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Evaluation Of The Duration Of Effectiveness Of Ceftiofur Crystalline Free Acid Sterile Suspension In Swine Using An *Actinobacillus pleuropneumoniae* Challenge Model

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Introduction and Objectives

Ceftiofur crystalline free acid (CCFA) is veterinary specific cephalosporin metabolized in vivo to desfuroylceftiofur and related metabolites, as are ceftiofur sodium (NAXCEL®/EXCENEL® Sterile Powder) and ceftiofur hydrochloride (EXCENEL RTU Sterile Suspension). The dosage form is a unique sustained-release, ready-to-use sterile suspension of CCFA (EXCEDE™ For Swine; Pfizer) that delivers a complete treatment against key respiratory pathogens of swine with a single intramuscular (IM) dose (5 mg ceftiofur-equivalents (CE)/kg BW).

Pharmacokinetic (PK) data using a single 5 mg CE/kg IM dose of CCFA in swine have demonstrated plasma levels of ceftiofur and desfuroylceftiofur metabolites to be maintained above 0.2 μg/mL (above the MICs for nearly 100% of target respiratory pathogens isolated and tested over the past 12 years) for an average of 8 days post-injection (1-3). The objective of this randomized, masked, negative-controlled study was to clinically validate this PK data by evaluating the duration of effectiveness of a single IM injection of 5 mg CE/kg CCFA at different times prior to intratracheal challenge with a highly virulent strain of *Actinobacillus pleuropneumoniae* (APP) (serotype 5). This study was conducted under close veterinary supervision and was pre-approved by an Institutional Animal Care and Use Committee.

Materials and Methods

One hundred and ninety (190) crossbred pigs, 4 to 5 weeks old, were blocked on weight and, within the same room, randomly assigned to 19 pens of 10 pigs each. The pens were randomly assigned to treatments (Table 1) such that each treatment was represented by three pens (replicates). A single pen of 10 pigs was assigned as a sentinel (NTX) pen.

Table 1: Treatment groups

Group	Treatment
T01	CCFA 13 days prior to challenge
T02	CCFA 10 days prior to challenge
T03	CCFA 7 days prior to challenge
T04	CCFA 4 days prior to challenge
T05	CCFA 1 day prior to challenge
T06	No CCFA / challenged
NTX (Sentinel)	No CCFA / not challenged

All pigs assigned to receive CCFA (T01–T05) were administered a single 5 mg CE/kg BW dose by deep IM injection in the neck. All pigs (except the sentinels) were subsequently challenged on the same day (day 0) by intratracheal inoculation with 5 mL of a broth culture of APP serotype 5, containing approximately 8 x 10^6 CFU/mL. The observation period extended to 9 days post-challenge. This peracute disease required that animal removal rate (animals removed from the study for welfare reasons and mortalities) was the primary efficacy variable. Removal (binary: 1=removed, 0=not removed) was transformed prior to analysis (Freeman-Tukey arcsine transformation on the proportion of animals removed from each pen within treatment). Weighted ANOVA (weight equal number of animals from each pen within treatment) included the fixed effect of treatment and the random residual effect. Rectal temperatures, general clinical appearances, respiratory indices, and lung lesion scores at necropsy (9 days following challenge), were included as ancillary variables. All scoring/recording was performed by personnel blinded to treatment.

Results and Discussion

Table 2 presents the results for the primary variable.

Table 2: Percent pig removal

Group	T01	T02	T03	T04	T05	T06	NTX
% removal[a]	86.4	96.4	23.3[b]	0[b]	0[b]	89.3	10.0

[a] back-transformed least square means from Freeman-Tukey arcsine scale
[b] significant difference ($p<0.05$) compared with T06 control

The challenge was successful and caused a peracute, severe pleuropneumonia which resulted in 89.3% of the untreated challenged control pigs (T06) being removed within 24 hours of challenge. In contrast, all pigs (100%) administered CCFA 1 and 4 days prior to challenge (T04 and T05) continued to termination ($p<0.001$ vs. controls), and of those pigs administered CCFA 7 days prior to challenge (T03) 76.7% continued to termination ($p<0.001$ vs. controls). No therapeutic activity was detected in either the 10 or 13 day pre-challenge CCFA-treated groups (T01 and T02). One pig in the sentinel NTX pen (10%) died from confirmed APP pleuropneumonia. Due to very high animal removal rate within the first 24 hours, the ancillary variables were not statistically analyzed.

Conclusion

This peracute, severe APP challenge model study demonstrated extended therapeutic activity of a single IM 5 mg CE/kg BW dose of CCFA to at least 7 days post-injection. It provides clinical validation of the existing PK data for CCFA (1). This complete treatment in a single dose provides benefits of improved convenience, dosing compliance and animal welfare.

References

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