Date of Approval: November 30, 2011

FREEDOM OF INFORMATION SUMMARY -

SUPPLEMENTAL NEW ANIMAL DRUG APPLICATION

NADA 141-322

IMPROVEST

Gonadotropin Releasing Factor Analog - Diphtheria Toxoid conjugate
Sterile Solution for Injection
Swine, intact males -

To extend the slaughter interval from 4 to 8 weeks after the second dose to 3 to 10 weeks after the second dose

Sponsored by:

Pfizer, Inc.

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GENERAL INFORMATION:

A. File Number:	NADA 141-322
B. Sponsor:	Pfizer, Inc. 235 East 42d St New York, NY 10017 Drug Labeler Code: 000069
C. Proprietary Name(s):	IMPROVEST
D. Established Name(s):	Gonadotropin Releasing Factor Analog - Diphtheria Toxoid conjugate (GnRF analog-DT conjugate)
E. Pharmacological Category:	Immunotherapeutic
F. Dosage Form(s):	Sterile Solution for Injection
G. Amount of Active Ingredient(s):	0.2 mg/mL
H. How Supplied:	20, 100, 250, and 500 mL vials
I. How Dispensed:	Rx
J. Dosage(s):	2, 2 mL (0.4 mg GnRF analog-DT conjugate) injections
K. Route(s) of Administration:	Injection, subcutaneous
L. Species/Class(es):	Swine, intact males
M. Indication(s):	For the temporary immunological castration (suppression of testicular function) and reduction of boar taint in intact male pigs intended for slaughter.
N. Effect of Supplement:	For the extension of the slaughter interval to 3-10 weeks after the second dose from 4-8 weeks after the second dose.

EFFECTIVENESS:

A. Dosage Characterization:

This supplemental approval does not change the previously approved 2 x 2 mL dosage regimen but changes the timing of the interval between the second dose and slaughter from that approved in the original NADA. The Freedom of Information (FOI) Summary for the original approval of NADA 141-322 dated March 22, 2011, contains dosage characterization information for intact male swine treated with IMPROVEST.

B. Substantial Evidence:

Substantial evidence was evaluated in 2 parts: 1) evidence to support the use of IMPROVEST to temporarily immunologically castrate (suppression of testicular function) intact males and, 2) evidence to support the use of IMPROVEST to reduce boar taint in intact males intended for slaughter.

Substantial evidence was based on the comparison of non-treated control boars (T04) and boars treated with IMPROVEST (T02 and T03). Pigs from Study No. 3322C-60-10-828 were used for the consumer panel sensory evaluation of pork samples in Study No. 3920Z-60-10-879.

1. Temporary Immunological Castration (suppression of testicular function)

Study No. 3322C-60-10-828. Growth Performance and Carcass Characteristics of IMPROVEST Treated Intact Male Pigs Raised in U.S. Commercial Swine Facilities.

Investigator and Study location:
Angela Supple (Delks), DVM
Suidae Health and Production -
Highview Research Farms, Titonka, IA -

Study Design:

1. Objective: To evaluate the effectiveness of IMPROVEST, administrated as two subcutaneous 2 mL (400 µg) injections at either 9 and 20 weeks or 16 and 20 weeks of age, to immunologically castrate intact male pigs. The study provided data on anti-GnRF antibody titers, serum testosterone concentrations, and scrotal widths at 3, 9, and 10 weeks after the second dose of IMPROVEST.

2. Study Animals: The study was conducted at a single site and had the following treatment groups, number of pens and pigs per pen.

Table 1. Study Design.

Treatment Group	Test Article	Gender	No. of pens	No. pigs per pen	Total No.
T02	IMPROVEST 2.0 mL on Day 42 (9 weeks of age), and Day 119 (20 weeks of age)	Intact males	12	9 pens of 19 and 3 pens of 18	225
T03	IMPROVEST Day 91 (16 weeks of age), and Day 119 (20 weeks of age)	Intact males	12	11 pens of 19 and 1 pen of 18	227
T04	Non-treated control	Intact males	12	10 pens of 19, 1 pen of 17, and 1 pen of 16	223

3. Test Article Administration: Animals assigned to group T04 were not treated with saline or vehicle (non-treated control). Animals in groups T02 and T03 received subcutaneous injections (2 mL per dose of IMPROVEST). Animals assigned to group T02 were injected subcutaneously in the post-auricular region of the left side of the neck on Day 42 (9 weeks of age), while animals assigned to group T03 were injected subcutaneously in the post-auricular region of the left side of neck on Day 91 (16 weeks of age). Animals in both T02 and T03 were injected a second time subcutaneously on the right side of the neck on Day 119 (20 weeks of age).

4. Measurements and Observations: In-life phase monitoring included daily general health observations, adverse event observations, and body and feed weights. Collection of blood samples were made at weighing 2 days prior to each slaughter at 3, 9 and 10 weeks after the second dose. At slaughter, carcass quality measurements were estimated, scrotal width measurements were taken (T02, T03, and T04) and back fat samples were collected for chemical analyses. Pork loins were also collected from T02, T03, and T04 pigs for consumer sensory testing under a separate protocol (3920Z-60-10-879).

5. Statistical Analyses: The effectiveness variables tested for immunological castration were anti-GnRF antibody titers, serum testosterone levels, and scrotal widths. Pen was the experimental unit. General linear mixed models with repeated measures were used for analysis; treatment, harvest day, and treatment by harvest day interaction were fixed effects; block and heterogeneous variances by treatment group were variance components. The anti-GnRF antibody titers were log-transformed prior to analysis and back-transformed for reporting. Least square means, their standard errors and 95% confidence intervals are reported. All hypothesis tests were two-sided alpha 0.05 level tests.

6. Adverse Reactions: No test article-related adverse reactions were observed during the study.

Results:

1. Serum anti-GnRF antibody titers (Table 2): At 3, 9, and 10 weeks post second dose, pigs dosed with IMPROVEST (T02 and T03) had significantly higher (P< 0.05) anti-GnRF titers compared with intact males (T04).

Table 2. Geometric Mean Anti-GnRF Antibody Titers (U) in IMPROVEST Treated Males and Intact Males.

Treatment	No. of Pens	Geometric mean	SE	Lower 95% Confidence Limit	Upper 95% Confidence Limit
First Slaughter, Day 138 (3 weeks post 2nd dose)					
T02, IMPROVEST on Day 42 and 119	12	231.7[b]	27.5	182.3	294.5
T03, IMPROVEST on Day 91 and 119	12	501.2[a]	65.9	384.3	653.7
T04, intact males	12	9.9[c]	0.8	8.3	11.8
[a, b, c] Means with different superscripts differ significantly (P< 0.05)					
Second Slaughter, Day 180 (9 weeks post 2nd dose)					
T02, IMPROVEST on Day 42 and 119	12	30.3[b]	3.6	23.9	38.5
T03, IMPROVEST on Day 91 and 119	12	65.0[a]	8.5	49.8	84.7
T04, intact males	12	9.9[c]	0.8	8.3	11.7
[a, b, c] Means with different superscripts differ significantly (P< 0.05)					
Third Slaughter, Day 187 (10 weeks post 2nd dose)					
T02, IMPROVEST on Day 42 and 119	12	28.6[b]	3.4	22.5	36.4
T03, IMPROVEST on Day 91 and 119	12	70.7[a]	9.3	54.2	92.2
T04, intact males	12	12.7[c]	1.1	10.7	15.1
[a, b, c] Means with different superscripts differ significantly (P< 0.05)					

2. Serum testosterone (Table 3): At 3, 9, and 10 weeks post second dose, pigs dosed with IMPROVEST (T02 and T03) had significantly lower (P< 0.05) serum testosterone (ng/mL) compared with intact males (T04).

Table 3. Serum Testosterone (ng/mL) in IMPROVEST Treated Males and Intact Males.

First Slaughter, Day 138 (3 weeks post 2nd dose)

Treatment	No. of Pens	Least Squares Mean	SE	Lower 95% Confidence Limit	Upper 95% Confidence Limit
T02, IMPROVEST on Day 42 and 119	12	0.000[a]	0.25	0.000	0.505
T03, IMPROVEST on Day 91 and 119	12	0.138[a]	0.30	0.000	0.748
T04, intact males	12	3.700[b]	1.50	0.643	6.756

[a, b] Means with different superscripts differ significantly (P< 0.05)

Second Slaughter, Day 180 (9 weeks post 2nd dose)

T02, IMPROVEST on Day 42 and 119	12	0.675[a]	0.25	0.170	1.180
T03, IMPROVEST on Day 91 and 119	12	1.932[b]	0.30	1.323	2.542
T04, intact males	12	9.797[c]	1.50	6.741	12.854

[a, b, c] Means with different superscripts differ significantly (P< 0.05)

Third Slaughter, Day 187 (10 weeks post 2nd dose)

T02, IMPROVEST on Day 42 and 119	12	0.915[a]	0.25	0.410	1.420
T03, IMPROVEST on Day 91 and 119	12	2.014[b]	0.30	1.405	2.624
T04, intact males	12	8.130[c]	1.50	5.073	11.186

[a, b, c] Means with different superscripts differ significantly (P< 0.05)

3. Scrotal width (Table 4): At 3, 9, and 10 weeks post second dose, pigs dosed with IMPROVEST (T02 and T03) had significantly decreased (P< 0.05) scrotal width (mm) compared with intact males (T04).

Table 4. Scrotal Width (mm) of IMPROVEST Treated Males and Intact Males.

Treatment	No. of Pens	Least Squares Mean	SE	Lower 95% Confidence Limit	Upper 95% Confidence Limit
First Slaughter, Day 138 (3 weeks post 2nd dose)					
T02, IMPROVEST on Day 42 and 119	12	67.90[c]	3.10	61.56	74.24
T03, IMPROVEST on Day 91 and 119	12	76.37[b]	3.64	69.00	83.74
T04, intact males	12	128.33[a]	2.65	122.93	133.74
[a, b, c] Means with different superscripts differ significantly (P< 0.05)					
Second Slaughter, Day 180 (9 weeks post 2nd dose)					
T02, IMPROVEST on Day 42 and 119	12	69.57[c]	3.10	63.22	75.91
T03, IMPROVEST on Day 91 and 119	12	83.78[b]	3.64	76.41	91.15
T04, intact males	12	146.25[a]	2.65	140.84	151.66
[a, b, c] Means with different superscripts differ significantly (P< 0.05)					
Third Slaughter, Day 187 (10 weeks post 2nd dose)					
T02, IMPROVEST on Day 42 and 119	12	85.66[b]	3.10	79.31	92.00
T03, IMPROVEST on Day 91 and 119	12	92.03[b]	3.64	84.66	99.40
T04, intact males	12	145.58[a]	2.65	140.18	50.99
[a, b] Means with different superscripts differ significantly (P< 0.05)					

Overall Conclusions on Temporary Immunological Castration:

These results confirm that boars treated with IMPROVEST had significantly increased anti-GnRF antibody titers, reduced circulating testosterone concentrations, and reduced scrotal size. These effects were observed as early as 3 weeks and through 10 weeks following administration of the second dose of IMPROVEST before slaughter. Therefore, the results of this study support the claim of temporary immunological castration (suppression of testicular function) as early as 3 weeks and no later than 10 weeks following the second dose of IMPROVEST before slaughter.

2. Reduction of Boar Taint in Intact Males Intended for Slaughter

Study No. 3920Z-60-10-879. Consumer panel sensory evaluation of pork samples from clinical IMPROVEST study 3322C-60-10-828.

Investigator and Study locations:

Jeff Kerr -
Peryam & Kroll Research Corporation
Chicago, IL -

Sample and processing shipping site:
Iowa State University Meat Laboratory, Ames IA

Consumer Sensory Evaluation Site:
Peryam & Kroll Research, Chicago, IL

Study Design:

1. Objective: To conduct sensitive consumer panel sensory evaluations (aroma and flavor) of pork samples generated from non-treated intact boars, boars that had received the second dose of IMPROVEST at 3 weeks prior to slaughter, and boars that received the second dose of IMPROVEST at 10 weeks prior to slaughter.

2. Study Animals: A total of 540 animals were selected from study 3322C-60-10-828; treatments T02, T03, and T04 were used for sensory evaluation. A total of 60 loins were collected from each treatment group (T02, T03, and T04) on each of the three slaughter days (Day 138,180 and 187, 3, 9 and 10 weeks post 2nd IMPROVEST dose, respectively).

3. Pork Samples: Loins collected from the study animals were processed into boneless loin chops and evaluated by consumers. Boneless loin chops from 238 pigs treated with 2 doses of IMPROVEST (T02 and T03) and 119 non-treated, intact male pigs (T04) were evaluated for aroma and flavor by sensitive consumers.

Samples from IMPROVEST treated pigs (T02 and T03) were prepared and cooked in a different kitchen than boar samples (T04). Within each block, animals were randomly assigned to groups so each group contained one T02, one T03, and one T04 animal. One T02 animal and one T04 animal were excluded from this study because they did not meet the inclusion criteria. Therefore, one T03 animal was randomly selected for exclusion to obtain an equal number of animals per treatment. Groups were randomly assigned an order to be evaluated (order of testing). Within the groups, the order that the treatment groups were evaluated (order of presentation) was randomly assigned.

4. Consumer Panelist: Consumers were representative of the U.S. population and were comprised of approximately equal numbers of adult (≥ 18 years old) males and females who like fresh pork and consumed it regularly (at least once per month). Consumers were screened for their ability to differentiate between boar and barrow samples. Consumers were screened (both aroma and flavor) for sensitivity to boar taint (Table 5 and Table 6).

Table 5. Consumer Panel Information for Pork Samples Generated From Intact Boars Receiving the 2nd Dose of IMPROVEST at 3 or 10 Weeks Prior to Slaughter.

	3 week samples		10 week samples	
Description	**Number**	**%**	**Number**	**%**
Total days session run	12	---	13	---
Total sessions run	58	---	61	---
Total consumers invited to participate	2318	---	2329	---
Total consumers screened	1806	77.9	1865	80.1
Total consumers passed aroma screen	492	27.2	533	28.6
Total consumers passed flavor screen and evaluated study samples	180	10	177	9.5
Total repeat consumers from previous studies[1]	35	19.4	20	11.3

[1] Consumers who passed the aroma screen in previous IMPROVEST consumer studies conducted at P&K were invited to participate. This number represents those repeat consumers that passed both levels of screening and evaluated study samples in this study.

Table 6. Consumer Panel Sensory Evaluation of Pork Samples Generated From Intact Boars Receiving the 2nd Dose of IMPROVEST at 3 or 10 Weeks Prior to Slaughter: Consumer Demographics.

	Recruitment Targets[1]	3 week samples		10 week samples	
Ethnicity	**%**	**Number**	**%**	**Number**	**%**
Male	50	62	34	64	36
Female	50	118	66	113	64
Caucasian	66	129	72	115	65
African American	13	23	13	34	19
Hispanic/Latino	15	22	12	25	14
Asian American	5	4	2	1	1
Other/Don't know	1	2	1	2	1

[1] Respondents who were invited to participate in the study were recruited based on ethnicity quotas to be close to the U.S. Census in 2008.

5. Measurements and Observations: The consumer panelists evaluated the first sample as unpleasant ('yes' or 'no'), first for aroma and second for flavor. When done, the consumer was presented with the second sample followed by the third sample, which was similarly evaluated. A panel of three consumers evaluated a block of three loin chops, one from each treatment group.

6. Statistical Analyses: If two of the three testers found the aroma unacceptable, the aroma of the chop was determined to be unacceptable. The same was true for taste.

The binary responses, aroma acceptability, and taste acceptability were analyzed using a generalized linear mixed model with a binomial distribution and logit link function. Treatment was a fixed effect in the model and the random effects were block, panel nested within block, and residual. The model also included an over-dispersion parameter. The analysis was done for first harvest and third harvest chops separately. The least squares means, their standard errors and 95% confidence intervals were back-transformed and reported.

Results:

1. Aroma (Table 7):

Table 7. Consumer Panel Sensory Evaluation of Pork Samples Generated from Clinical IMPROVEST Study 3322C-60-10-828: "Not Acceptable" Aroma Scores.

	Treatment[a]	"Not Acceptable" Aroma Scores (%)			
		Back-transformed LS Means	SE	Lower 95% Confidence Limit	Upper 95% Confidence Limit
3 week DOE[f] (Phase I)	T02 – IMPROVEST (9 & 20 weeks)	43.0[b]	6.7	30.4	56.7
	T03 – IMPROVEST (16 & 20 weeks)	50.0[c]	6.8	36.7	63.3
	T04 – None	70.1	6.1	56.6	80.8
10 week DOE (Phase II)	T02 – IMPROVEST (9 & 20 weeks)	20.6[d]	7.1	9.4	39.4
	T03 – IMPROVEST (16 & 20 weeks)	15.1[e]	5.7	6.6	31.2
	T04 – None	86.1	5.4	70.8	94.1

[a] 9 & 20 weeks and 16 & 20 weeks refer to the age of the pig at time of dosing with IMPROVEST.
[b] T02 vs T04, $P = 0.0029$
[c] T03 vs T04, $P = 0.0233$
[d] T02 vs T04, $P < 0.0001$
[e] T03 vs T04, $P < 0.0001$
[f] Duration of effect (DOE)

2. Flavor/Taste (Table 8):

Table 8. Consumer Panel Sensory Evaluation of Pork Samples Generated from Clinical IMPROVEST Study 3322C-60-10-828: "Not Acceptable" Flavor Scores.

	Treatment[a]	"Not Acceptable" Aroma Scores (%)			
		Back-transformed LS Means	SE	Lower 95% Confidence Limit	Upper 95% Confidence Limit
3 week DOE[f] (Phase I)	T02 – IMPROVEST (9 & 20 weeks)	14.0[b]	4.6	7.0	26.0
	T03 – IMPROVEST (16 & 20 weeks)	17.5[c]	5.3	9.2	30.8
	T04 – None	33.4	7.4	20.1	49.9
10 week DOE (Phase II)	T02 – IMPROVEST (9 & 20 weeks)	19.4[d]	5.1	11.3	31.3
	T03 – IMPROVEST (16 & 20 weeks)	21.1[e]	5.3	12.5	33.4
	T04 – None	58.6	6.9	44.7	71.3

[a] 9 & 20 weeks and 16 & 20 weeks refer to the age of the pig at time of dosing with IMPROVEST.
[b] T02 vs T04, $P = 0.0051$
[c] T03 vs T04, $P = 0.0248$
[d] T02 vs T04, $P < 0.0001$
[e] T03 vs T04, $P < 0.0001$
[f] Duration of effect (DOE)

Conclusions on Reduction of Boar Taint:

Aroma and flavor data from the consumer panel sensory evaluation study (Study no. 3920Z-60-10-879) provide significant evidence for the proposed indication for the reduction of boar taint in the meat of intact male swine slaughtered no earlier than 3 weeks and no later than 10 weeks after receipt of the second dose of IMPROVEST.

Overall Conclusions of the Temporary Immunological Castration (Suppression of Testicular Function) and Reduction of Boar Taint:

The data included in the supplemental application support the proposed extension of the slaughter interval for IMPROVEST after the second dose from 4 to 8 weeks to 3 to 10 weeks. -

TARGET ANIMAL SAFETY: -

CVM did not require target animal safety studies for this supplemental approval. The FOI Summary for the original approval of NADA 141-322 dated March 22, 2011, contains a summary of target animal safety studies for intact male swine. -

HUMAN FOOD SAFETY:

C. Microbial Food Safety:

GnRF analog-DT conjugate (IMPROVEST) is neither thought, nor has been reported to impact antimicrobial resistance among bacteria of public health concern in or on treated boars. The Agency has determined that an assessment of the microbial food safety for the use of IMPROVEST in intact boars pursuant to this supplemental approval (extension of the slaughter interval following injection of the second dose of IMPROVEST) was not necessary.

D. Impact of Residues on Human Intestinal Flora:

Residues and metabolites of GnRF analog-DT conjugate (IMPROVEST) in or on the edible tissues of treated boars are neither thought, nor have been reported to impact the intestinal flora of human consumers. The Agency has determined that an assessment of the impact of IMPROVEST on human intestinal flora pursuant to the conditions of this supplemental approval (extension of the slaughter interval following injection of the second dose of IMPROVEST) was not necessary.

E. Toxicology:

CVM did not require toxicology studies for this supplemental approval. The FOI Summary for the original approval of NADA 141-322, dated March 22, 2011, contains a summary of all toxicology studies. -

F. Assignment of the Final ADI:

No reassessment of the toxicological ADI or toxicological ASDI was needed for this supplemental approval. The FOI Summary for the original approval of NADA 141-322, dated March 22, 2011, contains a summary of all toxicology studies.

G. Safe Concentrations for Total Residues (edible tissues and injection sites):

No reassessment of the safe concentrations for total residues was needed for this supplemental approval. The FOI Summary for the original approval of NADA 141-322 dated March 22, 2011, contains a summary of all toxicology studies.

H. Residue Chemistry:

CVM did not require residue chemistry studies for this supplemental approval. The FOI Summary for the original approval of NADA 141-322 dated March 22, 2011, contains a summary of residue chemistry studies for intact male swine.

I. Analytical Method for Residues:

The FOI Summary for the original approval of NADA 141-322 dated March 22, 2011, contains the information regarding regulatory methods for IMPROVEST in intact male swine.

USER SAFETY: -

The product labeling contains the following information regarding safety to humans handling, administering, or exposed to IMPROVEST: -

CONTRAINDICATIONS: -
Not approved for use in female pigs and barrows. -

Do not use IMPROVEST in intact male pigs intended for breeding because of the disruption of reproductive function. -

WARNINGS:

WITHDRAWAL PERIODS:
No withdrawal period is required when used according to labeling.

Not for Human Use. Keep Out of Reach of Children.

USER SAFETY WARNINGS:

Warning for person administering IMPROVEST: Accidental self injection could affect reproductive physiology of both men and women and may adversely affect pregnancy. **Pregnant women should not administer this product. Women of childbearing age should exercise extreme caution when handling this product.** Special care should be taken to avoid accidental self injection and needle stick injury when administering the product. Protective clothing including, but not limited to, safety glasses and gloves should be worn. Use a safety injector, preferably one which has a dual safety system providing both a needle guard and a mechanism to prevent accidental operation of the trigger. In case of eye contact, rinse immediately with copious amounts of water. In case of skin contact, wash immediately with soap and water. The product should be stored safely out of the reach of children. As a reminder, it is the prescribing veterinarian's responsibility to inform drug administrators of the user safety warnings associated with IMPROVEST.

Advice to the user in the event of accidental self injection: In the event of accidental self injection, wash the injury thoroughly with clean running water. Seek prompt medical attention and take the package leaflet with you. Do not administer the product, and/or any other product with a similar action, in the future.

Advice to the physician: Accidental self injection could affect reproductive physiology of both men and women and may adversely affect pregnancy. If self injection with IMPROVEST is suspected, reproductive physiology should be monitored by assay of testosterone or estrogen levels (as appropriate). The risk of a physiological effect is greater after a second or subsequent accidental injection than after a first injection. The patient should be advised not to administer IMPROVEST, and/or any other product with a similar action, in the future.

For customer service, to report suspected adverse reactions or to obtain a copy of the Material Safety Data Sheet (MSDS) call 1-800-336-5288.

PRECAUTIONS: Subcutaneous injection in intact male pigs can cause a transient local injection site reaction that may result in trim loss at slaughter.

ADVERSE REACTIONS: IMPROVEST did not cause unusual clinical signs or an unexpected frequency or severity of injection site reactions. Adverse events, as reported, were not uniquely attributable to IMPROVEST.

AGENCY CONCLUSIONS:

The data submitted in support of this NADA satisfy the requirements of section 512 of the Federal Food, Drug, and Cosmetic Act and 21 CFR part 514. The data demonstrate that IMPROVEST, when used according to the label, is safe and effective for the temporary immunological castration (suppression of testicular function) and reduction of boar taint in intact male pigs intended for slaughter no earlier than 3 weeks and no later than 10 weeks after receipt of the second dose of IMPROVEST. Additionally, data demonstrate that residues in food products derived from intact male swine treated with IMPROVEST will not represent a public health concern when the product is used according to the label.

J. Marketing Status:

This product may be dispensed only by or on the lawful order of a licensed veterinarian. Adequate directions for lay use cannot be written because profession expertise is required to properly administer the injection and due to the significant impact on human reproductive function if self-injected.

K. Exclusivity:

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 the approval.

L. Supplemental Applications:

This supplemental NADA did not require a reevaluation of the safety or effectiveness data in the original NADA (21 CFR 514.106(b)(2)).