Date of Approval: May 20, 2005

FREEDOM OF INFORMATION SUMMARY

ORIGINAL NEW ANIMAL DRUG APPLICATION

NADA 141-220

CYDECTIN (moxidectin) Injectable Solution for Beef and Nonlactating Dairy Cattle

"for the treatment and control of internal and external parasites of cattle"

Sponsored by:
Fort Dodge Animal Health
Division of Wyeth

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1. GENERAL INFORMATION

A. File Number:	NADA 141-220
B. Sponsor:	Fort Dodge Animal Health Division of Wyeth 800 Fifth St. NW. Fort Dodge, IA 50501 Drug Labeler Code: 000856
C. Established Name:	Moxidectin
D. Proprietary Name:	CYDECTIN Injectable Solution for Beef and Nonlactating Dairy Cattle
E. Dosage Form:	Sterile injectable solution
F. How Supplied:	50 mL, 200 mL, and 500 mL polyethylene bottles
G. How Dispensed:	OTC
H. Amount of Active Ingredients:	10 mg moxidectin per mL
I. Route of Administration:	Subcutaneous injection
J. Species/Class:	Beef and Nonlactating Dairy Cattle
K. Recommended Dosage:	1 mL solution for each 110 pound (50 kg) body weight to provide 0.2 mg moxidectin/2.2 pound (1 kg) body weight
L. Pharmacological Category:	Antiparasitic

M. Indications: CYDECTIN Injectable when administered at the recommended dose level of 0.2 mg/2.2 lb (0.2 mg/kg) body weight is effective in the treatment and control of the following internal and external parasites of cattle:

Gastrointestinal Roundworms

Ostertagia ostertagi – Adults and inhibited L_4
Haemonchus placei Adults
Trichostrongylus axei – Adults
Trichostrongylus colubriformis – L_4
Cooperia oncophora – Adults
Cooperia punctata – Adults and L_4
Cooperia surnabada – Adults and L_4
Oesophagostomum radiatum – Adults and L_4
Trichuris spp. – Adults

Lungworms
Dictyocaulus viviparus – Adults and L_4

Cattle Grubs
Hypoderma bovis
Hypoderma lineatum

Mites
Psoroptes ovis (Psoroptes communis var. *bovis)*

Lice
Linognathus vituli
Solenopotes capillatus

Persistent Activity: CYDECTIN Injectable has been proven to effectively protect cattle from reinfection with *Dictyocaulus viviparus* and *Oesophagostomum radiatum* for 42 days after treatment, *Haemonchus placei* for 35 days after treatment, and *Ostertagia ostertagi* and *Trichostrongylus axei* for 14 days after treatment.

2. EFFECTIVENESS

A. Dosage Characterization

An earlier, aqueous-based injectable formulation of moxidectin has been extensively tested. Effectiveness studies with that formulation, evaluating doses of 0.1, 0.2, 0.3, and 0.4 mg moxidectin/kg body weight, demonstrated that the optimal dose level for the treatment and control of both endoparasites and ectoparasites of cattle is 0.2 mg moxidectin/kg body weight. A series of pre-clinical, non-pivotal effectiveness trials was conducted to directly compare the effectiveness of the present moxidectin 1% nonaqueous injectable formulation and the original aqueous formulation. In controlled effectiveness studies in cattle with naturally acquired helminth burdens, both the nonaqueous and the aqueous injectable formulations of moxidectin were effective against several species of internal parasites found in the studies.

The design of the studies conducted to support the label claims for US registration of the nonaqueous injectable formulation was based on the dose for the aqueous injectable formulation established outside of the US and the results of the non-pivotal effectiveness studies. Since the nonaqueous formulation did not increase the potency of moxidectin against the dose-limiting parasites, evaluating dose levels less than 0.2 mg moxidectin/kg body weight would not be beneficial. Therefore, the pivotal effectiveness trials with the nonaqueous injectable formulation were conducted with two dose levels of moxidectin: 0.2 and 0.3 mg moxidectin/kg body weight. As documented in the subsequent sections of this Freedom of Information Summary (FOI), the results of these studies confirm that 0.2 mg moxidectin/kg body weight provides effectiveness against the endo- and ectoparasites listed on the label.

B. Substantial Evidence for Endoparasite Indications

Nine pivotal dose confirmation studies were conducted to evaluate the effectiveness of moxidectin 1% nonaqueous injectable solution against adult and larval stages of gastrointestinal nematodes and lungworms in cattle. All the trials were conducted in accordance with Good Clinical Practices as outlined in the VICH GL 9 Final Guidance (May 9, 2001). Three of these studies were conducted using cattle with naturally acquired nematode infections. Six trials utilized experimental infections superimposed on natural nematode burdens or administered to cattle free of nematodes prior to infection. Counts were transformed by a $Y=\log_{10}$ (count +1). A one-way analysis of variance (ANOVA) was used to analyze log transformed count data. The geometric treatment means were tested for significance at alpha = 0.05. Percent efficacy was determined by comparing the geometric mean worm counts of the treated group (T) with those of the control group (C) for each parasite present in adequate numbers in at least six control animals using Abbott's formula: % efficacy = [(C-T/C) X 100].

For an indication to be granted, a minimum of two studies was required that had the following: an adequate level of infection in at least 6 control animals, the treatment effect was significant at alpha = 0.05, and 90% or greater efficacy using geometric means for each genus species of parasite. If there were more than 2 studies with an adequate level of

infection, then the geometric means of the percent efficacy against a genus species of parasite from each study was added together and divided by the number of studies with that genus species of parasite. If this average was greater than or equal to 90%, then the claim was granted.

The individual trials are summarized below.

B.1 Study Number 0693-B-US-3-96

1) Type of Study: Dose confirmation study in cattle with naturally acquired nematode infections.

2) Investigators:

Edward G. Johnson, D.V.M.	Gary L. Zimmerman, D.V.M., Ph.D.
Johnson Research	Zimmerman Research
Parma, ID	Livingston, MT

3) General Design:

   a. Purpose: This study was designed to confirm the effective dose for the treatment and control of nematode infections in cattle.

   b. Animals: Thirty beef crossbred heifers weighing between 128 and 235 kg were blocked by pretreatment fecal egg count and randomly assigned within blocks to three treatment groups of 10 animals each.

   c. Housing: These cattle were maintained in outdoor pens by treatment group.

   d. Infection: All cattle had naturally-acquired nematode infections.

   e. Dosage Form: Moxidectin 1% nonaqueous injectable solution, 10 mg/mL.

   f. Route of Administration: Single subcutaneous injection in the neck region.

   g. Doses: Moxidectin 1% nonaqueous injectable solution was administered once on Day 0 at either 0.02 or 0.03 mL/kg body weight to provide 0.2 or 0.3 mg moxidectin/kg body weight.

   h. Controls: Injectable vehicle containing no moxidectin was administered at 0.03 mL/kg to provide 0 mg moxidectin/kg body weight.

   i. Test Duration: All cattle were necropsied 14 days post-treatment.

   j. Pertinent Measurements/Observations: Nematodes recovered from animals at necropsy were counted and identified.

4) Results: There was an adequate level of infection in at least 6 control animals against specific parasite species and stages. The percent efficacies are summarized in Table 2.1:

Table 2.1 Study Number 0693-B-US-3-96

Nematode Species and Stage	Geometric Mean in Controls	% Efficacy of Moxidectin at Dose Level:	
		0.2 mg/kg	0.3 mg/kg
Ostertagia ostertagi, adult	2185.0	100	100
Ostertagia ostertagi, EL_4	323.8	100	100
Trichostrongylus axei, adult	412.5	100	100
Cooperia oncophora, adult	564.1	87.5	89.9
Oesophagostomum radiatum, adult	34.2	100	100

5) Adverse Reactions: Two study animals (1 from the control group and 1 from the 0.3 mg/kg treatment group) had injection site swellings at necropsy.

B.2 Study Number 0693-B-US-6-97

1) Type of Study: Dose confirmation study in cattle with naturally acquired nematode infections.

2) Investigator: Thomas A. Yazwinski, Ph.D.
University of Arkansas
Fayetteville, AR

3) General Design:

a. Purpose: This study was designed to confirm the effective dose for the treatment and control of nematode infections in cattle.

b. Animals: Thirty cattle of mixed beef breeding weighing between 109 and 179 kg were blocked by pretreatment fecal egg count and randomly assigned within blocks to three treatment groups of 10 animals each.

c. Housing: These cattle were maintained in indoor pens by treatment group.

d. Infection: All cattle had naturally-acquired nematode infections.

e. Dosage Form: Moxidectin 1% nonaqueous injectable solution, 10 mg/mL.

f. Route of Administration: Single subcutaneous injection in the neck region.

g. Doses: Moxidectin 1% nonaqueous injectable solution was administered once on Day 0 at 0.02 or 0.03 mL/kg body weight to provide 0.2 or 0.3 mg moxidectin/kg body weight.

h. Controls: Injectable vehicle containing no moxidectin was administered at 0.03 mL/kg to provide 0 mg moxidectin/kg body weight.

i. Test Duration: All cattle were necropsied 12 to 15 days post-treatment.

j. Pertinent Measurements/Observations: Nematodes recovered from animals at necropsy were counted and identified.

4) Results: There was an adequate level of infection in at least 6 control animals against specific parasite species and stages. The percent efficacies are summarized in Table 2.2:

Table 2.2 Study Number 0693-B-US-6-97

Nematode Species and Stage	Geometric Mean in Controls	% Efficacy of Moxidectin at Dose Level:	
		0.2 mg/kg	0.3 mg/kg
Ostertagia ostertagi, adult	2424.4	>99.9	>99.9
Ostertagia ostertagi, EL_4	1674.3	100	100
Trichostrongylus axei, adult	388.7	>99.9	100
Cooperia oncophora, adult	1915.9	97.3	98.8
Cooperia punctata, adult	106.8	>99.9	>99.9
Cooperia surnabada, adult	318.2	95.5	97.2

5) Adverse Reactions: Five study animals (1 from the control group, 2 from the 0.2 mg/kg treatment group, and 2 from the 0.3 mg/kg treatment group) had local injection site reactions at necropsy.

B.3 Study Number 0693-B-US-8-97

1) Type of Study: Dose confirmation study in cattle with naturally acquired nematode infections.

2) Investigator: Craig R. Reinemeyer, D.V.M., Ph.D.
University of Tennessee
Knoxville, TN

3) General Design:

a. Purpose: This study was designed to confirm the effective dose for the treatment and control of nematode infections in cattle.

b. Animals: Thirty beef crossbred steer calves weighing between 191 and 274 kg were blocked by pretreatment fecal egg count and randomly assigned within blocks to three treatment groups of 10 animals each.

c. Housing: These cattle were maintained in separate pastures by treatment group.

d. Infection: All cattle had naturally-acquired nematode infections.

e. Dosage Form: Moxidectin 1% nonaqueous injectable solution, 10 mg/mL.

f. Route of Administration: Single subcutaneous injection in the neck region.

g. Doses: Moxidectin 1% nonaqueous injectable solution was administered once on Day 0 at 0.02 or 0.03 mL/kg body weight to provide 0.2 or 0.3 mg moxidectin/kg body weight.

h. Controls: Injectable vehicle containing no moxidectin was administered at 0.03 mL/kg to provide 0 mg moxidectin/kg body weight.

i. Test Duration: All cattle were necropsied 12-16 days post-treatment.

j. Pertinent Measurements/Observations: Nematodes recovered from animals at necropsy were counted and identified.

4) Results: There was an adequate level of infection in at least 6 control animals against specific parasite species and stages. The percent efficacies are summarized in Table 2.3:

Table 2.3 Study Number 0693-B-US-8-97

Nematode Species and Stage	Geometric Mean in Controls	% Efficacy of Moxidectin at Dose Level:	
		0.2 mg/kg	0.3 mg/kg
Ostertagia ostertagi, adult	943.2	>99.9	>99.9
Ostertagia ostertagi, EL_4	223.6	100	100

5) Adverse Reactions: Eleven study animals (3 from the 0.2 mg/kg treatment group, and 8 from the 0.3 mg/kg treatment group) had injection site lesions (fibrosis, firmness, or inflammation) at necropsy.

B.4 Study Number 0693-B-US-9-97

1) Type of Study: Dose confirmation study in cattle with a combination of experimentally induced and naturally acquired nematode infection.

2) Investigator: Sivaja Ranjan, B.V.Sc., Ph.D.
Fort Dodge Animal Health
Princeton, NJ

3) General Design:

a. Purpose: This study was designed to confirm the effective dose for the treatment and control of nematode infections in cattle.

b. Animals: Thirty beef crossbred steers weighing between 73 and 133 kg were blocked by pretreatment fecal egg count and randomly assigned within blocks to three treatment groups of 10 animals each.

c. Housing: These cattle were maintained in indoor pens by treatment group.

d. Infection: All cattle had an experimentally-induced lungworm infection superimposed on a naturally-acquired nematode infection.

e. Dosage Form: Moxidectin 1% nonaqueous injectable solution, 10 mg/mL.

f. Route of Administration: Single subcutaneous injection in the neck region.

g. Doses: Moxidectin 1% nonaqueous injectable solution was administered once on Day 0 at 0.02 or 0.03 mL/kg body weight to provide 0.2 or 0.3 mg moxidectin/kg body weight.

h. Controls: Injectable vehicle containing no moxidectin was administered at 0.03 mL/kg to provide 0 mg moxidectin/kg body weight.

i. Test Duration: All cattle were necropsied 14 to 16 days post-treatment.

j. Pertinent Measurements/Observations: Nematodes recovered from animals at necropsy were counted and identified.

4) Results: There was an adequate level of infection in at least 6 control animals against specific parasite species and stages. The percent efficacies are summarized in Table 2.4:

Table 2.4 Study Number 0693-B-US-9-97

Nematode Species and Stage	Geometric Mean in Controls	% Efficacy of Moxidectin at Dose Level:	
		0.2 mg/kg	0.3 mg/kg
Ostertagia ostertagi, adult	960.2	100	100
Trichostrongylus axei, adult	140.3	100	100
Haemonchus placei, adult	257.3	100	100
Cooperia oncophora, adult	1145.3	89.7	98.9
Cooperia surnabada, adult	224.6	93.7	99.2
Trichuris spp., adult	114.7	99.7	99.3
Dictyocaulus viviparus, adult	36.2	99.8	99.8

5) Adverse Reactions: Fifteen study animals (4 from the control group, 7 from the 0.2 mg/kg treatment group, and 4 from the 0.3 mg/kg treatment group) had palpable injection site swellings at necropsy.

B.5 Study Number 0693-B-US-20-98

1) Type of Study: Dose confirmation study in cattle with a combination of experimentally induced and naturally acquired nematode infection.

2) Investigator: Gil Myers, Ph.D.
Gil Myers, Ph.D., Inc
Magnolia, KY

3) General Design:

a. Purpose: This study was designed to confirm the effective dose for the treatment and control of nematode infections in cattle.

b. Animals: Thirty beef crossbred calves weighing between 163 and 329 kg were blocked on the basis of existing parasite infection (*Bunostomum* and/or *Oesophagostomum*) and randomly assigned within blocks to three treatment groups of 10 animals each. One group of animals was treated with Moxidectin 1% nonaqueous injectable solution and one group served as untreated control. The other group in this study was not relevant to the present NADA.

c. Housing: These cattle were maintained on separate pastures by treatment group.

d. Infection: All cattle had an experimentally-induced *Bunostomum* and *Oesophagostomum* infection superimposed on a naturally-acquired nematode infection.

e. Dosage Form: Moxidectin 1% nonaqueous injectable solution, 10 mg/mL.

f. Route of Administration: Single subcutaneous injection in the neck region.

g. Doses: Moxidectin 1% nonaqueous injectable solution was administered on Day 0 at 0.02 mL/kg body weight to provide 0.2 mg moxidectin/kg body weight.

h. Controls: Control animals were not treated.

i. Test Duration: All cattle were necropsied 14 to 17 days post-treatment.

j. Pertinent Measurements/Observations: Nematodes recovered from animals at necropsy were counted and identified.

4) Results: There was an adequate level of infection in at least 6 control animals against specific parasite species and stages. The percent efficacies are summarized in Table 2.5:

Table 2.5 Study Number 0693-B-US-20-98

Nematode Species and Stage	Geometric Mean in Controls	% Efficacy of Moxidectin at a Dose Level of 0.2 mg/kg
Haemonchus placei, adult	89.8	100
Ostertagia ostertagi, adult	126.8	100
Oesophagostomum radiatum, adult	117.0	100
Oesophagostomum radiatum, L_4	44.8	100

5) Adverse Reactions: No adverse reactions to treatment were noted.

B.6 Study Number 0693-B-US-30-98

1) Type of Study: Dose confirmation study in cattle with an experimentally-induced nematode infection.

2) Investigators:

Edward G. Johnson, D.V.M.	Gary L. Zimmerman, D.V.M., Ph.D.
Johnson Research	Zimmerman Research
Parma, ID	Livingston, MT

3) General Design:

a. Purpose: This study was designed to confirm the effective dose for the treatment and control of nematode infections in cattle.

b. Animals: Forty-eight Holstein steer calves weighing between 156 and 245 kg were randomly assigned to six treatment groups of eight animals each. Two groups of animals were treated with moxidectin 1% nonaqueous injectable solution and two groups served as concurrent controls. The other two groups in this study were not relevant to the present NADA.

c. Housing: These cattle were maintained in separate outdoor pens by treatment group after experimental infections.

d. Infection: All cattle were inoculated with a mixed population of L_3 larvae containing *Cooperia* spp. and *Trichostrongylus colubriformis* on Day 0.

e. Dosage Form: Moxidectin 1% nonaqueous injectable solution, 10 mg/mL.

f. Route of Administration: Single subcutaneous injection in the neck region.

g. Doses: Moxidectin 1% nonaqueous injectable solution was administered on Day 6 or Day 23 at 0.02 mL/kg body weight to provide 0.2 mg moxidectin/kg body weight.

h. Controls: Control animals were not treated.

i. Test Duration: Each treated group and a control group were necropsied 14 days post-treatment.

j. Pertinent Measurements/Observations: Nematodes recovered from animals at necropsy were counted and identified.

4) Results: There was an adequate level of infection in at least 6 control animals against specific parasite species and stages. The percent efficacies are summarized in Table 2.6:

Table 2.6 Study Number 0693-B-US-30-98

Nematode Species and Stage	Geometric Mean in Controls	% Efficacy of Moxidectin at 0.2 mg/kg
Treatment during Larval Stage:		
Cooperia punctata	2645.6	99.5
Cooperia surnabada	258.9	90.6
Trichostrongylus colubriformis	485.8	100.0
Treatment during Adult Stage:		
Cooperia oncophora	188.6	89.5
Cooperia punctata	840.3	90.8
Cooperia surnabada	144.4	96.2

5) Adverse Reactions: No adverse reactions to treatment were noted.

B.7 Study Number 0693-B-US-31-98

1) Type of Study: Dose confirmation study in cattle with an experimentally-induced nematode infection.

2) Investigators: Larry L. Smith, D.V.M.
Larry Smith Research & Development
Lodi, WI

3) General Design:

a. Purpose: This study was designed to confirm the effective dose for the treatment and control of nematode infections in cattle.

b. Animals: Thirty Holstein male calves weighing between 80 and 194 kg were randomly assigned to three treatment groups of ten animals each.

c. Housing: These cattle were maintained in separate outdoor pens by treatment group after experimental infections.

d. Infection: On Day 0 all cattle were inoculated with a mixed population of L_3 larvae containing *Dictyocaulus viviparus, Haemonchus placei,* and *Trichostrongylus axei.* In addition, there were L_3 infective larvae of *Ostertagia* spp., *Cooperia* spp., and *Oesophagostomum* spp. present in the inoculum.

e. Dosage Form: Moxidectin 1% nonaqueous injectable solution, 10 mg/mL.

f. Route of Administration: Single subcutaneous injection in the neck region.

g. Doses: Moxidectin 1% nonaqueous injectable solution was administered to one group on Day 5 and to a second group on Day 28 at 0.02 mL/kg body weight to provide 0.2 mg moxidectin/kg body weight.

h. Controls: Control animals were not treated.

i. Test Duration: All cattle were necropsied on Days 42 and 43, 14 to 15 days after the second group was treated.

j. Pertinent Measurements/Observations: Nematodes recovered from animals at necropsy were counted and identified.

4) Results: There was an adequate level of infection in at least 6 control animals against specific parasite species and stages. The percent efficacies are summarized in Table 2.7:

Table 2.7 Study Number 0693-B-US-31-98

Nematode Species and Stage	Geometric Mean in Controls	% Efficacy of Moxidectin at 0.2 mg/kg
Treatment during Larval Stage:		
Dictyocaulus viviparus	76.6	100
Treatment during Adult Stage:		
Ostertagia ostertagi, adult	2849.1	100
Trichostrongylus axei, adult	498.0	>99.9
Dictyocaulus viviparus, adult	75.7	100
Dictyocaulus viviparus, L_4	0.9	100

5) Adverse Reactions: No adverse reactions to treatment were noted.

B.8 Study Number 0863-B-US-22-97

1) Type of Study: Dose confirmation study in cattle with an experimentally-induced nematode infection.

2) Investigators: Craig R. Reinemeyer, D.V.M., Ph.D.
East Tennessee Clinical Research
Knoxville, TN

3) General Design:

a. Purpose: This study was designed to confirm the effective dose for the treatment and control of nematode infections in cattle.

b. Animals: Forty-eight Holstein steer calves weighing between 112 and 241 kg were randomly assigned to three treatment groups of eight animals each to be used to evaluate efficacy against larval parasite stages and another three treatment groups of eight animals each to be used to evaluate efficacy against adult parasite stages. Within each parasite stage, one group was treated with moxidectin 1% nonaqueous injectable solution and another served as untreated control. The other two groups in this study were not relevant to the present NADA.

c. Housing: These cattle were maintained in separate, partially covered pens by treatment group after experimental infections.

d. Infection: For evaluation of efficacy against larval parasite stages, calves were infected on Day -16 with *Trichuris* spp larvated eggs and *Bunostomum* spp and *Oesophagostomum* spp infective larvae. For evaluation of efficacy against adult parasite stages, calves were infected on Day -63 with *Trichuris* spp larvated eggs and on Day -35 with *Bunostomum* spp and *Oesophagostomum* spp infective larvae.

e. Dosage Form: Moxidectin 1% nonaqueous injectable solution, 10 mg/mL.

f. Route of Administration: Single subcutaneous injection in the neck region.

g. Doses: Moxidectin 1% nonaqueous injectable solution was administered at 0.02 mL/kg body weight to provide 0.2 mg moxidectin/kg body weight.

h. Controls: Control animals were not treated.

i. Test Duration: All cattle were necropsied 14 to 16 days after treatment.

j. Pertinent Measurements/Observations: Nematodes recovered from animals at necropsy were counted and identified.

4) Results: There was an adequate level of infection in at least 6 control animals against specific parasite species and stages. The percent efficacies are summarized in Table 2.8:

Table 2.8 Study Number 0693-B-US-22-97

Nematode Species and Stage	Geometric Mean in Controls	% Efficacy of Moxidectin at 0.2 mg/kg
Treatment during Larval Stage:		
Oesophagostomum radiatum	92.7	100
Treatment during Adult Stage:		
Oesophagostomum radiatum, adult	283.3	100
Trichuris spp., adult	120.9	99.8

5) Adverse Reactions: Two animals in the moxidectin treatment group had subcutaneous nodules at the injection site at the time of necropsy.

B.9 Study Number 0863-B-US-26-98

1) Type of Study: Dose confirmation study in cattle with an experimentally-induced nematode infection.

2) Investigators: Sivaja Ranjan, B.V.Sc., Ph.D.
Fort Dodge Animal Health
Princeton, NJ

3) General Design:

a. Purpose: This study was designed to confirm the effective dose for the treatment and control of nematode infections in cattle.

b. Animals: Forty-eight Holstein steer calves weighing between 112 and 172 kg were randomly assigned to six treatment groups of eight animals each. Two groups of animals were treated with moxidectin 1% nonaqueous injectable solution and two groups served as concurrent controls. The other two groups in this study were not relevant to the present NADA.

c. Housing: These cattle were maintained in separate indoor pens by treatment group with 4 animals per pen.

d. Infection: All cattle were inoculated with a mixed population of L_3 larvae containing *Cooperia* spp. and *Trichostrongylus colubriformis* on Day 0. In addition, half of the groups were also infected with *Dictyocaulus viviparus* infective larvae.

e. Dosage Form: Moxidectin 1% nonaqueous injectable solution, 10 mg/mL.

f. Route of Administration: Single subcutaneous injection in the neck region.

g. Doses: Moxidectin 1% nonaqueous injectable solution was administered on Day 5 or Day 26 at 0.02 mL/kg body weight to provide 0.2 mg moxidectin/kg body weight.

h. Controls: Control animals were not treated.

i. Test Duration: Groups infected with *D. viviparus* and treated on Day 5 were necropsied 19 to 20 days post-treatment. The groups treated on Day 26 were necropsied 14 to 15 days post-treatment.

j. Pertinent Measurements/Observations: Nematodes recovered from animals at necropsy were counted and identified.

4) Results: There was an adequate level of infection in at least 6 control animals against specific parasite species and stages. The percent efficacies are summarized in Table 2.9:

Table 2.9 Study Number 0693-B-US-26-98

Nematode Species and Stage	Geometric Mean in Controls	% Efficacy of Moxidectin at 0.2 mg/kg
Treatment during Larval Stage:		
Cooperia punctata	1772.7	99.9
Cooperia surnabada	1266.2	97.6
Trichostrongylus colubriformis	618.5	99.7
Dictyocaulus viviparus	47.0	100
Treatment during Adult Stage:		
Cooperia oncophora, adult	501.9	90.3
Cooperia punctata, adult	1067.5	99.8
Cooperia surnabada, adult	409.3	79.8

5) Adverse Reactions: No adverse reactions to treatment were noted.

C. Endoparasite Persistent Activity

Three pivotal studies were conducted in the United States to evaluate the persistent activity of moxidectin 1% nonaqueous injectable solution in preventing infection of treated cattle by third stage larvae of several species of endoparasites. The studies had similar designs with separate groups of cattle receiving a single challenge of third-stage nematode larvae 14, 21, 28, 35, or 42 days following treatment with moxidectin 1% nonaqueous injectable solution administered in its final formulation at a dose level of 0.2 mg/kg body weight. Counts were transformed by a $Y=\log_{10}$ (count +1). A one-way analysis of variance (ANOVA) was used to analyze log transformed count data. The geometric treatment means were tested for significance at alpha = 0.05. Percent efficacy was determined at each time point by comparing the geometric mean worm counts of the treated group (T) with those of the control group (C) for each parasite present in adequate numbers in at least six control animals using Abbott's formula: % efficacy = [(C-T/C) X 100].

For an indication to be granted, a minimum of two studies was required that had the following: an adequate level of infection in at least 6 control animals, the treatment effect was significant at alpha = 0.05, and 90% or greater efficacy using geometric means for each genus species of parasite. If there were more than 2 studies with an adequate level of infection, then the geometric means of the percent efficacy against a genus species of parasite from each study was added together and divided by the number of studies with that genus species of parasite. If this average was greater than or equal to 90%, then the claim was granted. The period of persistent activity was defined as the time during which the reduction in parasite counts was ≥ 90%.

The three trials are individually summarized below.

C.1 Study Number 0693-B-US-33-99

1) Type of Study: Dose confirmation study in cattle with induced gastrointestinal roundworm and lungworm infections.

2) Investigator: Thomas A. Yazwinski, Ph.D.
University of Arkansas
Fayetteville, AR

3) General Design:

   a. Purpose: This study was designed to determine the period of time following treatment during which cattle are protected against infection with nematodes commonly found in the lungs, abomasum, and large intestine.

   b. Animals: Forty-eight cattle (39 heifers and 9 steers) of mixed beef breeding weighing between 100 and 172 kg at the time of treatment were randomly assigned within sex to six treatment groups of eight animals each.

c. Housing: These cattle were maintained on concrete-floored pens by treatment group.

d. Infection: All cattle were inoculated with a mixed population of L_3 larvae containing *Haemonchus placei, Trichostrongylus axei, Oesophagostomum radiatum, Ostertagia* spp., and *Dictyocaulus viviparus* on Day 0.

e. Dosage Form: Moxidectin 1% nonaqueous injectable solution, 10 mg/mL.

f. Route of Administration: Single subcutaneous injection in the neck region.

g. Doses: Moxidectin 1% nonaqueous injectable solution was administered once at 0.02 mL/kg body weight to provide 0.2 mg moxidectin/kg body weight. Separate groups of cattle were treated 42, 35, 28, 21, and 14 days prior to experimental larval challenge on Day 0.

h. Controls: Control animals were not treated.

i. Test Duration: All cattle were necropsied 20 to 23 days after infection.

j. Pertinent Measurements/Observations: Nematodes recovered from animals at necropsy were counted and identified.

4) Results: The period of time for which treatment resulted in a minimum of a 90% or greater reduction in the number of parasites recovered in the treated animals for each nematode species present in at least six control animals is shown in Table 2.10:

Table 2.10 Study Number 0693-B-US-33-99

Nematode Species	Geometric Mean in Controls	Duration and Effectiveness of Protection	
		Duration (Days)	Efficacy (%)
Ostertagia ostertagi	371.0	21	93.2
Haemonchus placei	318.7	42	97.5
Trichostrongylus axei	33.8	14	93.5
Oesophagostomum radiatum	757.2	42	99.9
Dictyocaulus viviparus	11.6	42	95.8

5) Adverse Reactions: No adverse reactions to treatment were noted.

C.2 Study Number 0693-B-US-34-99

1) Type of Study: Dose confirmation study in cattle with induced gastrointestinal roundworm and lungworm infections.

2) Investigator: Bert E. Stromberg, Ph.D.
University of Minnesota
St. Paul, MN

3) General Design:

   a. Purpose: This study was designed to determine the period of time following treatment during which cattle are protected against infection with nematodes commonly found in the lungs, abomasum, and large intestine.

   b. Animals: Forty-eight Holstein steers weighing between 104 and 180 kg at the time of treatment were randomly assigned to six treatment groups of eight animals each.

   c. Housing: These cattle were maintained on concrete-floored pens by treatment group.

   d. Infection: All cattle were inoculated with a mixed population of L_3 larvae containing *Haemonchus placei, Trichostrongylus axei, Oesophagostomum radiatum, Ostertagia* spp., and *Dictyocaulus viviparus* on Day 0.

   e. Dosage Form: Moxidectin 1% nonaqueous injectable solution, 10 mg/mL.

   f. Route of Administration: Single subcutaneous injection in the neck region.

   g. Doses: Moxidectin 1% nonaqueous injectable solution was administered once at 0.02 mL/kg body weight to provide 0.2 mg moxidectin/kg body weight. Separate groups of cattle were treated 42, 35, 28, 21, and 14 days prior to experimental larval challenge on Day 0.

   h. Controls: Control animals were not treated.

   i. Test Duration: All cattle were necropsied 21 to 24 days after infection.

   j. Pertinent Measurements/Observations: Nematodes recovered from animals at necropsy were counted and identified.

4) Results: The period of time for which treatment resulted in a minimum of a 90% or greater reduction in the number of parasites recovered in the treated animals for each nematode species present in at least six control animals is shown in Table 2.11:

Table 2.11 Study Number 0693-B-US-34-99

Nematode Species	Geometric Mean in Controls	Duration and Effectiveness of Protection	
		Duration (Days)	Efficacy (%)
Ostertagia ostertagi	885.7	14	99.6
Haemonchus placei	1779.2	35	91.0
Trichostrongylus axei	197.0	14	97.5
Oesophagostomum radiatum	636.8	42	97.5
Dictyocaulus viviparus	10.9	42	89.6

5) Adverse Reactions: No adverse reactions to treatment were noted.

C.3 Study Number 0693-B-US-35-99

1) Type of Study: Dose confirmation study in cattle with induced gastrointestinal roundworm and lungworm infections.

2) Investigator: Sivaja Ranjan, B.V.Sc., Ph.D.
Fort Dodge Animal Health
Princeton, NJ

3) General Design:

a. Purpose: This study was designed to determine the period of time following treatment during which cattle are protected against infection with nematodes commonly found in the lungs, abomasum, and large intestine.

b. Animals: Forty-eight Holstein steers weighing between 131 and 204 kg at the time of treatment were randomly assigned to six treatment groups of eight animals each.

c. Housing: These cattle were maintained on concrete-floored pens by treatment group.

d. Infection: All cattle were inoculated with a mixed population of L_3 larvae containing *Haemonchus placei, Trichostrongylus axei, Oesophagostomum radiatum, Ostertagia* spp., and *Dictyocaulus viviparus* on Day 0.

e. Dosage Form: Moxidectin 1% nonaqueous injectable solution, 10 mg/mL.

f. Route of Administration: Single subcutaneous injection in the neck region.

g. Doses: Moxidectin 1% nonaqueous injectable solution was administered once at 0.02 mL/kg body weight to provide 0.2 mg moxidectin/kg body weight. Separate

groups of cattle were treated 42, 35, 28, 21, and 14 days prior to experimental larval challenge on Day 0.

h. Controls: Control animals were not treated.

i. Test Duration: All cattle were necropsied 27 to 30 days after infection.

j. Pertinent Measurements/Observations: Nematodes recovered from animals at necropsy were counted and identified.

4) Results: The period of time for which treatment resulted in a minimum of a 90% reduction in the number of parasites recovered in the treated animals for each nematode species present in at least six control animals is shown in Table 2.12:

Table 2.12 Study Number 0693-B-US-35-99

Nematode Species	Geometric Mean in Controls	Duration and Effectiveness of Protection	
		Duration (Days)	Efficacy (%)
Ostertagia ostertagi	1576.6	14	99.7
Haemonchus placei	494.7	35	91.1
Trichostrongylus axei	161.8	14	93.4
Oesophagostomum radiatum	1795.6	42	89.1
Dictyocaulus viviparus	43.2	42	93.0

5) Adverse Reactions: No adverse reactions to treatment were noted.

D. Ectoparasites

Nine pivotal trials were conducted to evaluate the effectiveness of moxidectin 1% nonaqueous injectable solution against ectoparasites on cattle, including mange mites (Sections D.1 – D.3), grubs (Sections D.4 – D.6), and lice (Sections D.7 – D.9).

Psoroptic Mange: Three pivotal dose confirmation trials were conducted to evaluate the effectiveness of moxidectin 1% nonaqueous injectable solution against cattle mange mites. All cattle were experimentally infested with *Psoroptes ovis* and the live mite counts were monitored throughout the trials. Moxidectin 1% nonaqueous injectable solution in its final formulation was administered at dose levels of 0.2 mg or 0.3 mg moxidectin/kg body weight. The efficacy was determined by comparing the arithmetic means of mite counts of treated cattle with those of control cattle. The trials are individually summarized in Sections D.1 - D.3.

D.1 Study Number 0693-B-US-4-96

1) Type of Study: Dose confirmation study in cattle with experimentally induced infestations with *Psoroptes ovis*.

2) Investigator: John Campbell, Ph.D.
Southwest Bio-Labs, Inc.
Las Cruces, NM

3) General Design:

   a. Purpose: This study was designed to confirm the effective dose for the treatment and control of *Psoroptes ovis* infestations on cattle.

   b. Animals: Twenty-seven Angus x Hereford crossbred heifers weighing between 159 and 296 kg were randomly assigned to three treatment groups of nine animals each based on pre-treatment mite counts.

   c. Housing: All animals were individually housed in separate stanchions.

   d. Infestation: Cattle were experimentally infested with *Psoroptes ovis* mites.

   e. Dosage Form: Moxidectin 1% nonaqueous injectable solution, 10 mg/mL.

   f. Route of Administration: Single subcutaneous injection in the neck region.

   g. Doses: Moxidectin 1% nonaqueous injectable solution was administered on Day 0 at doses of 0.1 or 0.15 mL/5 kg body weight to provide 0.2 or 0.3 mg moxidectin/kg body weight.

   h. Control: Injectable vehicle containing no moxidectin was administered on Day 0 at the dose of 0.15 mL/5 kg to provide 0 mg moxidectin/kg body weight.

   i. Test Duration: 56 days.

j. Pertinent Measurements/Observations: The numbers of live mites on each individual animal were determined on days 4, 7, 11, 14, 21, 28, 42, and 56 post-treatment except for controls which were removed from the study after Day 28 for humane reasons. Efficacy calculations for the treated groups for Days 42 and 56 were based on the mite counts of control group on Day 28.

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4) Results: Efficacy data against psoroptic mange are summarized in Table 2.13:

Table 2.13 Study Number 0693-B-US-4-96

Day	Arithmetic Mean Mite Counts in Control Animals	% Efficacy of Moxidectin at Dose Level:	
		0.2 mg/kg	0.3 mg/kg
4	244.8	92.7	95.0
7	208.1	99.4	100.0
11	245.4	100.0	100.0
14	431.8	100.0	100.0
21	440.4	100.0	100.0
28	196.1	100.0	100.0
42	--*	100.0	100.0
56	--	100.0	100.0

*All control animals remained infested with live mites up to Day 28 when they were removed from the study for humane reasons.

5) Adverse Reactions: Twenty-two percent of the animals showed minor injection site reaction through Day 7, after which time they were not monitored.

D.2 Study Number 0693-B-US-5-97

1) Type of Study: Dose confirmation study in cattle with experimentally induced infestations with *Psoroptes ovis*.

2) Investigator: William Barton, Ph.D.
CAVL
Amarillo, TX 79118

3) General Design:

a. Purpose: This study was designed to confirm the effective dose for the treatment and control of *Psoroptes ovis* infestations on cattle.

b. Animals: Thirty mixed breed beef heifers weighing between 154 and 225 kg were randomly assigned to three treatment groups of ten animals each based on pre-treatment mite counts.

c. Housing: All animals were individually housed in separate stanchions.

d. Infestation: Cattle were experimentally infested with *Psoroptes ovis* mites.

e. Dosage Form: Moxidectin 1% nonaqueous injectable solution, 10 mg/mL.

f. Route of Administration: Single subcutaneous injection in the neck region.

g. Doses: Moxidectin 1% nonaqueous injectable solution was administered on Day 0 at doses of 0.1 or 0.15 mL/5 kg body weight to provide 0.2 or 0.3 mg moxidectin/kg body weight.

h. Control: Injectable vehicle containing no moxidectin was administered on Day 0 at the dose of 0.15 mL/5 kg to provide 0 mg moxidectin/kg body weight.

i. Test: 56 days.

j. Pertinent Measurements/Observations: The numbers of live mites on each individual animal were determined on days 3, 7, 10, 14, 17, 21, 28, 42, and 56 post-treatment except for controls which were removed from the study after Day 28 for humane reasons. Efficacy calculations for the treated groups for Days 42 and 56 were based on the mite counts of control group on Day 28.

4) Results: Efficacy data against psoroptic mange are summarized in Table 2.14:

Table 2.14 Study Number 0693-B-US-5-97

Day	Arithmetic Mean Mite Counts in Control Animals	% Efficacy of Moxidectin at Dose Level:	
		0.2 mg/kg	0.3 mg/kg
3	82.4	45.2	42.5
7	74.6	97.3	99.1
10	86.8	99.3	99.9
14	135.9	100.0	100.0
17	129.8	100.0	100.0
21	78.6	100.0	100.0
28	65.0	100.0	100.0
42	--*	99.5	100.0
56	--	99.5	100.0

*All control animals remained infested with live mites up to Day 28 when they were removed from the study for humane reasons.

5) Adverse Reactions: Forty-five percent of treated animals had swelling at the injection site which was not observed for resolution.

D.3 Study Number 0693-B-US-13-97

1) Type of Study: Dose confirmation study in cattle with experimentally induced infestations with *Psoroptes ovis*.

2) Investigator: William Barton, Ph.D.
CAVL
Amarillo, TX

3) General Design:

a. Purpose: This study was designed to confirm the effective dose for the treatment and control of *Psoroptes ovis* infestations on cattle.

b. Animals: Thirty mixed breed beef heifers weighing between 158 and 235 kg were randomly assigned to three treatment groups of ten animals each based on pre-treatment mite counts.

c. Housing: All animals were individually housed in separate stanchions.

d. Infestation: Cattle were experimentally infested with *Psoroptes ovis* mites.

e. Dosage Form: Moxidectin 1% nonaqueous injectable solution, 10 mg/mL.

f. Route of Administration: Single subcutaneous injection in the neck region.

g. Doses: Moxidectin 1% nonaqueous injectable solution was administered on Day 0 at doses of 0.1 or 0.15 mL/5 kg body weight to provide 0.2 or 0.3 mg moxidectin/kg body weight.

h. Control: Injectable vehicle containing no moxidectin was administered on Day 0 at the dose of 0.15 mL/5 kg to provide 0 mg moxidectin/kg body weight.

i. Test Duration: 56 days.

j. Pertinent Measurements/Observations: The numbers of live mites on each individual animal were determined on days 7, 14, 21, 28, 35, 42, 49, and 56 post-treatment except for controls which were removed from the study after Day 28 for humane reasons. Efficacy calculations for the treated groups for Days 35, 42, 49, and 56 were based on the mite counts of control group on Day 28.

4) Results: Efficacy data against psoroptic mange are summarized in Table 2.15:

Table 2.15 Study Number 0693-B-US-13-97

Day	Arithmetic Mean Mite Counts in Control Animals	% Efficacy of Moxidectin at Dose Level:	
		0.2 mg/kg	0.3 mg/kg
7	102.7	9.2	80.7
14	99.9	97.9	97.6
21	112.9	99.7	100.0
28	164.1	99.9	100.0
35	--*	100.0	100.0
42	--	100.0	100.0
49	--	100.0	100.0
56	--	100.0	100.0

* All control animals remained infested with live mites up to day 28 when they were removed from the study for humane reasons.

5) Adverse Reactions: Transient minor injection site swelling was noticed in 20% of treated animals at Day 7. All swellings were resolved after Day 21.

Grubs: Three pivotal dose confirmation trials were conducted to evaluate the effectiveness of moxidectin 1% nonaqueous injectable solution against the migrating larval stages of grubs, *Hypoderma* spp., in cattle. All animals had naturally acquired grub infestations as determined by enzyme linked immunosorbent assay evaluations of *Hypoderma* antibody levels in blood. Each trial included three treatment groups of 10 or 15 animals each. One group of animals was maintained as placebo-treated control to determine the levels of grub infestation and identify the grub species present in the natural infestations. The remaining two groups received a single administration of the Moxidectin 1% nonaqueous injectable solution at either 0.2 or 0.3 mg moxidectin/kg body weight. The appearance of *Hypoderma* larvae was determined by the backline palpations at approximately two-week intervals throughout the trial. Live *Hypoderma* larvae were harvested when they had matured to the late 2nd or 3rd instar. Recovered larvae were counted and identified. Efficacy was determined by comparing the arithmetic mean of larvae from the treated group with that of the control group. The three trials are individually summarized in Section D.4 - D.6.

D.4 Study Number 0693-B-US-15-97

1) Type of Study: Dose confirmation study in cattle with naturally acquired grubs at the migrating larval stages.

2) Investigator: John E. Lloyd, Ph.D.
University of Wyoming
Laramie, WY

3) General Design:

a. Purpose: This study was designed to confirm the effective dose of moxidectin 1% nonaqueous injectable solution for the treatment and control of grub infestations in cattle.

b. Animals: Forty-five steers weighing between 160 and 278 kg were randomly assigned to three treatment groups of fifteen animals.

c. Housing: Treatment groups were maintained in separate outdoor pens from the day prior to treatment until 14 days post-treatment, at which time all animals were combined into a single pen.

d. Infestation: Cattle were naturally infested with *Hypoderma* spp.

e. Dosage Form: Moxidectin 1% nonaqueous injectable solution, 10 mg/mL.

f. Route of Administration: Single subcutaneous injection in the neck region.

g. Doses: Moxidectin 1% nonaqueous injectable solution was administered on Day 0 at doses of 0.02 or 0.03 mL/kg body weight to provide 0.2 or 0.3 mg moxidectin/kg body weight.

h. Control: Injectable vehicle containing no moxidectin was administered on Day 0 at the dose of 0.03 mL/kg to provide 0 mg moxidectin/kg body weight.

i. Test Duration: 200 days.

j. Pertinent Measurements/Observations: Backline palpations for the appearance of grub larvae were conducted between Days 56 and 200 at approximately 14 day intervals. The mature live larvae were collected and subsequently identified at each palpation time point.

4) Results: Efficacy data against *H. bovis* and *H. lineatum* are summarized in Table 2.16:

Table 2.16 Study Number 0693-B-US-15-97

Grub Species	Arithmetic Mean Grub Counts Control Animals	% Efficacy by Moxidectin at Dose Level:	
		0.2 mg/kg	0.3 mg/kg
H. bovis	11.8	100	100
H. lineatum	8.8	100	100

5) Adverse Reactions: Injection site swellings were noted in two animals (1 in the 0.2 mg/kg treatment group and 1 in the 0.3 mg/kg treatment group). These resolved by 21 days post-treatment.

D.5 Study Number 0693-B-US-16-97

1) Type of Study: Dose confirmation study in cattle with naturally acquired grubs at the migrating larval stages.

2) Investigator: John E. Lloyd, Ph.D.
University of Wyoming
Laramie, WY

3) General Design:

a. Purpose: This study was designed to confirm the effective dose of moxidectin 1% nonaqueous injectable solution for the treatment and control of grub infestations in cattle.

b. Animals: Forty-five heifers weighing between 144 and 242 kg were randomly assigned to three treatment groups of fifteen animals.

c. Housing: Treatment groups were maintained in separate outdoor pens from the day prior to treatment until 14 days post-treatment, at which time all animals were combined into a single pen.

d. Infestation: Cattle were naturally infested with *Hypoderma* spp.

e. Dosage Form: Moxidectin 1% nonaqueous injectable solution, 10 mg/mL.

f. Route of Administration: Single subcutaneous injection in the neck region.

g. Doses: Moxidectin 1% nonaqueous injectable solution was administered on Day 0 at doses of 0.02 or 0.03 mL/kg body weight to provide 0.2 or 0.3 mg moxidectin/kg body weight.

h. Control: Injectable vehicle containing no moxidectin was administered on Day 0 at the dose of 0.03 mL/kg to provide 0 mg moxidectin/kg body weight.

i. Test Duration: 200 days.

k. Pertinent Measurements/Observations: Backline palpations for the appearance of grub larvae were conducted between Days 56 and 200 at approximately 14 day intervals. The mature live larvae were collected and subsequently identified at each palpation time point.

4) Results: Efficacy against *H. bovis* could not be determined because no control animals were infested by *H. bovis* in this trial. Efficacy data against *H. lineatum* are summarized in Table 2.17.

Table 2.17 Study Number 0693-B-US-16-97

Grub Species	Arithmetic Mean Grub Counts Control Animals	% Efficacy by Moxidectin at Dose Level:	
		0.2 mg/kg	0.3 mg/kg
H. lineatum	8.7	100	100

5) Adverse Reactions: Hard swelling was noted at the injection site of 5 animals (two in the 0.2 mg/kg group, 2 in the control group, and one in the 0.3 mg moxidectin/kg group) at 7 days post-treatment. All swellings resolved by Day 21 post-treatment.

D.6 Study Number 0693-B-US-18-97

1) Type of Study: Dose confirmation study in cattle with naturally acquired grubs at the migrating larval stages.

2) Investigator: Larry L. Smith, D.V.M.
Larry Smith Research & Development, Inc.
Lodi, WI

3) General Design:

a. Purpose: This study was designed to confirm the effective dose of moxidectin 1% nonaqueous injectable for the treatment and control of grub infestations in cattle.

b. Animals: Thirty crossbred beef calves weighing between 145 and 353 kg were randomly assigned to three treatment groups of ten animals.

c. Housing: Treatment groups each were maintained in separate pens from the day prior to treatment until 31 days post-treatment, at which time all animals were combined into a single pen.

d. Infestation: Cattle were naturally infested with *Hypoderma* spp.

e. Dosage Form: Moxidectin 1% nonaqueous injectable solution, 10 mg/mL.

f. Route of Administration: Single subcutaneous injection in the neck region.

g. Doses: Moxidectin 1% nonaqueous injectable solution was administered on Day 0 at doses of 0.02 or 0.03 mL/kg body weight to provide 0.2 or 0.3 mg moxidectin/kg body weight.

h. Control: Injectable vehicle containing no moxidectin was administered on Day 0 at the dose of 0.03 mL/kg to provide 0 mg moxidectin/kg body weight.

i. Test Duration: 170 days.

j. Pertinent Measurements/Observations: Backline palpations for the appearance of grub larvae were conducted between Days 58 and 170 at an approximately 14 day intervals. The mature live larvae were collected and subsequently identified at each palpation time point.

4) Results: Efficacy against *H. lineatum* could not be determined because no control animals were infested by *H. lineatum* in this trial. Efficacy data against *H. bovis* are summarized in Table 2.18:

Table 2.18 Study Number 0693-B-US-18-97

Grub Species	Arithmetic Mean Grub Counts Control Animals	% Efficacy by Moxidectin at Dose Level:	
		0.2 mg/kg	0.3 mg/kg
H. bovis	2.8	100	100

5) Adverse Reactions: No adverse reactions to treatment were noted.

Lice: Three pivotal dose confirmation trials were conducted to evaluate the efficacy of moxidectin 1% nonaqueous injectable solution for the treatment and control of lice on cattle. All animals used in these studies had natural lice infestations. Each trial included three treatment groups of 10 animals each. One group was maintained as a placebo-treated control to monitor the natural progression of the lice infestation throughout the trial. The remaining two groups received the final formulation of moxidectin at levels providing either 0.2 or 0.3 mg moxidectin/kg body weight, dosed to individual animal weights. All treatments were administered as a single subcutaneous injection in the neck. Individual animal lice counts were made prior to treatment and at weekly intervals for eight weeks following treatment. Efficacy was calculated by comparing the arithmetic mean lice counts of the treated group with that of the control group. The three trials are individually summarized in Sections D.7 – D.9.

D.7 Study Number 0693-B-US-12-97

1) Type of Study: Dose confirmation study in cattle with naturally acquired lice infestation.

2) Investigator: Donald A. Rutz, Ph.D.
Cornell University
Ithaca, NY

3) General Design:

a. Purpose: This study was designed to confirm the effective dose of moxidectin 1% nonaqueous injectable solution for the treatment and control of lice infestations on cattle.

b. Animals: Thirty mixed-beef breed calves weighing between 127 and 262 kg were assigned to three treatment groups of ten animals each based on their *Solenopotes capillatus* counts on Day -1.

c. Housing: Treatment groups were maintained in three pens.

d. Infestation: Cattle were naturally infested with cattle lice.

e. Dosage Form: Moxidectin 1% nonaqueous injectable solution, 10 mg/mL.

f. Route of Administration: Single subcutaneous injection in the neck region.

g. Doses: Moxidectin 1% nonaqueous injectable solution was administered on Day 0 at doses of 0.02 or 0.03 mL/kg body weight to provide 0.2 or 0.3 mg moxidectin/kg body weight.

h. Control: Injectable vehicle containing no moxidectin was administered on Day 0 at the dose of 0.03 mL/kg to provide 0 mg moxidectin/kg body weight.

i. Test Duration: 56 days.

j. Pertinent Measurements/Observations: Lice on individual animals were counted and identified weekly from Days 7 to 56 post-treatment.

4) Results: Efficacy data against two lice species (*Linognathus vituli* and *Solenopotes capillatus*) are summarized in Table 2.19:

Table 2.19 Study Number 0693-B-US-12-97

Lice Species	Dose (mg/kg)	Arithmetic Mean Control Lice Counts and Percent Efficacy for Moxidectin Treatment on Trial Days							
		7	14	21	28	35	42	49	56
Solenopotes capillatus	0.0	208.9	159.6	161.8	145.4	136.1	111.9	103.0	95.7
	0.2	100	100	100	100	100	100	100	100
	0.3	100	100	99.6	99.6	99.4	99.6	99.6	99.8
Linognathus vituli	0.0	41.3	51.9	32.7	30.3	28.5	14.8	15.4	11.4
	0.2	100	100	100	100	100	100	100	100
	0.3	100	100	100	100	100	100	100	100

5) Adverse Reactions: No adverse reactions to treatment were noted.

D.8 Study Number 0693-B-US-17-97

1) Type of Study: Dose confirmation study in cattle with naturally acquired lice infestation.

2) Investigator: John E. Lloyd, Ph.D.
University of Wyoming
Laramie, WY

3) General Design:

a. Purpose: This study was designed to confirm the effective dose of moxidectin 1% nonaqueous injectable solution for the treatment and control of lice infestations on cattle.

b. Animals: Thirty steer and heifer beef calves weighing between 155 and 302 kg were assigned to three treatment groups of ten animals each based on their *Solenopotes capillatus* and/or *Linognathus vituli* counts on Day -1.

c. Housing: Animals were separated into two pens of five animals each per treatment group throughout the post-treatment phase of this study.

d. Infestation: Cattle were naturally infested with cattle lice.

e. Dosage Form: Moxidectin 1% nonaqueous injectable solution, 10 mg/mL.

f. Route of Administration: Single subcutaneous injection in the neck region.

g. Doses: Moxidectin 1% nonaqueous injectable solution was administered on Day 0 at doses of 0.02 or 0.03 mL/kg body weight to provide 0.2 or 0.3 mg moxidectin/kg body weight.

h. Control: Injectable vehicle containing no moxidectin was administered on Day 0 at the dose of 0.03 mL/kg to provide 0 mg moxidectin/kg body weight.

i. Test Duration: 56.

j. Pertinent Measurements/Observations: Lice recovered from individual cattle were counted and identified weekly from Days 7 to 56 post-treatment.

4) Results: Efficacy data against two lice species (*Linognathus vituli* and *Solenopotes capillatus*) are summarized in Table 2.20:

Table 2.20 Study Number 0693-B-US-17-97

Lice Species	Dose (mg/kg)	Arithmetic Mean Control Lice Counts and Percent Efficacy for Moxidectin Treatment on Trial Days							
		7	14	21	28	35	42	49	56
Solenopotes capillatus	0.0	49.5	47.5	47.8	56.2	42.8	38.9	56.2	69.8
	0.2	100	100	100	100	100	100	100	100
	0.3	100	100	100	100	100	100	100	100
Linognathus vituli	0.0	97.1	66.5	65.7	53.5	34.5	35.4	30.0	29.4
	0.2	100	100	100	100	100	100	100	100
	0.3	100	100	100	100	100	100	100	100

5) Adverse Reactions: No adverse reactions to treatment were noted.

D.9 Study Number 0693-B-US-19-97

1) Type of Study: Dose confirmation study in cattle with naturally acquired lice infestation.

2) Investigator: Larry L. Smith, D.V.M.
Larry Smith Research & Development, Inc.
Lodi, WI

3) General Design:

a. Purpose: This study was designed to confirm the effective dose of moxidectin 1% nonaqueous injectable solution for the treatment and control of lice infestations on cattle.

b. Animals: Thirty beef crossbred calves weighing between 119 and 258 kg were assigned to three treatment groups of ten animals each based on their *Haematopinus eurysternus* lice counts on Day -4.

c. Housing: Treatment groups were maintained in separate pens throughout the study.

d. Infestation: Cattle were naturally infested with cattle lice.

e. Dosage Form: Moxidectin 1% nonaqueous injectable solution, 10 mg/mL.

f. Route of Administration: Single subcutaneous injection in the neck region.

g. Doses: Moxidectin 1% nonaqueous injectable solution was administered on Day 0 at doses of 0.02 or 0.03 mL/kg body weight to provide 0.2 or 0.3 mg moxidectin/kg body weight.

h. Control: Injectable vehicle containing no moxidectin was administered on Day 0 at the dose of 0.03 mL/kg to provide 0 mg moxidectin/kg body weight.

i. Test Duration: 56 days.

j. Pertinent Measurements/Observations: Lice recovered from individual animals were counted and identified weekly from Days 7 to 56 post-treatment.

4) Results: Efficacy data against one lice species (*Linognathus vituli*) are summarized in Table 2.21:

Table 2.21 Study Number 0693-B-US-19-97

Lice Species	Dose (mg/kg)	Arithmetic Mean Control Lice Counts and Percent Efficacy for Moxidectin Treatment on Trial Days							
		7	14	21	28	35	42	49	56
Linognathus vituli	0.0	76.3	23.3	16.7	12.4	11.4	6.9	3.0	5.9
	0.2	100	100	100	100	100	100	100	100
	0.3	100	100	100	100	100	100	100	100

5) Adverse Reactions: No adverse reactions to treatment were noted.

E. Clinical Field Studies

Five studies were conducted in different geographical locations to further evaluate the effectiveness of moxidectin 1% nonaqueous injectable solution and to gain experience on the safety of the product when used under field conditions. The animals were housed on pasture in four studies and in feedlot pens in the fifth trial. Since these trials were conducted following a similar protocol, the results of all five trials are summarized in a single section.

1) Type of Study: Clinical Field Study

2) Investigators:

Study Number: 0693-B-US-22-98
William Barton, Ph.D.
CAVL
Amarillo, TX

Study Number: 0693-B-US-23-98
Gil Myers, Ph.D.
Gil Myers, Ph.D. Inc.
Magnolia, KY

Study Number: 0693-B-US-24-98
Craig R. Reinemeyer, Ph.D., D.V.M.
University of Tennessee
Knoxville, TN

Study Number: 0693-B-US-25-98
Larry Cruthers, Ph.D.
PLRS Inc.
Corapeake, NC

Study Number: 0693-B-US-26-98
Larry L. Smith, D.V.M.
Larry Smith Research & Development, Inc.
Lodi, WI

3) General Design:

a. Purpose: These studies were designed to confirm the effectiveness and safety of the recommended dose of moxidectin 1% nonaqueous injectable solution when used under pasture conditions for the treatment and control of endoparasites in cattle.

b. Animals: At each study site approximately 100 cattle were treated with moxidectin 1% nonaqueous injectable solution and approximately 50 cattle were treated with vehicle. Because of the unequal numbers of treated and control cattle, it was necessary to divide animals into three groups of fifty animals each in order to blind the study personnel. Cattle were assigned to one of the three groups based on their averages of two fecal strongyle egg counts prior to treatment. Blocks of three animals each were created and a random number was assigned to each animal. The random numbers were used to assign cattle to one of three groups (one control and two treated groups). Table 2.22 lists the study sites and number of animals used.

Table 2.22 Summary of five sites used in the clinical field study.

Study Number	Control Cattle #	Treated Cattle #	Weight (pounds)	Breed
0693-B-US-22-98	49	98	345-590	English cross steers/bulls
0693-B-US-23-98	48	96	300-750	Holstein, crossbred cattle
0693-B-US-24-98	51	102	428-738	Mixed breed steers
0693-B-US-25-98	50	100	393-1228	Mixed breed beef cattle
0693-B-US-26-98	50	100	335-568	Mixed breed beef steers

c. Housing: The cattle were maintained on pasture throughout the studies in four trials and in feedlot pens in study 0693-B-US-22-98.

d. Infection: Cattle had naturally acquired nematode infections.

e. Dosage Form: Moxidectin 1% nonaqueous injectable solution, 10 mg/mL.

f. Route of Administration: Single subcutaneous injection in the neck region.

g. Doses: Moxidectin 1% nonaqueous injectable solution was administered on Day 0 at a dose of 0.02 mL/kg body weight to provide 0.2 mg moxidectin/kg body weight.

h. Control: Injectable vehicle containing no moxidectin was administered on Day 0 at the dose of 0.02 mL/kg to provide 0 mg moxidectin/kg body weight.

i. Test Duration: 21 days.

j. Pertinent Measurements/Observations: Individual animal fecal strongyle egg counts were determined twice before treatment and 14 and 21 days after treatment using a flotation procedure.

4) Results: The arithmetic means of fecal strongyle egg counts, presented as eggs per gram (EPG), from these clinical field trials are summarized in Table 2.23. The % efficacy of treatment was calculated by comparing EPG counts of the treated group to that of the control group.

Table 2.23 Percent efficacy comparing EPG counts by site.

Study No. (Study Site)	Day	Control	Moxidectin	% Efficacy
0693-B-US-22-98 (Texas)	Pre-treatment	377.86	405.72	
	14	209.80	2.89	98.6
	21	199.58	8.11	95.6
0693-B-US-23-98 (Kentucky)	Pre-treatment	49.96	52.72	
	14	73.15	5.89	91.9
	21	113.64	19.09	83.2
0693-B-US-24-98 (Tennessee)	Pre-treatment	56.51	56.04	
	14	96.04	15.19	84.2
	21	103.88	39.95	61.5
0693-B-US-25-98 (North Carolina)	Pre-treatment	99.70	101.90	
	14	71.36	3.37	95.3
	21	50.78	6.21	87.8
0693-B-US-26-98 (Wisconsin)	Pre-treatment	102.51	100.15	
	14	63.80	0.22	99.6
	21	58.24	0.23	99.6

5) Adverse Reactions: Table 2.24 summarizes the adverse reactions.

Table 2.24 Adverse reactions by study site.

Study No. (Study Site)	Adverse Reactions
0693-B-US-22-98 (Texas)	Injection site swellings were noted in 27.6% of treated animals on Day 14 and in 15.2% of treated animals on Day 21.
0693-B-US-23-98 (Kentucky)	Injection site swellings were noted in 29% of treated animals on Day 14 and in 14% of treated animals on Day 21.
0693-B-US-24-98 (Tennessee)	Injection site swellings were noted in 30% of treated animals and 15% of controls on Day 14 and in 21% of treated animals and 17% of controls on Day 21.
0693-B-US-25-98 (North Carolina)	Injection site swellings were noted in 18% of treated animals and 1% of controls on Day 14 and in 11% of treated animals and 1% of controls on Day 21.
0693-B-US-26-98 (Wisconsin)	Injection site swellings were noted in 1% of treated animals on Day 14. There were no swellings noted on Day 21.

3. Target Animal Safety

Specific nonclinical laboratory experiments were carried out in accordance with the applicable regulations (Good Laboratory Practices, GLP, 21 CFR Part 58, or Good Target Animal Study Practices: Clinical Investigators and Monitors, May 1997) in the target species to address safety-in-use considerations. Margin of safety (toxicity) as delineated by repeated treatment at up to 5X the recommended use level and toxic syndrome as defined by the results of a drug tolerance test were evaluated in a single study. In separate trials, breeding bulls, estrual cows, pregnant cows, and young calves were treated at 3X or 4.5X the recommended dose. A residue study was conducted that did evaluate treatment effects at the injection site. All target animal safety studies were carried out using the final moxidectin 1% nonaqueous injectable solution formulation.

A. Drug Toxicity/Tolerance - Study Number 0693-B-US-21-98

1) Type of Study: Target animal toxicity test/drug tolerance.

2) Investigator: T. W. J. Olchowy, D.V.M.
Fort Dodge Animal Health
Princeton, NJ

3) General Design:

a. Purpose: The purpose of this study was twofold. The animal toxicity phase of the study was designed to evaluate the clinical and pathological effects of the administration of moxidectin 1% nonaqueous injectable solution by subcutaneous injection at 0.2, 0.6, or 1.0 mg moxidectin/kg body weight (1X, 3X, or 5X the recommended dose, respectively) weekly for three consecutive weeks in cattle. The tolerance phase of the study was conducted to determine the clinical and pathological effects of a single administration of moxidectin 1% nonaqueous injectable solution by subcutaneous injection at 2.0 mg moxidectin/kg body weight (10X the recommended dose).

b. Animals: Forty Angus and Angus crossbred cattle, 20 steers and 20 heifers, approximately 14 months of age and weighing an average of 267 kg were allotted to five treatment groups of four steers and four heifers per group.

c. Dosage Form: Moxidectin 1% nonaqueous injectable solution, 10 mg/mL

d. Control: Physiological saline

e. Route of Administration: Subcutaneous injection

f. Doses: Animals in Groups B, C, and D received moxidectin 1% nonaqueous injectable solution injectable at 0.02, 0.06, or 0.10 mL/kg body weight (1X, 3X, and 5X the recommended dose), respectively, three times at weekly intervals. The

animals in Group A (control) received saline at 0.10 mL/kg body weight at the same time intervals. Animals in Group E received moxidectin 1% nonaqueous injectable solution injectable at 0.2 mL/kg body weight (10X the recommended dose) at the same time that the other groups received the third dose.

g. Test Duration: 20 days for the toxicity phase and 6 days for the tolerance phase

h. Pertinent Measurements/Observations: Physical examinations were conducted one day prior to treatment and 6 days after the final treatment. Venous blood, urine and feces were collected 3 and 1 days prior to the initial treatment of each group of cattle, 6 days after each treatment in the toxicity phase (Groups A to D), and 2, 4, and 6 days after treatment in the tolerance phase (Group E) for hematological, clinical chemistry, urinalysis, and fecal analysis. Health observations were made twice daily from 3 days prior to treatment to the end of the study. Ocular examinations were done daily to evaluate pupillary size and pupillary light reflexes during this same period. All animals were necropsied 7 to 10 days after the last treatment and evaluated for gross pathology. Tissues from all animals in the control, 5X, and 10X treatment groups, as well as tissues from animals with macroscopic abnormalities, were examined for histopathology.

4) Analysis: Variables measured once were analyzed by analysis of variance with fixed effects of treatment, sex, and sex by treatment with block nested within sex as a random effect. Variables measured multiple times were analyzed by repeated analysis of co-variance with treatment, sex, treatment by sex, day, treatment by day, treatment by sex by day as fixed effects with block nested within sex as a random effect. Alpha levels were set at 0.10 for treatment and treatment by day interaction and at 0.05 for treatment by sex interaction.

5) Results:

a. Clinical Observations:

Toxicity Phase: There were no treatment-related effects based on the physical examinations, daily observations, or ocular examinations.

Tolerance Phase: Mild, transient ataxia characterized by toe dragging, poor tracking, and/or circumduction in the rear legs was seen periodically from one to six days after treatment in a total of five of the eight animals receiving the 10X dose. These signs were evident by careful observation of the animals when walking during the daily observations. There were no effects of treatment based on the pre- vs. post-treatment physical examinations or the ocular examinations.

b. Hematology/Serum Chemistry:

Toxicity Phase: There were no biologically meaningful effects observed.

Tolerance Phase: Overall, biologically meaningful effects observed were limited. At two days post-treatment, average serum iron was decreased compared to pretreatment levels (45.75 vs. 123.69 mcg/dL, $P<0.10$), and average serum creatinine phosphokinase was increased compared to pretreatment levels (452.00 vs. 177.06 U/L, $P<0.10$). The levels of both serum parameters returned to normal ranges for cattle by four days post-treatment.

c. Urinalysis and Fecal Examination: No test article-related effects were observed in either phase of the study.

d. Gross and Histopathologic Observations: No lesions suggestive of treatment-related toxicity were observed for any animal at necropsy or during the microscopic examination of the tissues from the animals receiving the 5X or the 10X treatments. There was an increase in immature neutrophils for the 10X treatment group.

6) Conclusions: The administration of moxidectin 1% nonaqueous injectable solution three times at weekly intervals at levels up to 5X the recommended dose had no adverse effects on cattle. Mild, transient ataxia was seen in 5 of 8 cattle receiving a single 10X dose.

B. Breeding Bull Safety - Study Number 0693-B-US-2-96

1) Type of Study: Reproductive safety study in bulls.

2) Investigator: Robert G. Mortimer, M.S., D.V.M.
Colorado State University
Fort Collins, CO

3) General Design:

a. Purpose: To assess the effects of moxidectin 1% nonaqueous injectable solution administered by subcutaneous injection at 0.9 mg moxidectin/kg body weight (4.5X the recommended use level) on the seminal quality of breeding bulls.

b. Animals: Twenty healthy, sexually mature Black Angus bulls, 22 to 24 months of age and weighing 1105 to 1335 pounds at the time of treatment, were randomly allocated to two treatment groups (A or B) of 10 bulls each.

c. Dosage Form: Moxidectin 1% nonaqueous injectable solution, 10 mg/mL

d. Control: Physiological saline

e. Route of Administration: Subcutaneous injection

f. Doses: Bulls in Group B received a single treatment with moxidectin 1% nonaqueous injectable solution at the rate of 4.5 mL/50 kg (4.5X the recommended use level). Bulls in Group A received a similar volume of saline.

g. Test Duration: 10 weeks

h. Pertinent Measurements/Observations: Breeding Soundness Exams were conducted in accordance with the 1992 Society of Theriogenology guideline. Physical examinations (including evaluation of internal accessory sex organs, and scrotal circumference) were performed on Days -14, 0, 7, and 70. Semen evaluations were performed three times per week for two weeks pretreatment and 10 weeks post-treatment. Semen was evaluated for progressive motility, morphology, volume, and sperm concentration. The numbers and types of morphological abnormalities of the sperm were determined.

4) Analysis: Variables measured multiple times were analyzed by repeated analysis of co-variance with treatment, collection group, treatment by collection group, week, treatment by week, treatment by collection group by week as fixed effects with block nested within collection group as a random effect.

5) Results: No abnormalities were identified during the physical examinations. There were no biologically meaningful differences in scrotal circumference, semen quality, or the number and type of sperm morphological abnormalities between the control and treated groups of bulls. Mild, transient ataxia was reported in three of 10 treated bulls at 48 hours post-treatment. This resolved within 24 hours of onset.

6) Conclusions: A single administration of moxidectin 1% nonaqueous injectable solution providing 0.9 mg moxidectin/kg body weight, 4.5X the recommended dose, did not have any adverse effects on scrotal measurements, semen quality, or sperm characteristics of breeding bulls.

C. Estrual Female Safety

C.1 Study Number 0693-B-US-1-96

1) Type of Study: Reproductive safety study in cows treated before or after expected ovulation and during early gestation.

2) Investigator: D. Owen Rae, D.V.M., M.P.V.M.
University of Florida
Gainesville, FL

3) General Design:

a. Purpose: To assess the effects of moxidectin 1% nonaqueous injectable solution administered by subcutaneous injection at 0.9 mg moxidectin/kg body weight (4.5X

the recommended use level) before or after ovulation on the reproductive performance of breeding female cattle.

b. Animals: One hundred eighty estrus-synchronized Angus, Brahman, or Angus x Brahman beef cows ranging from 3 to 14 years of age were blocked by breed group and within each breed ranked by age and blocked into groups of six. The six cows within each block were randomized to the six treatment groups resulting in thirty cows being randomly assigned to each treatment group.

c. Dosage Form: Moxidectin 1% nonaqueous injectable solution, 10 mg/mL

d. Control: No treatment

e. Route of Administration: Subcutaneous injection

f. Doses: Cows in Groups A to E were treated once with moxidectin 1% nonaqueous injectable solution at 0.09 mL/kg body weight (4.5X the recommended use level) at one of five time points relative to anticipated ovulation (defined as Day 0): Group A on Day –7; Group B on Day +7; Group C on Day +14; Group D on Day +21; and Group E on Day +40. Cows in Group F were untreated controls.

g. Test Duration: 12 months

h. Procedures/Pertinent Measurements: All cows were artificially inseminated on Day –1 or Day 0. Cows observed in estrus on Days 1 through 4 were inseminated again. Any cow observed in estrus between Day 5 and Day 23 (end of estrus observations) was deemed not pregnant for purposes of this study. All potentially pregnant cows (not observed in estrus after Day 4) were examined by rectal palpation on Day 62 to determine pregnancy status. Conception rate was calculated as the percentage of cows pregnant on Day 62. Calving rate was calculated both as the percentage of cows treated and the percentage of cows pregnant on Day 62, a measure of pregnancy maintenance. Calf health, body weight, and vigor were determined at birth. Calf health and body weight were determined again at approximately 60 days.

4) Analysis: Calf birth weights were analyzed using analysis of variance with treatment as a fixed effect and block as a random effect. Calf Day 60 weights were analyzed using analysis of co-variance with treatment as a fixed effect, block as a random effect, and birth weight as a covariate. Fisher's Exact Test was used for the categorical variables.

5) Results: There were no differences in conception rates for cows treated 7, 14, or 40 days post-breeding and the controls ($P>0.10$). Conception rates were significantly lower ($P<0.10$) for groups treated 7 days prior to breeding (43.3% vs 70.0%) and 21 days post-breeding (52.2% vs 80.8%) compared to their respective control groups. Calving rates (% of cows treated) were not different ($P>0.10$) between each treated and corresponding control group. Calving rates as a percent of cows pregnant on Day 62 tended to be

higher in all treated groups compared to the corresponding control, but the differences were not significant (P>0.10).

Calf weights at birth and at 60 days of age were similar or higher in all treated groups compared to the control group, but only the birth weights for calves in Group D were significantly higher than Control (P<0.10). There were no significant differences (P>0.10) between the treated groups and control in calf health at birth or 60 days of age. The percent of calves with normal vigor at birth was lower (P<0.10) in Group B compared to control, in which all calves were normal. This could be attributed to two stillbirths in Group B caused by dystocia (1) and osteopetrosis (1), a genetic disorder in Angus cattle. There were no differences (P>0.10) among the other treated groups and control in calf vigor.

6) Conclusions: A single administration of moxidectin 1% nonaqueous injectable solution providing 0.9 mg moxidectin/kg body weight, 4.5X the recommended dose, to breeding cows prior to or after the expected time of ovulation had no adverse effect on the maintenance of pregnancy, the incidence of birth defects in calves, or calf health and body weight at birth or at 60 days of age. Conception rate was reduced significantly compared to controls for cows treated 7 days prior to or 21 days following breeding, but was not different from controls for cows treated 7, 14, or 40 days following breeding.

C.2 Study Number 0693-B-US-32-98

1) Type of Study: Reproductive safety study in heifers treated before or after expected ovulation and during early gestation.

2) Investigator: E. G. Johnson, D.V.M.
Johnson Research
Parma, ID 83660

3) General Design:

a. Purpose: To further assess the effects of moxidectin 1% nonaqueous injectable solution administered by subcutaneous injection at 0.6 mg moxidectin/kg body weight (3X the recommended use level) before or after ovulation on the conception rates of breeding heifers as a follow-up to Study Number 0693-B-US-1-96

b. Animals: A total of 246 mixed-breed, virgin beef heifers with normal reproductive tracts were estrus synchronized for use in this study. Of these, 191 heifers, ranging in weight from approximately 315 to 500 kg, participated in the study.

c. Dosage Form: Moxidectin 1% nonaqueous injectable solution, 10 mg/mL

d. Control: No treatment

e. Route of Administration: Subcutaneous injection

f. Doses: Heifers in Groups A to E were treated once with moxidectin 1% nonaqueous injectable solution at 0.06 mL/kg body weight (3X the recommended use level) at one of five time points relative to anticipated ovulation (defined as Day 0): Group A on Day –7; Group B on Day +7; Group C on Day +14; Group D on Day +28; and Group E on Day +40. Group F animals remained as untreated control.

g. Test Duration: 90 days

h. Procedures/Pertinent Measurements: On Day –7, 30 heifers were randomly allocated to Group A (treated Day –7) and 30 heifers to Group F (control). All heifers to be used in the study were artificially inseminated on Day –1 or Day 0. Heifers observed in estrus on Days 1 through 4 were inseminated again. Any heifer observed in estrus between Day 5 and Day 40 (end of estrus observations) was deemed not pregnant and was unavailable for selection for the study for any remaining treatment groups (Groups B to E) for which selection had not been made. "Eligible heifers" were defined as heifers for which no signs of estrus were observed from Day 5 to Day 40. That is, on each scheduled treatment day (i.e. 7, 14, 28, and 40), thirty "eligible heifers" were randomly chosen from the remaining pool of heifers that had not been observed in estrus. At each selection time (selection for Groups B to E), the heifers in the control group at the time of selection (Group F) were checked for signs of estrus. Any heifer that had been observed in heat between Day 5 and the scheduled treatment day (Day 7, 14, 28, or 40) was removed from the control group and replaced by a randomly selected "eligible heifer." In this manner, each treated group of 30 presumably pregnant heifers had a contemporary control group of 30 presumably pregnant heifers. A total of 45 control heifers were included in the study. Two heifers were replaced at Day 7; two at Day 14; seven at Day 28; and four at Day 42 for a total of 15 heifers. All heifers, including all 45 control heifers, were examined by rectal palpation on Day 62 and Day 90 to determine pregnancy status. However, only the concurrent control for each treatment group was included in the conception rate for that treatment group. Conception rate was calculated based on both the Day 62 and Day 90 palpation results.

4) Analysis: Fisher's Exact Test was used for the categorical variables.

5) Results: There was no significant difference ($P>0.10$) between any treated group and its concurrent control group in conception rates at either Day 62 or Day 90. The overall conception rate on Day 62 ranged from 27-53% for the heifers in the treated groups and 40-67% for the heifers used during the study in the control group. The overall conception rate on Day 90 ranged from 27-50% for the heifers in the treated groups and 33-60% for the heifers used during the study in the control group.

6) Conclusions: A single administration of moxidectin 1% nonaqueous injectable solution providing 0.6 mg moxidectin/kg body weight, 3X the recommended use level, before or after ovulation had no effect on the conception rate in heifers.

D. Pregnant Cow Safety - Study Number 0693-B-US-7-97

1) Type of Study: Reproductive safety study in cows treated during early, mid or late gestation.

2) Investigator: L. R. Cruthers, Ph.D.
PLRS, Inc.
Corapeake, NC

3) General Design:

a. Purpose: To assess the effects of moxidectin 1% nonaqueous injectable solution administered by subcutaneous injection at 0.9 mg moxidectin/kg body weight (4.5X the recommended use level) during early, mid, or late gestation on the maintenance of pregnancy in beef cows and on the fetal and neonatal development of the calves.

b. Animals: One hundred eighty multiparous, beef-type cows were selected from a larger herd for use in this study based on a positive pregnancy check (rectal palpation) 67 to 68 days after the start of the breeding season. The cows were rotationally allotted to four groups of 45 animals each at the time of selection into the study.

c. Dosage Form: Moxidectin 1% nonaqueous injectable solution, 10 mg/mL

d. Control: No treatment

e. Route of Administration: Subcutaneous injection

f. Doses: Cows in Groups B, C, and D were treated once with moxidectin 1% nonaqueous injectable solution at 0.09 mL/kg body weight (4.5X the recommended use level) at early, mid, or late gestation, respectively. Cows in Group A were maintained as untreated controls.

g. Test Duration: 13 months

h. Pertinent Measurements/Observations: All cows were palpated prior to each treatment time (early, mid, late gestation). At the same time they were weighed and assigned a body condition score. Any cow in the mid or late gestation groups found open prior to treatment was not treated and removed from the study. Control cows similarly found open and not calving during the study were not included in the comparisons with the mid and late gestation treated groups. Calves were examined and weighed within 48 hours of birth and again at approximately 60 days of age. Calving rate, calf abnormalities, calf birth weight, calf 60 day weight, and the 60 day average daily gain of the calves were the primary parameters evaluated in the study.

4) Analysis: Continuous variables were analyzed by analysis of variance with fixed effects of treatment, calf sex, and treatment by calf sex. Fisher's Exact Test was used for the categorical variables.

5) Results: There were no differences ($P>0.10$) between any treated group and the appropriate control in the numbers of cows producing live calves, dead calves (still births), or not calving (abortions). There was no treatment effect ($P>0.10$) on calf weight recorded within 48 hours of birth based on a combined sex analysis. However, there were significant treatment effects ($P\leq0.10$) for calf weight measured at approximately 60 days of age and the rate of calf weight gain to approximately 60 days of age in calves from cows treated in the 1st trimester having lower average weight and weight gain than controls. There were no differences between groups treated in the 2nd or 3rd trimester and controls in these parameters ($P>0.10$). There was no treatment effect ($P>0.10$) on numbers of calves surviving to approximately 60 days of age.

6) Conclusions: A single administration of moxidectin 1% nonaqueous injectable solution providing 0.9 mg moxidectin/kg body weight, 4.5X the recommended dose, to pregnant cows during early, mid, or late gestation did not have any adverse effect on the maintenance of pregnancy, the development of the fetus, or survival through the first 60 days of life. There were no treatment effects on calf weight measured at birth. Calves from cows treated in the first trimester had reduced Day 60 weights and growth rate at 60 days of age when compared to calves from the control group; however this was not clinically significant. Performance of calves from cows treated in the 2nd or 3rd trimester was similar to controls.

E Calf Safety - Study Number 0693-B-US-27-98

1) Type of Study: Safety study in young calves

2) Investigator: E. G. Johnson, D.V.M.
Johnson Research
Parma, ID

3) General Design:

a. Purpose: To assess the effects of the administration of moxidectin 1% nonaqueous injectable solution by subcutaneous injection at 0.2 or 0.6 mg/kg bodyweight (1X or 3X the recommended dose) in eight week old calves.

b. Animals: Thirty mixed beef breed calves and their dams were randomly assigned to three groups of 10 pairs each. The calves ranged in age from 49 to 61 days at the time of treatment.

c. Dosage Form: Moxidectin 1% nonaqueous injectable solution, 10 mg/mL

d. Control: Vehicle

e. Route of Administration: Subcutaneous injection

f. Doses:

Control - Vehicle administered once to calves at the rate of 0.06 mL/kg body weight (equivalent to 3X the recommended dose) and to their dams at 0.02 mL/kg body weight (equivalent to 1X the recommended dose).

1X Dose - Moxidectin 1% nonaqueous injectable solution administered once to both calves and their dams at the rate of 0.02 mL/kg body weight (1X the recommended dose).

3X Dose - Moxidectin 1% nonaqueous injectable solution administered once to calves at the rate of 0.06 mL/kg body weight (3X the recommended dose) and to their dams at 0.02 mL/kg body weight (1X the recommended dose).

g. Test Duration: 14 days

h. Pertinent Measurements/Observations: From Day -1 through Day 14 post-treatment each cow and calf was observed twice daily for adverse clinical signs. Prior to treatment and once daily for 7 days post-treatment ocular examinations (pupil size, pupillary reflexes to light, menace response and presence or absence of epiphora) were performed on each calf.

4) Analysis: Observations were qualitative in nature and were not statistically analyzed.

5) Results: No adverse signs related to moxidectin 1% nonaqueous injectable solution treatment were noted in the cows. Various clinical signs, including diarrhea, respiratory symptoms, lameness, and epiphora, were noted in the calves. These were generally distributed uniformly among the treatment groups. Thus, they were considered unrelated to moxidectin treatment.

6) Conclusions: A single administration of moxidectin 1% nonaqueous injectable solution providing 0.2 mg moxidectin, 1X recommended dose, or 0.6 mg moxidectin/kg body weight, 3X the recommended dose, demonstrated no adverse effects in calves 49 to 61 days of age following treatment at either 1X or 3X the recommended dose.

F. Injection Site Tolerance - Study Number 0889-B-US-1-95

1) Type of Study: Evaluation of tissue irritation at the injection site.

2) Investigator: L. S. de Montigny, D.V.M.
Fort Dodge Animal Health
Princeton, NJ

3) General Design:

a. Purpose: To assess the effects of the administration of moxidectin 1% nonaqueous injectable solution by subcutaneous injection at 0.2 mg moxidectin/kg body weight (1X the recommended use level) on tissue at the site of injection.

b. Animals: Thirty-three Angus crossbred cattle (16 steers and 17 heifers) approximately 10 months of age and 262 to 330 kg body weight were used for this study. Three control animals were randomly chosen from the group. The remaining 30 animals were blocked by weight within sex and randomly assigned within blocks to five groups of six animals each for necropsy at weekly intervals from two to six weeks post-treatment.

c. Dosage Form: Moxidectin 1% nonaqueous injectable solution, 10 mg/mL

d. Control: Untreated

e. Route of Administration: Subcutaneous injection

f. Doses: Moxidectin 1% nonaqueous injectable solution was administered to all animals once at the rate of 0.02 mL/kg body weight (1X the recommended dose).

g. Test Duration: 42 Days

h. Pertinent Measurements/Observations: Animals were observed on Days 1, 2, 3, 5, and 7 postinjection and at necropsy for swelling at the injection site. At necropsy, the injection sites were examined for gross pathology.

4) Analysis: Summary statistics were reported.

5) Results: Fifty percent of the animals had identifiable swelling at the injection site one day post-treatment. Both the incidence and the volume of injection site swelling decreased by 7 days after treatment. Minor swelling and gross tissue abnormalities were present on three of six animals necropsied 2 weeks after dosing. No swelling was present on any of the 24 animals at necropsy 3, 4, 5, or 6 weeks after dosing. Two treated animals had yellow fluid or granular material in the injection site area at necropsy.

6) Conclusions: The administration of moxidectin 1% nonaqueous injectable solution was well tolerated by cattle treated at the recommended dose of 0.2 mg moxidectin/kg body weight. Although mild, transient swelling was observed at some of the injection sites, it dissipated by 21 days post-treatment.

   One animal necropsied at 28 days post-injection was noted to have scar tissue at the injection site. Another animal, necropsied at 35 days post-injection showed dark yellow discoloration of subcutaneous fat at the injection site. There were no other signs of pathology in any of the other treated animals. The presence of visible lesions at the injection site in animals necropsied after the withdrawal period (21 days) will necessitate a trim-out statement on the label.

4. HUMAN FOOD SAFETY

A. Toxicity

Toxicology studies for moxidectin were presented in the original NADA 141-099 FOI Summary dated January 28, 1998, and the supplemental NADA 141-099 FOI Summary dated November 2, 1999. No additional toxicology data were required for the approval of this NADA.

B. Safe Concentrations of Total Residues

The safe concentrations for moxidectin in edible tissues of cattle have been established in the FOI Summary dated November 2, 1999, for supplemental NADA 141-099 (use of the pour-on in lactating dairy cows) as follows: 0.5 ppm in muscle, 1.5 ppm in liver, 3.0 ppm in kidney, and fat, and 0.06 ppm in milk.

C. Total Residue Depletion and Metabolism Studies

Total residues and the metabolic transformation of moxidectin in the edible tissues of cattle, and the metabolism of moxidectin in laboratory rats were presented in the NADA 141-099 FOI Summary dated January 28, 1998. No additional data were required for the approval of this NADA.

D. Comparative Metabolism Studies

Comparative metabolism studies for moxidectin were presented in the original NADA 141-099 FOI Summary dated January 28, 1998. No additional toxicology data were required for the approval of this NADA.

E. Residue Depletion Studies

A study was conducted to determine the depletion of the marker residue in the edible tissues of cattle following treatment with the final formulation of moxidectin 1% nonaqueous injectable at the recommended dose.

1. Study No. 0889-B-US-1-95: Title: “Moxidectin (CL 301,423): Tissue Residue Depletion Study in Cattle Following Treatment with a Nonaqueous Formulation of Moxidectin 1% Injectable Solution” (Report No. GASR 01-05.00).

2. Investigator: L. S. de Montigny, D.V.M.

3. Location: Agricultural Research Center, Princeton, New Jersey

4. Design: Thirty-three Angus crossbred cattle (17 heifers and 16 steers) weighing an average of 307 kg were randomly assigned to five, six-animal treated groups with equal sex distribution and an untreated control group (one steer and two heifers). The treated groups

received a single subcutaneous injection of the final moxidectin 1% nonaqueous injectable formulation at the recommended dose of 0.2 mg moxidectin/kg body weight. All cattle comprising a treated group were sacrificed at either 14, 21, 28, 35, or 42 days post-treatment and samples of liver, kidney, loin muscle, omental fat, and injection site were taken for residue analysis. Two control animals (one steer and one heifer) were sacrificed at the initial time point and the third control animal (heifer) was sacrificed at the final time point. The same tissues were harvested from the control animals for residue analysis. Moxidectin residues in the tissues were determined with a validated analytical procedure.

5. Findings: No detectable residues were found in the control animals. The mean moxidectin (marker residue) concentrations in tissues of treated animals at the various times post-treatment are summarized in the table below:

Days After Treatment	Moxidectin Residues, ppb[a]				
	Omental Fat	Injection Site	Liver	Kidney	Loin Muscle
14	263 ± 76	15123 ± 23134	16.5 ± 5.3[b]	22.5 ± 6.0	<10 - 11.2
21	199 ± 42	335 ± 294	<10	16.5 ± 3.9	<10
28	145 ± 46	1195 ± 1393	<10	<10 - 18	<10
35	110 ± 71[b]	<10 - 876	<10	<10 - 17	<10
42	58 ± 37	<10 - 28	<10 - 17	<10 - 10	<10

[a] Based on six animals per time point; values are mean ± standard deviation or the range when two or more values for a specific tissue were below the validated Limit of Quantitation (LOQ) of the analytical method (10 ppb).
[b] One animal had a residue of <10 ppb (method LOQ); a value of 9 was used to calculate the mean.

6. Conclusions: There were no differences between males and females in tissue residues. This study confirmed omental fat as the target tissue for monitoring moxidectin residue depletion.

F. Tolerance and Withdrawal Time

Tolerance: The parent compound, moxidectin, was established as the marker residue and fat as the target tissue in the NADA 141-099 FOI Summary dated January 28, 1998. Data in the referenced NADA demonstrate that the extractablility of radiolabeled residues from fat is ≥ 99%, indicating the absence of bound residues. Moxidectin accounts for >80% of the total residues in fat. Based on a safe concentration in fat of 3 ppm, a tolerance for parent moxidectin in fat could be set as high as 2.4 ppm (3 ppm x 0.8). However, in keeping with the Agency's policy of not establishing a tolerance at a level higher than that reflected by the permitted use of the drug, a value of 900 ppb unchanged moxidectin is assigned as the tolerance in fat of cattle.

Because USDA/FSIS, in its monitoring program, assays muscle and liver samples of cattle with a multi-residue method capable of detecting and measuring moxidectin, FDA has established

tolerances of 50 ppb and 200 ppb for parent moxidectin in muscle and liver, respectively, of cattle (21 CFR 556.426).

Withdrawal Time: Statistical analysis of the marker residue, moxidectin, in fat, the target tissue, from the residue depletion study indicated that at all withdrawal times evaluated residues in fat were below 2.4 ppm, which is the maximum tolerance the residue data could have supported. However, the withdrawal period was established as 21 days in order to account for the occasional high injection site residue that was found prior to that time. The 21 day withdrawal period corresponds to a tolerance of 900 ppb, the value formally established as the tolerance for moxidectin in cattle fat.

G. Regulatory Method for Residues

Moxidectin Determinative Assay Procedure: The determinative analytical method is an HPLC procedure with fluorescence detection that is capable of measuring moxidectin in cattle fat at concentrations as low as 10 ppb. Moxidectin is extracted from cattle fat with acetonitrile, partitioned with hexane, and concentrated. The compound is reacted with acetic anhydride and 1-methylimidazole in dimethylformamide to produce a conjugated dehydration product which is fluorescent. Quantitation of moxidectin is accomplished by liquid chromatography with fluorometric detection and the external standard technique.

Moxidectin Confirmatory Assay Procedure: The moxidectin confirmatory assay utilizes the same extraction and purification steps as the determinative method. The structural confirmation of moxidectin is based on LC/MS analysis.

Method Validation: A sponsor-monitored method validation trial of the determinative and the confirmatory assay procedures has been completed and the procedures have been accepted as the regulatory method for the detection and confirmation of moxidectin in cattle fat.

Display of the Method: The method is on file with the Center for Veterinary Medicine, Food and Drug Administration, 7500 Standish Place, Rockville, MD 20875.

H. User Safety Concerns

Not for use in humans. Keep this and all drugs out of the reach of children. The material safety data sheet (MSDS) provides more detailed occupational safety information and a copy can be obtained by calling the 1-888 number on the product label. The product label will instruct users who experience adverse reactions to report these using the 1-800 number provided on the product label.

5. 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 of the implementing regulations. The data demonstrate that CYDECTIN (moxidectin) Injectable Solution for Beef and Nonlactating Dairy Cattle at the dose rate of 0.2 mg moxidectin/2.2 lb (0.2 mg/kg) body weight is effective for treatment and control of various internal and external parasites in cattle.

An Acceptable Daily Intake (ADI) of 0.004 mg/kg/day has been established for moxidectin. A tolerance of 900 ppb for residues of parent moxidectin (marker residue) in fat (target tissue) of cattle has been established. A withdrawal period of 21 days is required for this use of moxidectin in cattle. Tolerances of 50 ppb and 200 ppb have also been established for residues of moxidectin in muscle and liver of cattle, respectively.

The data submitted for the CYDECTIN (moxidectin) Injectable Solution for Beef and Nonlactating Dairy Cattle support the marketing of the product as an over-the-counter new animal drug. Adequate directions for use have been written for the layman, and the conditions for use prescribed on the labeling are likely to be followed in practice. Therefore, CVM has concluded that this product shall have over-the-counter marketing status.

Under Section 512(c)(2)(F)(ii) of the Federal Food, Drug, and Cosmetic Act, this approval qualifies for THREE years of marketing exclusivity beginning on the date of approval because the applicant has conducted and/or sponsored substantial effectiveness and target animal safety studies to support this application.

CYDECTIN (moxidectin) Injectable Solution for Beef and Nonlactating Dairy Cattle is under the following US patent numbers:

U.S. Patent Number	Date of Expiration
4,916,154	April 10, 2007
5,965,603	July 8, 2018

6. ATTACHMENTS

Facsimile Labeling is attached as indicated below:

A. Insert Label, (5% reduction)

B. Bottle Labels: 50 mL, 200 mL, and 500 mL

C. Carton Labels: 50 mL, 200 mL (30% reduction), and 500 mL (40% reduction)