Zuprevo® 18% Competitive 5-day *Histophilus somni* Challenge Study

In a blind study conducted at Oklahoma State University by Dr. Anthony Confer, 3- to 4-month-old Holstein calves free from concurrent BVDV infection, received the test articles five days prior to experimental challenge with a strain of *Histophilus somni* equally susceptible to both Zuprevo® 18% and Draxxin®. The objective of this study was to determine the effectiveness of Zuprevo 18% five days after administration in the control of an experimentally induced *Histophilus somni* infection of the respiratory tract in cattle, as compared to isotonic saline (NaCl) and to an approved reference article (Draxxin, Zoetis Animal Health). Ultimately, the study determined:

- **Zuprevo-treated calves 24, 48, and 72 hours after challenge had lower clinical scores than did the other two groups.** Zuprevo was superior to Draxxin in reducing clinical signs to pre-challenge levels. These findings are consistent with necropsy findings and bacteriology results that indicated that few lesions were present and *H. somni* was not isolated from Zuprevo-treated calves.
- **Zuprevo-treated calves had lower rectal temperatures 48 and 72 hours after-challenge than did the other two groups.** All calves had increased rectal temperatures by 24 hours after challenge, which is expected because of the large bolus of bacteria given intrabronchially. Zuprevo-treated calves responded rapidly with reduction of rectal temperature, which parallels lower clinical scores, fewer and less-severe lesions, and lack of *H. somni* isolation.
- **Zuprevo-treated calves had significantly lower lung weights, percent pneumonia and lung weight/body weight percentages than did the other two groups.** Both percent lung weight/body weight and percent pneumonia scores demonstrated that Zuprevo-treated calves had less pneumonia than either the Control or Draxxin-treated calves. The Control and Draxxin-treated groups had less severe lung lesion scores as measured by both techniques.
- **Total histopathologic lesion scores were lower for the Zuprevo-treated calves compared to Control group lesion scores, and were lower for the Draxxin-treated group compared to the Control group scores.** Examination of histopathology of pneumonic lung sections did not particularly enhance the findings of the study determined by clinical and gross necropsy evaluations. Both antibiotic-treated groups had lower histopathology and necrosis scores than did the Control group. One histopathologic finding that stood out was that the Zuprevo-treated calves had only a minimal amount of necrosis within the lungs. The implication of that finding is if those calves had been allowed to survive, lung scarring would be limited, whereas because of the extent of necrosis in the other two groups, lung scarring would be greater if they had been allowed to survive.
- ***H. somni* was not reisolated from bronchi of Zuprevo-treated cattle at necropsy and *P. multocida* was isolated from only one Zuprevo-treated calf (12.5%) compared to 87.5% and 75% of the Control and Draxxin-treated calves, respectively.** These data may indicate that in Zuprevo metaphylaxis, not only is *H. somni* inhibited but the potential for a secondary bacterial pneumonia from *P. multocida* also is reduced.

IMPORTANT SAFETY INFORMATION

FOR USE IN ANIMALS ONLY. NOT FOR HUMAN USE. KEEP OUT OF REACH OF CHILDREN. TO AVOID ACCIDENTAL INJECTION, DO NOT USE IN AUTOMATICALLY POWERED SYRINGES WHICH HAVE NO ADDITIONAL PROTECTION SYSTEM. IN CASE OF HUMAN INJECTION, SEEK MEDICAL ADVICE IMMEDIATELY AND SHOW THE PACKAGE INSERT OR LABEL TO THE PHYSICIAN. DO NOT USE Zuprevo® 18% IN SWINE. Fatal adverse events have been reported following the use of tildipirosin in swine. NOT FOR USE IN CHICKENS OR TURKEYS. Cattle intended for human consumption must not be slaughtered within 21 days of the last treatment. Do not use in female dairy cattle 20 months of age or older. A withdrawal period has not been established in pre-ruminating calves. Do not use in calves to be processed for veal. The effects of Zuprevo® 18% on bovine reproductive performance, pregnancy and lactation have not been determined. Swelling and inflammation, which may be severe, may be seen at the injection site after administration. Subcutaneous injection may result in local tissue reactions which persist beyond slaughter withdrawal period. This may result in trim loss of edible tissue at slaughter.

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THE STUDY DESIGN

On November 20, 2014, 24 Holstein and Holstein-cross steers, approximately 3-4 months old, were purchased from a major south-central Oklahoma dairy, delivered to Oklahoma State University Bovine Research Park, and randomly allocated to one of three treatment groups. At acquisition, each animal was weighed and identified with a tag in the right ear (numbers 1-24).

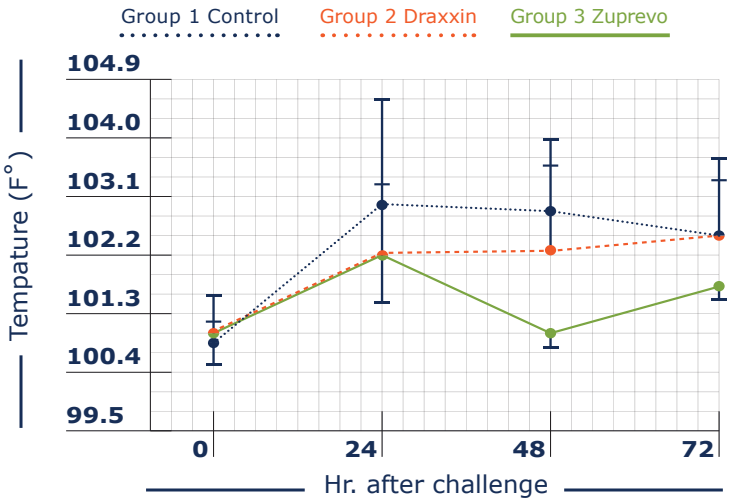
Calves were housed in a BSL-2 barn, four to a pen, fed a complete commercial calf ration twice a day, and given access to water ad libitum. Animal care was overseen by the Animal Resources Unit at Oklahoma State University, an Association for Assessment and Accreditation of Laboratory Animal Care International, or AALAC, accredited facility.
The study was conducted under Institutional Animal Care and Use Committee, or IACUC, approved protocol VM1045.

Clinical scores (mean ± SD) after challenge. Maximum score 10 for times 0, 12, 24, & 48 hr. Maximum score of 7 for time 72 hr, because harvested before feeding and anorexia could not be evaluated.

Group	Time after challenge				
	0	12hr	Day 1*	Day 2*	Day 3*
Zuprevo	0.0 ± 0.0	4.4 ± 2.7**	0.5 ± 1.0[a]	0.3 ± 0.5[a]	0.3 ± 0.5[a]
Draxxin	0.13 ±0.35	4.6 ± 2.6**	2.4 ± 0.5[b]	1.7 ± 1.2[b]	1.9 ± 1.5[b]
Saline	0.0 ± 0.0	6.3 ± 2.3**	3.5 ± 0.9[c]	3.4 ± 1.2[c]	2.8 ± 1.2[b]

*Clinical scores are the mean of assessments in early morning and late evening
** $p < 0.001$ compared to day 0 by paired *t* test
Within columns, superscript differences indicate significant difference at p <0.05

Mean rectal temperature responses ± SD for each group after intra-bronchial challenge with *H. somni* strain 7735.



Body weight in kilograms (BW ± SD) at receiving, challenge, and necropsy. Lung weights in grams (LW) at necropsy, percentage LW/BW challenge, and % pneumonia.

Group	BW (kg) receiving	BW (kg) challenge	BW (kg) necropsy	LW (g)	%LW/BW challenge	% pneumonia
Zuprevo	78.9±5.9	81.9±10.3	79.0±5.9	1065.8±171.4[a]	1.31±0.2[a]	6.0±2.3[a]
Draxxin	76.7±9.3	78.8±8.6	76.7±9.4	1253.9±274.1[ac]	1.61±0.4[b]	30.9±21.5[b]
Saline	74.3±7.0	78.7±5.3	74.2±7.0*	1270.5±88.1[c]	1.62±0.1[b]	26.3±17.6[b]

* $p < 0.001$ compared to BW challenge by paired *t* test

Within columns, superscript differences indicate significant difference at p <0.05

Lung histopathology scores (LHS ± SD).*

Group	RLung**	LLung**	Necrosis***	Total LHS
Zuprevo	2.9±0.6[a]	0.5±0.8[a]	0.3±0.7[a]	3.6±1.5[a]
Draxxin	3.5±0.8[ab]	1.4±1.2[a]	1.4±1.2[a]	6.3±2.6[ab]
Saline	4.0±0.0[c]	1.9±1.5[b]	2.1±1.6[b]	8.0±2.2[c]

*Lung histopathology score (LHS) is the summation of lesion score for sections from each lung and the Extent score.

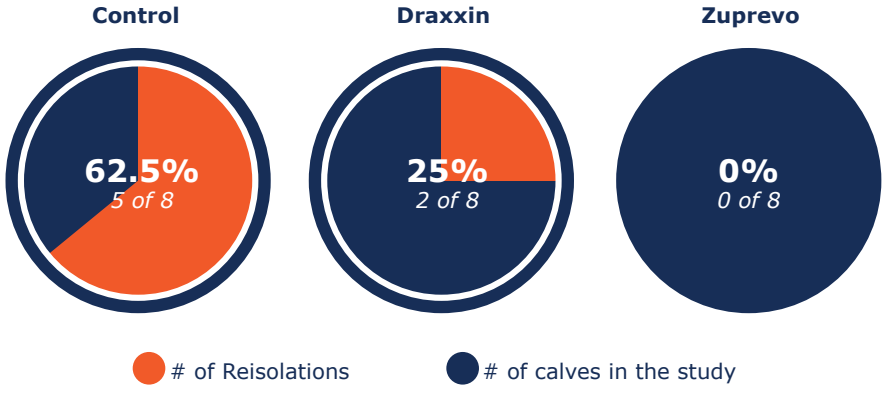
**Lesion scores: 0 = no lesion, essentially normal lung; 1 = Minimal changes; 2 = Mild changes; 3 = Moderate changes;
4 = Severe changes.

***Necrosis score is extent of necrosis present in the lung. 0 = no lesion, essentially normal lung; 1 = Minimal changes; 2 = Mild changes; 3 = Moderate changes; 4 = Severe changes.

Within columns, superscript differences indicate significant difference at p <0.05

H. somni in Zuprevo, Draxxin and Control-treated cattle

H. somni Reisolation in Zuprevo Treated Cattle



H. somni was reisolated from the main bronchi in two Draxxin-treated, five Controls, and none of the Zuprevo-treated calves. There was a significant difference ($p < 0.01$) between the numbers of Control calves from which *H. somni* was reisolated compared to the number of Zuprevo-treated calves. The differences between isolation of *H. somni* in the Draxxin-treated and Zuprevo-treated or Draxxin-treated and Control groups were not significant ($p > 0.05$).

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