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Randomized clinical trial of famciclovir or acyclovir for the treatment of herpes zoster in adults

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ABSTRACT

Background: This study investigated the safety and efficacy of famciclovir compared to acyclovir in patients with herpes zoster, to determine whether the two regimens are equally effective for the treatment of patients with uncomplicated herpes zoster over a period of 7 days.
Methods: Patients were randomly assigned to receive either famciclovir 500 mg (one tablet) three times daily or acyclovir 800 mg (two capsules) five times daily for 7 days. The primary endpoint was defined as the time to full crusting of herpes zoster lesions. Secondary endpoints were the proportion of patients who achieved complete cure and the change in score of signs/symptoms (pain, vesicular lesions, loss of sensitivity, burning pain, and pruritus) according to the patient diary. This study has been registered at ClinicalTrials.gov (NCT01327144).
Results: One hundred and seventy-four patients were enrolled and randomized; 151 of these patients completed treatment ($n = 75$ famciclovir, $n = 76$ acyclovir). A similar proportion of patients who received acyclovir (94.74%) and famciclovir (94.67%) achieved complete cure. The mean time to full crusting of herpes zoster lesions was 15.033 days in the acyclovir group and 14.840 days in the famciclovir group (log-rank p-value = 0.820). The most common adverse events in the pooled groups were headache, diarrhea, nausea, back pain, cold, and drowsiness, but none of these was deemed to be clinically important.
Conclusions: Both interventions obtained high rates of cure and had a similar time to full crusting of lesions. Analysis of the primary efficacy endpoint proved that famciclovir is non-inferior to acyclovir, as the confidence interval for the difference in efficacy did not violate the non-inferior margin. Therefore, the results are not different enough to be clinically relevant.

Introduction

Herpes zoster (HZ), or shingles, is a clinical syndrome resulting from the reactivation of latent varicella zoster virus (VZV) within the sensory ganglia, manifesting as a unilateral vesicular skin eruption involving one to three dermatomes (Pearce, 2005; Thyregod et al., 2007). Approximately one out of every three people will present an episode of shingles during their lifetime. The number of new cases per year varies between 1.2 and 3.4 per 1000 people among healthy adults and between 3.9 and 11.8 per 1000 people among those over 65 years of age, reaching 4.5 per 1000 person-years above 75 years of age (Wilson, 2011; Dworkin et al., 2007a; Rodrigues et al., 2010; Centers for Disease Control and Prevention, 2017; Dworkin et al., 2008; Johnson et al., 2010; Reis et al., 2003). According to an epidemiological study conducted in Brazil, 95% of adults have already been exposed to VZV (Reis et al., 2003). Although it is more common among the elderly, HZ can occur at any age, provided that the individual has already been infected by VZV.

In the course of viral reactivation, the virus spreads centrally and peripherally from the dorsal ganglia, producing intense inflammation in the skin, affecting the peripheral nerves and nerve roots; it may also reach the spinal cord. The vesicular rash is often painful and the pain can occur before the onset of rash, or may occur without the development of a rash in rare cases (herpes sine herpete) (Sampathkumar et al., 2009; Cohen, 2013; Wilson, 2011; Dworkin et al., 2007a).

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The management of uncomplicated HZ involves antiviral therapy to promote faster healing of the cutaneous lesions. In patients with moderate to severe acute neuritis, analgesic treatment may also be given. Famciclovir, the oral prodrug of penciclovir, belongs to the same family of anti-herpetic agents as acyclovir and valaciclovir (oral prodrug of acyclovir), but has different pharmacokinetic and antiviral properties (Field and Vere Hodge, 2013). Although penciclovir and acyclovir appear to have similar effects in VZV-infected cells, penciclovir triphosphate persists far longer than acyclovir triphosphate, resulting in more prolonged antiviral activity (Degreef and Famciclovir Herpes Zoster Clinical Study Group, 1994).

This study investigated the safety and efficacy of famciclovir compared to acyclovir in patients with HZ, to determine whether the two regimens are equally effective for the treatment of uncomplicated HZ patients over a period of 7 days.

Patients and methods

Design overview

This was a multicenter, single-blind, active-controlled, parallel-group, non-inferiority phase 3 study to compare the efficacy and safety of famciclovir and acyclovir in immunocompetent adults with uncomplicated HZ. Patients were followed for 28 days, with intermediate visits on days 7 and 14. The study was conducted in accordance with the ethical principles laid out in the Declaration of Helsinki, and the protocol was approved by the ethics committees of all participating sites. All patients provided written informed consent to participate. This study has been registered at ClinicalTrials.gov (NCT01327144).

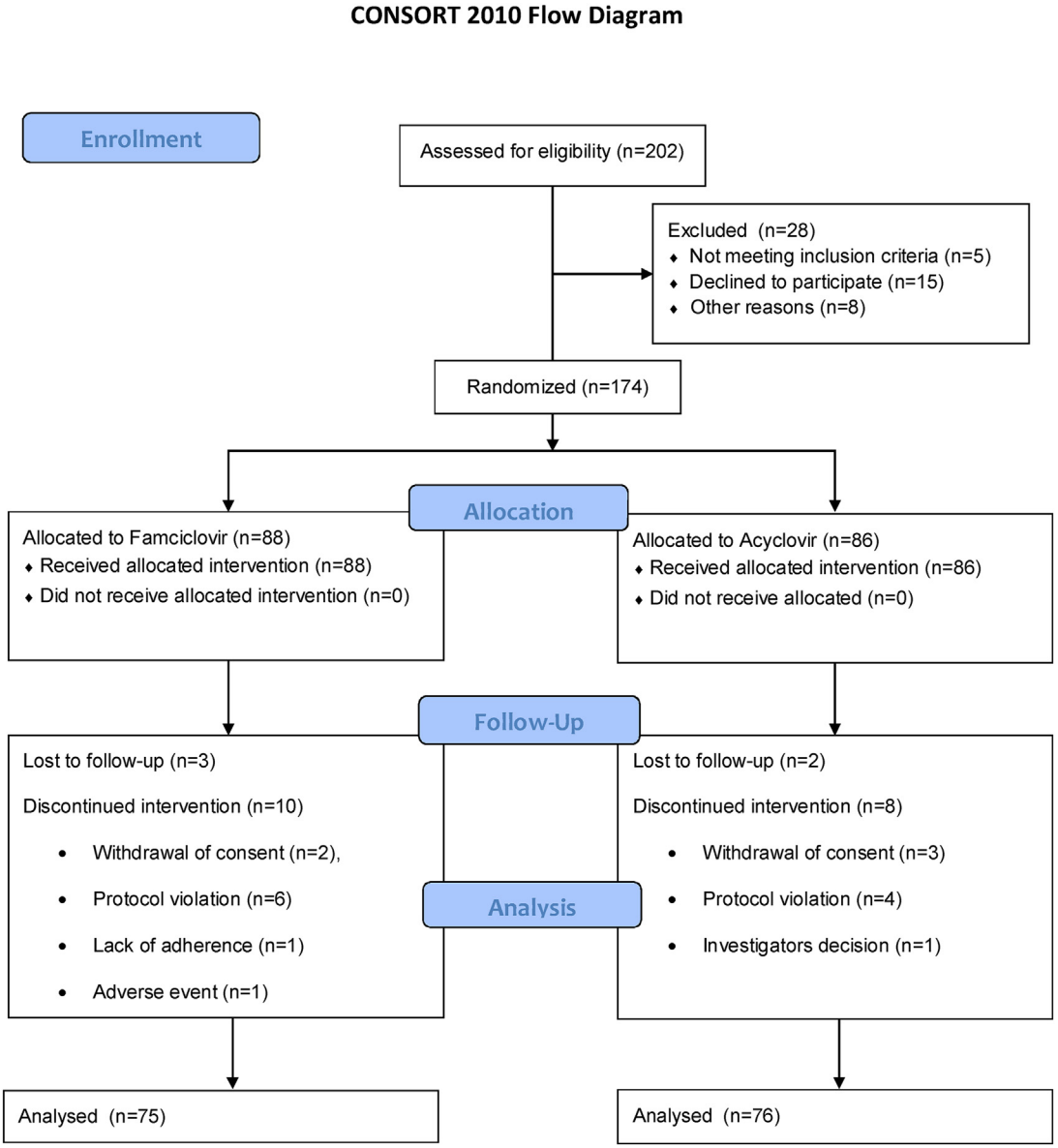

Figure 1. Trial flowchart.

Participants

Patients were enrolled if they met the following criteria: immunocompetent adults older than 18 years with uncomplicated HZ and with a score of 40 mm or more on the visual analog scale (VAS) for at least two of the following symptoms/signs: pain, loss of sensitivity, burning, and pruritus. Uncomplicated HZ infection was defined as a unilateral vesicular rash affecting one to three adjacent dermatomes, often accompanied or preceded by pain. Key exclusion criteria included a clinical diagnosis of severe HZ infection, history of hypersensitivity to famciclovir or acyclovir, previous use of antiviral drugs or corticosteroid therapy, severe systemic disease, and breastfeeding or pregnancy.

Randomization and intervention

Eligible patients were randomly assigned (1:1) to either famciclovir 500 mg (one tablet) three times daily or acyclovir 800 mg (two capsules) five times daily according to a computer-generated randomization code. All therapy was given orally for 7 days.

Study assessments

Efficacy

After the baseline assessment, lesions were evaluated by the investigator after 7 days of treatment and on days 7 and 21 post-therapy. The primary endpoint was defined as the time to full crusting of HZ lesions. Secondary endpoints were the proportion of patients who achieved complete cure and the individual score change for signs/symptoms (pain, vesicular lesions, loss of sensitivity, burning pain, and pruritus) according to the patient self-reported diary. Each sign/symptom was evaluated once daily for 28 days based on a VAS. Each patient self-administered the questionnaire, filling out the form before the beginning of treatment and then every day, on the basis of symptoms in the previous 24 h.

Safety

Serum electrolytes, liver enzymes, creatinine, and the full blood count were assessed at admission and before outpatient discharge. Decisions regarding discharge were made on an individual basis after a substantial improvement in symptoms.

Statistical methods

For all efficacy endpoints, the statistical analyses were performed in the per-protocol (PP) population, which included patients who were more compliant with the study protocol.

The sample size was estimated to detect non-inferiority in the differences between the rates of completely cured patients in each group, presuming a cure rate of log(1.20) in the arm that received acyclovir, and a non-inferiority margin of -log(1.50). Assuming a dropout rate of 10% after randomization, 76 randomized patients per group (152 total) provided 80% power to show that the rate cured patients with famciclovir was noninferior to that of acyclovir at the 5% significance level.

All analyses were conducted using R 3.4.3 (The R Project for Statistical Computing, 2017) in R-studio 1.0.136 (RStudio Inc., Boston, MA, USA).

Results

A total of 174 patients were enrolled and randomized. These 174 patients started treatment between December 2015 and July 2017. Twenty-three patients were discontinued (Figure 1). Common reasons for discontinuation were loss to follow-up (two in the acyclovir group and three in the famciclovir group), withdrawal of consent (three on acyclovir and two on famciclovir), and protocol violation (four on acyclovir and six on famciclovir). Other reasons included lack of adherence (one on famciclovir), adverse event (one on famciclovir), and investigator decision (one on acyclovir).

There were no clinically meaningful differences between the treatment groups in patient characteristics at baseline (Table 1). More than half of the patients were female (64.9%). The median age was 59 years (range 18–92 years), and the mean baseline VAS scores for the symptoms/signs were 6.16 ± 2.86 for pain, 6.43 ± 1.88 for vesicular lesions, 3.59 ± 3.31 for loss of sensitivity, 6.26 ± 2.90 for burning pain, and 5.34 ± 3.45 for pruritus.

Efficacy

The distribution of each efficacy parameter was estimated by Kaplan–Meier method and the differences between the treatments were determined using the Cox proportional hazards model considering treatment, age, sex, and baseline pain as co-variables. The mean time to full crusting of the HZ lesions was 15.033 days for the acyclovir group and 14.840 days for the famciclovir group (log-rank p-value = 0.820) (Figure 2).

Secondary outcomes

Similar proportions of patients who received acyclovir (94.74%) and famciclovir (94.67%) achieved complete cure (Table 2). The difference in complete cure rate between acyclovir and famciclovir was 0.07% (95% confidence interval −7.18% to 7.32%). Therefore, non-inferiority of famciclovir to acyclovir was verified according to this analysis.

As indicated in Table 3, the intensity scores for each of the assessed signs/symptoms over the follow-up period showed no statistically significant difference between the two treatment groups.

Safety

Adverse events (AEs) were consistent with those reported in previous clinical trials of famciclovir and acyclovir; no additional or unique adverse events occurred.

Overall frequencies of adverse events were similar in the two groups during the entire treatment. There were 142 episodes of adverse events, of which 79 (55.63%) occurred in the acyclovir group and 63 (44.37%) in the group treated with famciclovir. No serious, grade 2, grade 3, or grade 4 adverse events were identified

Table 1
Descriptive statistics for demographic data and baseline visual analog scale (VAS) scores for signs and symptoms; mean ± standard deviation values, unless stated otherwise.

Variable	Overall $N = 174$	Famciclovir $n = 88$	Acyclovir $n = 86$	p-Value
Female, n (%)	113 (64.9%)	60 (68.18%)	55 (61.63%)	0.428[a]
Age (years)	54.94 ± 17.28	55.90 ± 17.84	53.95 ± 16.75	0.460[b]
Weight (kg)	73.98 ± 15.70	73.81 ± 16.02	74.16 ± 15,47	0.887[b]
Height (cm)	164.15 ± 9.86	163.59 ± 10.40	164.73 ± 9.29	0.449[b]
Baseline evaluation (VAS, mm)				
Pain	6.16 ± 2.86	6.32 ± 2.81	5.99 ± 2.92	0.449[b]
Vesicular lesions	6.43 ± 1.88	6.55 ± 2.09	6.31 ± 1.65	0.419[b]
Loss of sensitivity	3.59 ± 3.31	3.44 ± 3.27	3.74 ± 3.37	0.550[b]
Burning pain	6.26 ± 2.90	6.61 ± 1.97	5.90 ± 2.80	0.103[b]
Pruritus	5.34 ± 3.45	5.41 ± 3.69	5.27 ± 3.21	0.788[b]

[a] Fisher's test.
[b] The t-test.

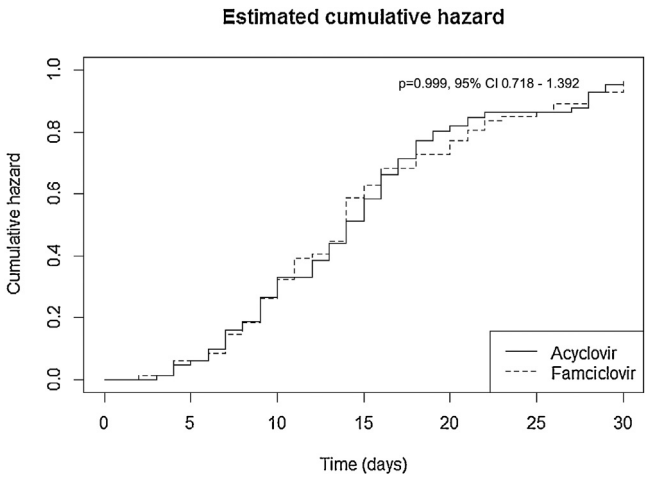

Figure 2. Cumulative hazard rate of time to full crusting of the vesicular lesions captured over time (follow-up duration 30 days) among treatment groups, sex, age, and baseline pain score; Cox proportional hazards model.

Table 2
Efficacy analysis.

Complete cure		*p*-Value	Difference	95% CI	
Acyclovir *n* = 76	Famciclovir *n* = 75			Lower bound	Upper bound
72 (94.74)	71 (94.67)	0.985	0.07	−0.0718	0.0732

CI, confidence interval.

in the participants in either group. The most common AEs were headache in 49 patients, diarrhea (*n* = 9), nausea (*n* = 8), back pain (*n* = 6), cold (*n* = 6), and drowsiness (*n* = 4), but none of these was deemed to be clinically important.

All AEs reported or observed during the study were mild, transient, subsided without specific interventions, and did not result in any clinical impact. No clinically significant laboratory abnormalities were identified in any patient.

Discussion

This study investigated the safety and efficacy of famciclovir and acyclovir, and demonstrated that both interventions obtained high rates of cure and had a similar time to full crusting of lesions. Analysis of the primary efficacy endpoint proved that famciclovir is non-inferior to acyclovir, as the confidence interval for the difference in efficacy did not violate the non-inferior margin. Therefore, the results are not different enough to be clinically relevant.

After 28 days of treatment, the VAS score for vesicular lesions fell to zero in both treatment groups, demonstrating the efficacy of the treatments. Other symptoms (loss of sensitivity, burning pain, and pruritus) measured by VAS during the follow-up period also dropped to zero, corroborating the efficacy of the two treatments, with no statistical difference.

At the end of follow-up, of the 76 patients in the acyclovir group who completed the study, 72 were completely cured, with a mean time to the achievement of complete cure of 15.033 days. For the famciclovir group, of the 75 patients who completed the study, 71 were completely cured, with a mean time to the achievement of complete cure of 14.840 days. The data presented above

Table 3
Visual analog scale (VAS) scores for signs/symptoms at 7, 15, and 28 days after starting treatment.

		Treatment (*n*)	Mean (SD)	Levene test	*t*-test	Difference	95% CI	
							Lower bound	Upper bound
Day 7	Pain	Famciclovir (75)	3.84 (3.03)	0.643	0.707	−0.20	−1.22	0.83
		Acyclovir (76)	3.64 (3.34)					
	Vesicular lesions	Famciclovir (75)	3.19 (2.33)	0.458	0.522	−0.25	−1.03	0.53
		Acyclovir (76)	2.93 (2.51)					
	Loss of sensitivity	Famciclovir (75)	1.25 (2.63)	0.060	1.83	0.60	−0.29	1.49
		Acyclovir (76)	1.86 (2.89)					
	Burning	Famciclovir (75)	4.40 (3.28)	0.471	0.283	−0.60	−1.69	0.50
		Acyclovir (76)	3.80 (3.52)					
	Pruritus	Famciclovir (75)	2.85 (3.51)	0.644	0.635	−029	−1.48	0.91
		Acyclovir (76)	2.57 (3.91)					
Day 15	Pain	Famciclovir (75)	4.99 (2.85)	0.986	0.580	−0.25	−1.16	0.65
		Acyclovir (75)	4.73 (2.75)					
	Vesicular lesions	Famciclovir (75)	4.81 (2.49)	0.079	0.885	0.05	−0.67	0.78
		Acyclovir (75)	4.87 (1.98)					
	Loss of sensitivity	Famciclovir (75)	2.19 (2.89)	0.050	0.242	0.59	−0.40	1.57
		Acyclovir (75)	2.77 (3.22)					
	Burning	Famciclovir (75)	5.36 (3.29)	0.587	0.703	−0.20	−1.23	0.83
		Acyclovir (75)	5.16 (3.12)					
	Pruritus	Famciclovir (75)	3.73 (4.09)	0.095	0.741	0.21	−1.06	1.49
		Acyclovir (75)	3.95 (3.80)					
Day 28	Pain	Famciclovir (76)	5.59 (2.87)	0.769	0.738	−0.16	−1.10	0.78
		Acyclovir (74)	5.43 (2.98)					
	Vesicular lesions	Famciclovir (76)	6.19 (2.29)	0.009	0.363	−0.29	−093	0.34
		Acyclovir (74)	5.89 (1.61)					
	Loss of sensitivity	Famciclovir (76)	2.78 (3.15)	0.413	0.277	0.57	−0.46	1.61
		Acyclovir (74)	3.36 (3.26)					
	Burning	Famciclovir (76)	6.16 (3.15)	0.904	0.348	−0.48	−1.48	0.52
		Acyclovir (74)	5.68 (3.06)					
	Pruritus	Famciclovir (76)	4.49 (4.22)	0.044	0.867	0.11	−1.14	1.35
		Acyclovir (74)	4.59 (3.46)					

SD, standard deviation; CI, confidence interval.

corroborate the observation of a shortened time to achieving complete cure through the use of antivirals. In addition, treatment with famciclovir may be considered non-inferior to acyclovir for the time to full crusting of lesions, as the upper limit of the 95% confidence interval for the difference between the log of the cure rate for the famciclovir and acyclovir groups was less than the established margin.

Nonetheless, pain is the most common symptom of shingles, affecting approximately 75% of patients in the form of altered sensitivity or pain circumscribed to the involved dermatome where the rash will later appear (Dworkin et al., 2007b). In the course of viral reactivation, acute hyperalgesia is usually the first symptom and occurs in approximately 70–80% of patients. Also, the type and intensity of pain may vary over time, persisting at all stages of the disease (Dworkin et al., 2007b). Before starting the study, the mean score in the subjective assessment for the pain symptom was 6.11 ± 2.95 mm in the acyclovir treatment group and 6.25 ± 2.86 mm in the famciclovir treatment group. For the burning pain symptom, similar results (6.05 ± 2.79 mm and 6.73 ± 2.96 mm for the acyclovir and famciclovir groups, respectively) were found. The evaluation of the intensity of symptoms recorded through the VAS showed that the study population experienced moderate to severe acute pain during the viral reactivation episode.

Thus, the management of uncomplicated HZ involves antiviral therapy, along with associated analgesic treatment in patients with moderate to severe acute neuritis. In such cases, antiviral agents such as famciclovir, valaciclovir, and acyclovir have been used widely to reduce the severity and duration of pain associated with acute neuritis, to promote faster healing of cutaneous lesions, to avoid the formation of new lesions, to decrease viral spread and reduce the risk of transmission, and to avoid post-herpetic neuropathy (Hillebrand et al., 2015; Field and Vere Hodge, 2013). The assessment of intensity scores for pain, vesicular lesions, loss of sensitivity, burning pain, and pruritus over the follow-up period showed no statistically significant difference between the two treatment groups.

The safety profile of famciclovir has already been evaluated in immunocompetent patients with HZ, using the incidence of adverse events and monitoring the outcome of laboratory variables. Saltzman et al. (1994) compiled safety data from 808 patients who received famciclovir in three clinical studies with patients receiving famciclovir for the treatment of HZ or genital herpes and demonstrated that this agent is well-tolerated and has a safety profile comparable to that of placebo, favoring its use in the treatment of HZ, a disease in which treatment alternatives with acceptable safety profiles are limited (Saltzman et al., 1994). In the present study, the safety assessment was performed by assessing the incidence of adverse events in each of the groups, as well as the relationship of these events to the medication used and severity of the reported events. During the follow-up period, there were 142 episodes of adverse events, 79 episodes (55.63%) in the acyclovir group and 63 episodes (44.37%) in the famciclovir group, all of them non-serious; only two episodes did not recover (one in each group). Concerning adverse events, the main event was headache, with 30 (21.12%) episodes in the acyclovir group and 19 (13.38%) in the famciclovir group. Saltzman et al. (1994) reported similar headache rates in patients receiving famciclovir and those receiving placebo in 816 patients with HZ (four studies), 409 patients with genital herpes virus infection (seven studies), and 382 patients in two studies of genital herpes suppression. They also found no relationship between the duration of exposure to famciclovir and the incidence of laboratory abnormalities (Saltzman et al., 1994). Similarly, the present study demonstrated that 97.37% of the patients treated with acyclovir and 88% of those treated with famciclovir did not present significant alterations in the safety laboratory tests at both visits. Hence, the two treatments demonstrated similar laboratory profile.

In conclusion, the treatment of HZ with antiviral agents has been shown to be effective in reducing or blocking viral replication, accelerating wound healing, limiting the severity and duration of acute pain and other symptoms such as pruritus, loss of sensitivity, and burning pain. This study showed that the efficacies of famciclovir and acyclovir for the treatment of uncomplicated herpes zoster did not differ enough to be clinically relevant. Therefore, famciclovir 500 mg three times daily for 7 days as the antiviral agent in patients with HZ appears to be an effective, convenient, well-tolerated, and safe alternative comparable to the traditionally prescribed treatment, acyclovir.

Acknowledgements

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Ethical approval

We confirm that any aspect of the work covered in this manuscript that has involved either experimental animals or human patients has been conducted with the ethical approval of all relevant bodies and that such approvals are acknowledged within the manuscript.

Conflict of interest

All authors report receiving consulting fees from EMS Industry. No other disclosures are reported.

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