	SYNOVEX ONE GRASS Completed
Steers						
ID	70	1 (1)	69	70	1 (1)	69
WI	70	1 (1)	69	70	1 (1)	69
MO	70	4 (2)	66	70	3 (2)	67
NV	70	2 (2)	68	70	0 (0)	70
SUM	280	8 (6)	272	280	5 (4)	275
Heifers						
ID	70	0 (0)	70	70	1 (0)	69
WI	70	2 (1)	68	70	0 (0)	70
AR	70	0 (0)	70	70	0 (0)	70
NV	71	1 (1)	70	69	0 (0)	69
SUM	281	3 (2)	278	279	1 (0)	278

Average daily gain results for steers and heifers are provided in Table 17. Two control steers and three treated steers were removed prior to obtaining an interim body weight. Two control heifers were removed prior to obtaining an interim body weight. These animals were excluded from the rate of weight gain outcomes. In steers, ADG was increased (P = 0.0057) in the SYNOVEX ONE GRASS group as compared to the negative control group. In heifers, ADG was increased (P = 0.0037) in the SYNOVEX ONE GRASS group as compared to the negative control group.

Table 17. Pooled Statistical Analysis - LSMeans for Average Daily Gain (ADG) of Pasture Steers and Heifers With or Without SYNOVEX ONE GRASS Implants.

Variables	Control	SYNOVEX ONE GRASS	SEM	p-value
Steers, ADG (lb/d)	1.45	1.70	0.184	0.0057
Heifers, ADG (lb/d)	1.41	1.57	0.128	0.0037

f. Individual Site Details

Steers and heifers were given preventative treatments reflective of current industry practices. These included USDA-licensed vaccines against *Clostridial* species, *Moraxella bovis* (pinkeye), bovine rhinotracheitis, *Pasteurella haemaolytica*, bovine viral diarrhea, parainfluenza, and bovine syncytial virus, FDA-approved injectable dewormers, and/or topical EPA-registered insecticides. At all sites, animals were allowed to graze forage ad libitum throughout the study. Supplemental mineral mix and water was available ad libitum. All animals were maintained together on the same pasture area and rotated to a new pasture area to maintain optimum grazing and weight gain. Steers and heifers were maintained on pastures as shown in Table 18.

Table 18. Pasture Type, Rotation Schedule, and Supplemental Forage Used at Each Study Site for Pasture Steers and Heifers.

	Pasture Type	Rotation Schedule	Supplemental Forage
ID	native grasses, fescue, and clover that were typical for the Mountain West region	1 to 5 d	none
WI	Sudan grass, Kura clover, orchard grass, alfalfa, red clover, bluegrass, and bromegrass that were typical for the Upper Midwest region	1 to 2 d	mixed grass and legume baleage or haylage after September 5, 2008
MO	clover, fescue, and orchard grass that were typical for the Midwest region	2 to 3 d	mixed grass hay bales after August 29, 2008
AR	50% fescue and 50% Bermuda grasses that were typical for the Midwest region	15 to 28 d	none
NV	sedges, wiregrass, saltgrass, wild rye, creeping wild rye, Kentucky bluegrass, meadow barley, and western wheatgrass that were typical for the Mountain West region	7 d	alfalfa hay after November 14, 2008

No treatment-related adverse events were observed during the study. In steers, the 13 removals (10 of those due to death or euthanasia) were due to rear limb instability (3), bloat (3), drowning (1), respiratory problems (1), lung abscess (1), neurological disorder (1), clostridium infection (1), and an undetermined cause (2). In heifers, the four removals (two of those due to death or euthanasia) were due to injury (2), bloat (1), and chronic weight loss and suspected pneumonia (1).

Table 19. Abnormal Health Observations by Study Site for Pasture Steers (S) and Heifers (H) With or Without SYNOVEX ONE GRASS Implants.

	ID-S	WI-S	MO-S	NV-S	SUM	ID-H	WI-H	AR-H	NV-H	SUM
Total Animals with any Abnormal Observation										
Control	4	3	27	24	58	6	6	5	35	52
SYNOVEX ONE GRASS	9	9	26	20	64	8	7	7	35	57
Observations By System[1]										
Control										
Musculoskeletal	0	0	7	13	20	1	0	0	33	34
Eye	2	2	19	11	34	4	4	2	3	13
Respiratory	0	1	3	5	9	0	0	0	2	2
Digestive tract	0	0	5	0	5	0	1	0	0	1
Systemic	1	0	5	3	9	0	1	1	1	3
Other	1	0	2	1	4	1	1	3	0	5
SYNOVEX ONE GRASS										
Musculoskeletal	1	0	10	9	20	2	0	1	29	32
Eye	4	7	14	9	34	3	7	1	6	17
Respiratory	1	0	1	3	5	1	0	0	3	4
Digestive tract	0	2	3	0	5	1	0	0	0	1
Systemic	1	0	5	0	6	2	0	0	0	2
Other	2	0	1	1	4	1	0	6	1	8

[1] A single animal may have had multiple observations by system

All abnormal health observations during the studies, including those that resulted in removal or death, are shown in Table 19. There were 58 control steers and 64 treated steers with abnormal health observations, and 52 control heifers and 57 treated heifers with abnormal health observations. A single animal may have had multiple observations by system. Generally, abnormal health observations were infrequent and were a result of common conditions in pasture cattle. Some other health observations were not common conditions, but occurred with a low frequency. The most common observations included disorders of the musculoskeletal (primarily lameness or foot rot), eye (primarily pinkeye conjunctivitis), respiratory tract (primarily pneumonia and other respiratory disease), digestive tract (primarily bloat or diarrhea), or other systems (skin dermatitis or abscess, or neurological disorders), or systemic disorders (primarily lethargy or loss of condition). The observations of lameness at the Nevada site were due to foot rot and were likely related to the wet (sub-irrigated) pastures in which the animals were maintained. The incidence of foot rot was evenly distributed among treatment groups,

and likely had little impact on the outcome of the study. There was no pattern of abnormal health observations based on treatment group.

Implant site evaluations determined by palpation on Day 42 are shown in Table 20. Generally, implants were not detected in control animals, and were generally not missing in SYNOVEX ONE GRASS animals. At the Nevada steer site and the Wisconsin heifer site, an implant was detected in one control animal. Study records did not support that the presence of an implant in these animals had any impact on the outcome of the studies. There were few reported injection site reactions and few differences between the SYNOVEX ONE GRASS and control treatments. Implant reactions, when present, were described as scar tissue, mild scar, mild inflammation, fluid accumulation, fibrous reaction, nodule, or fibrous nodule.

Table 20. Day 42 Implant Evaluation by Study Site for Pasture Steers (S) and Heifers (H) With or Without SYNOVEX ONE GRASS Implants.

	ID-S	WI-S	MO-S	NV-S	SUM	ID-H	WI-H	AR-H	NV-H	SUM
Control										
Total Animals	69	70	70	69	278	70	69	70	70	279
Implant Present	0	0	0	1	1	0	1	0	0	1
Implant Absent	69	70	70	68	277	70	68	70	70	278
Implant Reaction	4	0	1	2	7	1	0	1	2	4
SYNOVEX ONE GRASS										
Total Animals	69	69	69	70	277	70	70	70	69	279
Implant Present	69	69	67	64	269	67	70	69	68	274
Implant Absent	0	0	2	6	8	3	0	1	1	5
Implant Reaction	0	0	5	2	7	2	0	0	1	3

Average daily gains for steers and heifers at each site are in Table 21.

Table 21. Average Daily Gain by Study Site for Pasture Steers (S) and Heifers (H) With or Without SYNOVEX ONE GRASS Implants.

	ID-S	WI-S	MO-S	NV-S	ID-H	WI-H	AR-H	NV-H
Control								
Initial Weight, lb	606.2	474.5	574.6	416.0	576.6	452.5	553.3	442.2
Final Weight, lb	945.3	776.9	758.5	763.2	877.9	702.0	769.9	776.7
Average Daily Gain, lb/d	1.68	1.49	0.90	1.72	1.49	1.41	1.07	1.66
SYNOVEX ONE GRASS								
Initial Weight, lb	607.6	475.5	575.6	416.6	569.5	453.5	564.7	431.0
Final Weight, lb	1017.1	817.4	819.3	795.1	909.4	737.8	804.4	791.8
Average Daily Gain, lb/d	2.03	1.69	1.20	1.87	1.68	1.63	1.19	1.79

g. Adverse Reactions: Some animals exhibited mild implantation site reactions such as inflammation, scars or nodules. These reactions were observed in less than 2.5% of animals on these studies. There were no adverse effects on animal health attributable to the drug.

h. Conclusions: For pasture steers and heifers, SYNOVEX ONE GRASS was effective for significantly ($P \leq 0.05$) increasing rate of weight gain for up to 200 days over that of control animals.

III. TARGET ANIMAL SAFETY:

CVM did not require target animal safety studies for this approval. The target animal safety for SYNOVEX ONE FEEDLOT relied on information used for the previous original and supplemental approvals of NADA 141-043 for SYNOVEX PLUS, the uncoated product that forms the core of SYNOVEX ONE. Refer to the original and supplemental approval FOI Summaries for NADA 141-043 dated February 22, 1996, and September 30, 1998, for information supporting the target animal safety in steers and heifers fed in confinement for slaughter, respectively. These studies also support the target animal safety of the lower dose SYNOVEX ONE GRASS implant. Furthermore, the target animal safety of SYNOVEX ONE FEEDLOT and SYNOVEX ONE GRASS were evaluated under intended use conditions in the dose confirmation effectiveness studies (see Section II.B above). There were no animal safety concerns raised by the evaluation of animal health data in these studies. Taken together, the target animal safety studies cited under NADA 141-043 and the animal health data from the effectiveness studies support the current new animal drug application for steers and heifers fed in confinement for slaughter and pasture steers and heifers.

Because CVM relied on the target animal safety of SYNOVEX PLUS for this approval, target animal safety warnings required for the labeling of SYNOVEX PLUS were also required for the labeling of SYNOVEX ONE FEEDLOT and SYNOVEX ONE GRASS. These include warnings that bulling, vaginal and rectal prolapse, udder development, ventral edema and elevated tailheads have occasionally been reported in treated heifers. Product labeling also warns against the use of this product in veal calves, and dairy and replacement heifers.

IV. HUMAN FOOD SAFETY:

A. Antimicrobial Resistance:

SYNOVEX ONE FEEDLOT and SYNOVEX ONE GRASS (trenbolone and estradiol extended release implant) are not known to have antimicrobial properties; additionally, SYNOVEX ONE FEEDLOT and SYNOVEX ONE GRASS implants have not been shown to impact antimicrobial resistance among bacterial populations. Therefore, at this time, the agency does not think that the use of SYNOVEX ONE FEEDLOT implants to increase rate of weight gain and improve feed efficiency in steers and heifers fed in confinement for slaughter or the use of SYNOVEX ONE GRASS implants to increase rate of weight gain in pasture steers and heifers (slaughter, stocker and feeder) will impact antimicrobial resistance among bacteria of public health concern in or on treated animals.

B. Impact of Residues on Human Intestinal Flora:

Residues and metabolites of SYNOVEX ONE FEEDLOT and SYNOVEX ONE GRASS implants are not known to have antimicrobial properties; additionally, residues and metabolites of SYNOVEX ONE FEEDLOT and SYNOVEX ONE GRASS implants have not been shown to impact bacterial populations. Therefore, at this time, the agency does not think that residues and metabolites of SYNOVEX ONE FEEDLOT and SYNOVEX ONE GRASS implants in or on edible food products from treated animals will impact the intestinal flora of human consumers.

C. Toxicology:

The FOI Summary for the original approval of NADA 141-043 dated February 22, 1996, contains a summary of all toxicology studies and information. The Acceptable Daily Intake (ADI) for total residues of trenbolone is 0.4 micrograms/kg/d (21 CFR 556.739(a)).

Estradiol is regulated on the basis of allowable incremental increases (21 CFR 556.240). No residues of estradiol, resulting from the use of estradiol or any of the related esters, are permitted in excess of the following increments above the concentrations of estradiol naturally present in untreated animals: in uncooked edible tissues of heifers, steers, and calves, (1) 120 parts per trillion for muscle; (2) 480 parts per trillion for fat; (3) 360 parts per trillion for kidney; and (4) 240 parts per trillion for liver.

D. Residue Chemistry:

1. Summary of Residue Chemistry Studies

CVM did not require residue chemistry studies for this approval. In addition to the residue chemistry data summarized in the FOI Summary for the original approval of NADA 141-043 dated February 22, 1996, data provided in Study 0738-B-US-2-98 (summarized in Section II.A.3. above) demonstrate that SYNOVEX ONE implants have a similar pharmacokinetic profile to SYNOVEX PLUS implants.

2. Target Tissue and Marker Residue

Neither a target tissue nor a marker residue assignment is needed for TBA (see the FOI Summary for the original approval of NADA 141-043 dated February 22, 1996).

A specific target tissue is not identified for residues of estradiol. Allowable incremental increases for estradiol residues are assigned for each of the edible tissues.

3. Tolerance(s)

A tolerance for TBA in uncooked edible tissues of cattle is not needed (21 CFR 556.739).

Residues of estradiol are regulated on the basis of the codified allowable incremental increases (21 CFR 556.240).

4. Withdrawal Period and Milk Discard Time

Zero day withdrawal is assigned (see the FOI Summary for the original approval of NADA 141-043 dated February 22, 1996).

E. Analytical Method for Residues:

A regulatory analytical method is not required (see the FOI Summary for the original approval of NADA 141-043 dated February 22, 1996).

V. USER SAFETY:

The product labeling contains the following information regarding safety to humans handling, administering, or exposed to SYNOVEX ONE FEEDLOT or SYNOVEX ONE GRASS:

NOT FOR USE IN HUMANS. FOR ANIMAL USE ONLY. Keep this and all drugs out of the reach of children.

VI. AGENCY CONCLUSIONS:

The data submitted in support of this NADA satisfy the requirements of section 512 of the Federal Food, Drug, and Cosmetic Act and 21 CFR part 514. The data demonstrate that SYNOVEX ONE FEEDLOT, when used according to the label, is safe and effective for increased rate of weight gain and improved feed efficiency for up to 200 days in steers and heifers fed in confinement for slaughter. The data demonstrate that SYNOVEX ONE GRASS, when used according to the label, is safe and effective for increased rate of weight gain for up to 200 days in pasture steers and heifers (slaughter, stocker and feeder). Additionally, data demonstrate that residues in food products derived from species treated with SYNOVEX ONE FEEDLOT or SYNOVEX ONE GRASS will not represent a public health concern when the product is used according to the label.

A. Marketing Status:

This product can be marketed over-the-counter (OTC) because the approved labeling contains adequate directions for use by laypersons and the conditions of use prescribed on the labeling are reasonably certain to be followed in practice.

B. Exclusivity:

SYNOVEX ONE FEEDLOT and SYNOVEX ONE GRASS, as approved in our approval letter, qualify for THREE years of marketing exclusivity beginning as of the date of our approval letter. These drugs qualify for exclusivity under section 512(c)(2)(F)(ii) of the Federal Food, Drug, and Cosmetic Act because the sponsor submitted an original NADA that contains new studies that demonstrate effectiveness of SYNOVEX ONE FEEDLOT and SYNOVEX ONE GRASS.

C. Patent Information:

For current information on patents, see the Animal Drugs @ FDA database or the Green Book on the FDA CVM internet website.