Effect of stannous fluoride and zinc phosphate dentifrice on dental plaque and gingivitis

A randomized clinical trial with 6-month follow-up

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ABSTRACT

Objective. The objective of this study was to compare a stabilized stannous fluoride (SnF_2) dentifrice with zinc phosphate (Colgate Total^{SF}) with SnF_2 with zinc lactate and control fluoride dentifrices for gingivitis and plaque control over a 6-month period.

Methods. A total of 135 adult participants were enrolled in this study. After randomization and blinding of examiners and patients, enrolled participants were provided instructions for use of assigned dentifrice. At 3 visits (0, 3, and 6 months), various gingival and plaque indexes were collected to determine the clinical efficacy of a stabilized SnF_2 dentifrice. These results were compared with a SnF_2 with zinc lactate dentifrice and with a control fluoride dentifrice.

Results. A total of 135 participants completed the study. All groups reported statistically significant reductions in gingival inflammation and improvement in plaque control at 3- and 6-month follow-up. Both SnF_2 dentifrices showed statistically significant reductions in all indexes compared with the control dentifrice ($P < .001$). However, the test dentifrice showed higher but nonsignificant improvements in plaque and gingival indexes compared with the other SnF_2 dentifrice.

Conclusions. This study reports similar efficacy of a test dentifrice to a commercial SnF_2-containing dentifrice for plaque control and reduction in gingival inflammation and provides supporting evidence that the test dentifrice maintains its clinical efficacy with change of formulation.

Practical Implications. This newly formulated SnF_2 stabilized with zinc phosphate dentifrice may be of benefit to patients in controlling plaque biofilm and gingivitis.

Key Words. Stannous fluoride; gingivitis; dental plaque.

Publication of this article was supported by Colgate-Palmolive Company.

JADA 2019:150(4 suppl):S25-S31
https://doi.org/10.1016/j.adaj.2019.01.003

Periodontal disease and caries are the 2 most common oral diseases[1,2] and affect between 20% and 50% of the global population.[3] Both periodontal disease and caries are initiated via the presence of a pathogenic dental biofilm. Dental biofilm is an organized matrix that is composed of a complex[4-6] and diverse microbial community,[7,8] comprising hundreds of bacterial species.[9] Initially, certain bacteria (early colonizers) populate the oral surfaces (both hard and soft tissues) and provide a framework for a diverse bacterial colonization.[10] The key strategy in prevention of periodontal disease and caries is frequent mechanical disruption of the dental biofilm[11] using proper toothbrushing methods and effective dentifrices.[12]

With the advancement in formulation of dentifrices, modern oral health care products can significantly reduce the dental biofilm burden[12] and aid in preventing periodontal disease. Stannous fluoride (SnF_2) dentifrices show scientific evidence for reducing biofilm burden and affect bacterial acid production with notable substantivity.[13-17] The effects of SnF_2 have largely been attributed to the presence of free stannous ions, which, if oxidized to stannic ions, become ineffective in

providing the desired dental therapeutic benefits.[18] As a result, finding a mechanism to restrict the oxidative process is crucial to maintaining the efficacy of SnF_2 dentifrices.

Colgate-Palmolive Company has developed a mechanism for effective stabilization of SnF_2 (via avoiding oxidation) through the incorporation of zinc phosphate. This new and innovative formulation has undergone rigorous laboratory and clinical testing. In this study, the test dentifrice, containing SnF_2 (0.454%) with zinc phosphate in a silica base (Colgate Total^{SF}, Colgate-Palmolive Company), was compared with a commercial dentifrice containing 0.454% SnF_2 stabilized with sodium hexametaphosphate in a silica base with low water content (Crest Pro-Health Toothpaste, Procter & Gamble) and a regular fluoride (0.76% sodium monofluorophosphate, 1,000 parts per million fluoride) dentifrice in a dicalcium phosphate dihydrate base (Colgate-Palmolive Company) to compare reductions in plaque and gingivitis over a 6-month period. Another article in this supplement discusses the effect of the test dentifrice on gingival and plaque indexes in a Chinese cohort.[19]

METHODS

Study design

The study was reviewed and approved by the Institutional Review Board of the Faculty of Dentistry and Pharmacy, Mahidol University (Bangkok, Thailand). The sample size was determined on the basis of the standard deviation for the response measures of 0.58, a significance level of $\alpha = 0.05$, a 10% attrition rate, and an 80% power level, which allowed this study to detect a minimal statistically significant difference between the study group means of 15%. The sample size calculation used historical data from a previous study.[20] This randomized, single-center, double-blind, and parallel-group study included a total of 135 participants using the following inclusion and exclusion criteria. The dentifrices compared were

- 0.454% SnF_2 stabilized zinc phosphate in a silica base (Colgate-Palmolive Company) (test);
- 0.454% SnF_2 stabilized with sodium hexametaphosphate in a silica base with a low-water content (Procter & Gamble) (Crest Pro-Health);
- 0.76% sodium monofluorophosphate (1,000 ppm) in a dicalcium phosphate dihydrate base (Colgate-Palmolive Company) (control).

Inclusion criteria

Participants 18 through 70 years of age in good general health who had at least 20 uncrowned permanent natural teeth (excluding third molars) were available for the duration of study and were willing to sign an informed consent. Participants were required to have an initial mean gingival index score of at least 1.0, determined via the Löe-Silness Gingival Index,[21] and an initial mean plaque index score of at least 1.5, determined via the Turesky modification of the Quigley-Hein Plaque Index.[22]

Exclusion criteria

Participants were excluded from the study if they had orthodontic bands, partial removable dentures, tumors of the soft or hard tissues of the oral cavity, advanced periodontal disease (purulent exudates, tooth mobility, extensive loss of periodontal attachment or alveolar bone, or all of these), or 5 or more carious lesions requiring immediate restorative treatment. They were also excluded from the study if they had a history of allergies to oral health care, personal health care, or both consumer products or their ingredients; if they had an existing medical condition that prohibited abstaining from eating or drinking for up to 4 hours; if they used antibiotics anytime during the 1 month before entry into the study; or if they were using any other prescription medicines that might interfere with the study outcome. Pregnant or lactating women were excluded from participation, as were participants with a history of alcohol or drug abuse. Participants who participated in any other clinical study or test panel within 1 month before entry into the study or who received a dental prophylaxis in the 2 weeks before the baseline examination were also excluded from the study.

Clinical examination and instructions

After study treatment assignment, participants were provided with their assigned dentifrice and an adult, soft-bristled toothbrush for home use. They were instructed to brush twice daily (morning and evening) for 1 minute with approximately 1.5 grams of the assigned dentifrice for 6 months. Qualifying participants and all clinical study site personnel were blinded to product assignment.

ABBREVIATION KEY

GInt: Gingival interproximal index.
GS: Gingival severity index.
PI: Plaque index.
PInt: Plaque interproximal index.
PS: Plaque severity index.
SnF_2: Stannous fluoride.

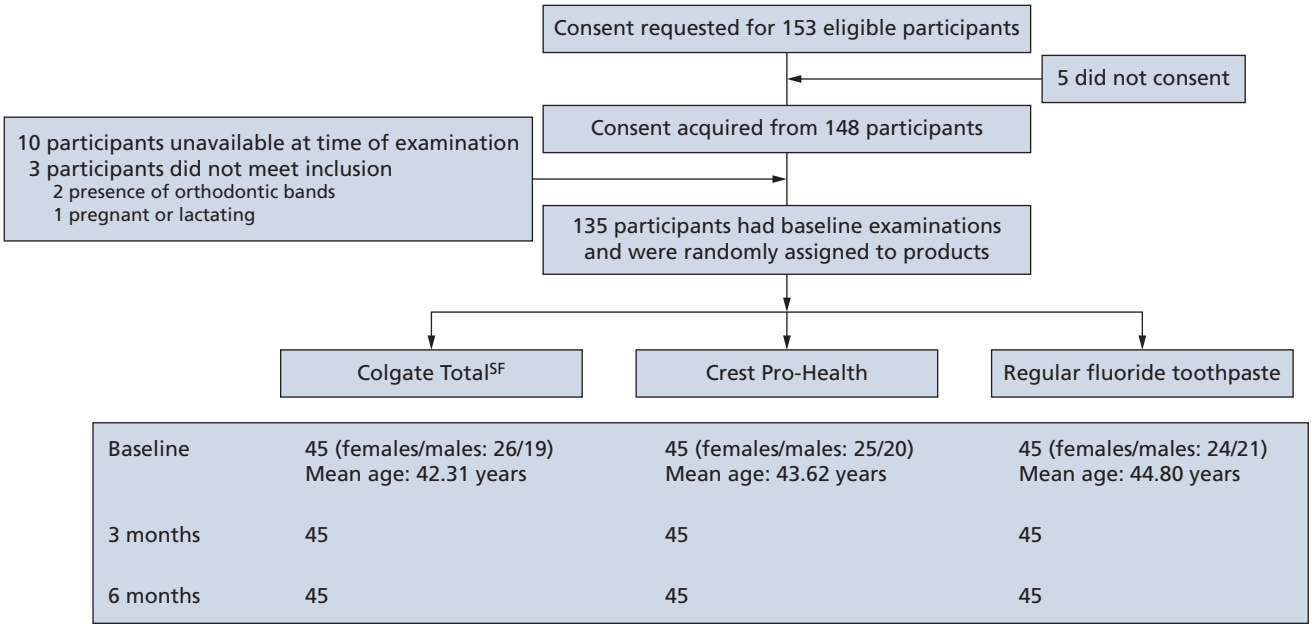

Figure 1. Consolidated Standards of Reporting Trials flow diagram.

Products were covered with white overwrapping paper to conceal product identity. Label information on each tube consisted of a toothpaste code (study group code), instructions for at-home use, and safety information, including emergency contact information.

At all clinical visits (baseline and 3 and 6 months), an oral and perioral examination was performed to determine the status of teeth, soft tissues of the mouth, salivary glands, and tonsillar and pharyngeal regions. Adverse events were obtained from interviews with the participants and from oral examination.

Statistical analysis

For age and sex, independent *t* test and χ^2 test were performed, respectively. For gingival and plaque indexes, subjectwise whole-mouth scores were calculated via adding the scores for all sites and dividing by the total number of recorded sites. For gingival and plaque severity indexes, gingival recordings with scores of 2 or 3 and plaque recordings with scores of 3, 4, or 5 were divided by the total number of recorded sites. Similarly, gingival and plaque interproximal indexes were calculated via adding recording from interproximal sites and dividing by the total number of mesial and distal recorded sites. Average scores for each group at various time points were then calculated along with 95% confidence intervals. Comparisons of average of all indexes within and between treatment groups were performed using independent *t* test and analysis of covariance, respectively. All statistical tests were 2 sided and used a level of significance of $\alpha = 0.05$.

RESULTS

The population enrolled and who completed the study is presented in the Consolidated Standards of Reporting Trials diagram (Figure 1). A total of 135 participants completed the study with 6-month follow-up. The treatment groups did not differ significantly with respect to sex ($P = .914$) and age ($P = .596$) (Table 1).

Baseline

At baseline, mean gingival indexes for test, Crest Pro-Health, and control dentifrices were 1.77, 1.76, and 1.75, respectively. The mean gingival severity indexes were 0.66, 0.65, and 0.64 for test, Crest Pro-Health, and control dentifrices. Similarly, mean gingival interproximal index was 1.85 for both test and Crest Pro-Health groups and 1.84 for the control group. For all gingival indexes, no statistically significant difference was noted between groups (Table 2).

At baseline, mean plaque index, mean plaque severity index, and mean plaque interproximal index for test group were 3.42, 0.80, and 3.48, respectively. For the Crest Pro-Health group, these measures were 3.41, 0.77, and 3.49, respectively. Similarly, for the control group, these indexes

Table 1. Summary of age and sex distribution of the study participants.*

TREATMENT GROUP	PARTICIPANTS BY SEX		AGE, Y	
	Male	Female	Mean	Range
Test (n = 45)	19	26	42.31	21-60
Crest Pro-Health (n = 45)	20	25	43.62	22-58
Control (n = 45)	21	24	44.80	24-60

* No significant differences were noted between participants on the basis of age and sex.

Table 2. Statistical parameters for comparisons made within each treatment group at 3- and 6-month intervals.*

EVALUATION	WITHIN-TREATMENT ANALYSIS						
	Baseline	3 Months			6 Months		
	Mean (Standard Deviation)	Adjusted Mean (Standard Error)	Adjusted 95% Confidence Interval	*P* Value	Adjusted Mean (Standard Error)	Adjusted 95% Confidence Interval	*P* Value
Test							
GI†	1.77 (0.17)	1.39 (0.01)	1.37 to 1.41	< .001	1.16 (0.02)	1.12 to 1.20	< .001
PI‡	3.42 (0.30)	2.62 (0.02)	2.58 to 2.66	< .001	2.28 (0.03)	2.22 to 2.34	< .001
GS§	0.66 (0.13)	0.44 (0.01)	0.42 to 0.46	< .001	0.30 (0.01)	0.28 to 0.32	< .001
PS¶	0.80 (0.10)	0.55 (0.02)	0.51 to 0.59	< .001	0.38 (0.02)	0.34 to 0.42	< .001
GInt#	1.85 (0.20)	1.46 (0.02)	1.42 to 1.50	< .001	1.24 (0.03)	1.18 to 1.30	< .001
PInt**	3.48 (0.37)	2.65 (0.02)	2.61 to 2.69	< .001	2.34 (0.03)	2.28 to 2.40	< .001
CPH							
GI	1.76 (0.19)	1.41 (0.01)	1.39 to 1.43	< .001	1.21 (0.02)	1.17 to 1.25	< .001
PI	3.41 (0.30)	2.65 (0.02)	2.61 to 2.69	< .001	2.36 (0.03)	2.30 to 2.42	< .001
GS	0.65 (0.13)	0.46 (0.01)	0.44 to 0.48	< .001	0.33 (0.01)	0.31 to 0.35	< .001
PS	0.77 (0.11)	0.59 (0.02)	0.55 to 0.63	< .001	0.43 (0.02)	0.39 to 0.47	< .001
GInt	1.85 (0.22)	1.49 (0.02)	1.45 to 1.53	< .001	1.29 (0.03)	1.23 to 1.35	< .001
PInt	3.49 (0.36)	2.67 (0.02)	2.63 to 2.71	< .001	2.40 (0.03)	2.34 to 2.46	< .001
Control							
GI	1.75 (0.20)	1.68 (0.01)	1.66 to 1.70	< .001	1.62 (0.02)	1.58 to 1.66	< .001
PI	3.43 (0.32)	3.24 (0.02)	3.20 to 3.28	< .001	3.11 (0.03)	3.05 to 3.17	< .001
GS	0.64 (0.13)	0.65 (0.01)	0.63 to 0.67	= .598	0.58 (0.01)	0.56 to 0.60	< .001
PS	0.81 (0.09)	0.82 (0.02)	0.78 to 0.86	= .002	0.78 (0.02)	0.74 to 0.82	= .440
GInt	1.84 (0.25)	1.76 (0.02)	1.72 to 1.80	< .001	1.68 (0.03)	1.62 to 1.74	< .001
PInt	3.52 (0.36)	3.29 (0.02)	3.25 to 3.33	< .001	3.16 (0.03)	3.10 to 3.22	< .001

* At 3- and 6-month intervals, all indexes were significantly improved, except gingival severity in the control group at 3 months and plaque severity in the control group at 6 months. † GI: Gingival index. ‡ PI: Plaque index. § GS: Gingival severity index. ¶ PS: Plaque severity index. # GInt: Gingival interproximal index. ** PInt: Plaque interproximal index.

measured 3.43, 0.81, and 3.52, respectively. No statistically significant difference was noted between groups for plaque indexes at baseline (Table 2).

3-Month follow-up

The gingival and plaque indexes, as measured at baseline, were also measured at 3-month follow-up after twice daily toothbrushing with assigned dentifrices. All dentifrice groups reported reductions in plaque and gingival indexes from baseline. For test and Crest Pro-Health groups, all gingival and plaque indexes showed statistically significant reductions. However, for the control dentifrice, the reduction in gingival severity index was not statistically significant at the 3-month observation ($P = .598$) (Table 2). Graphical representation of the gingival and plaque reductions relative to baseline are shown in Figures 2A and 2B and Figures 3A and 3B.

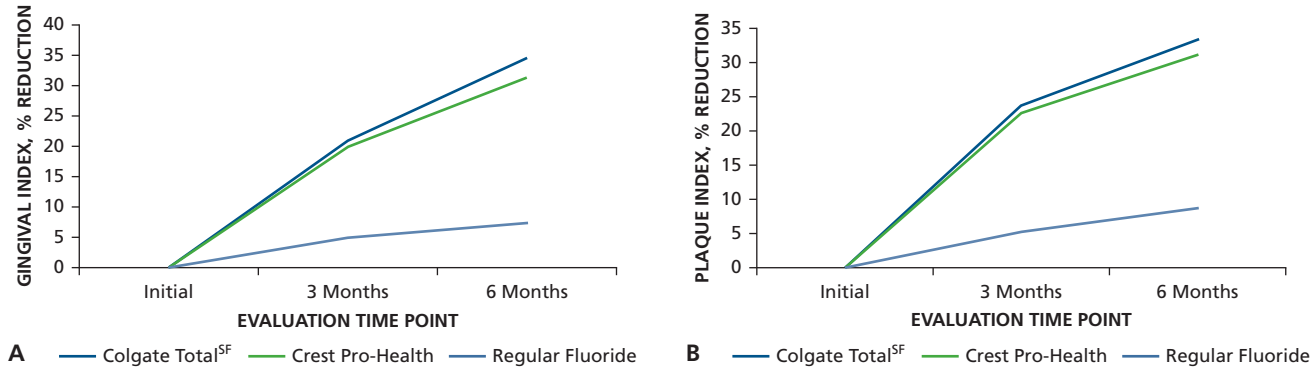

Figure 2. Graphical representation of the percentage reduction relative to baseline for the gingival index (**A**) and plaque index (**B**).

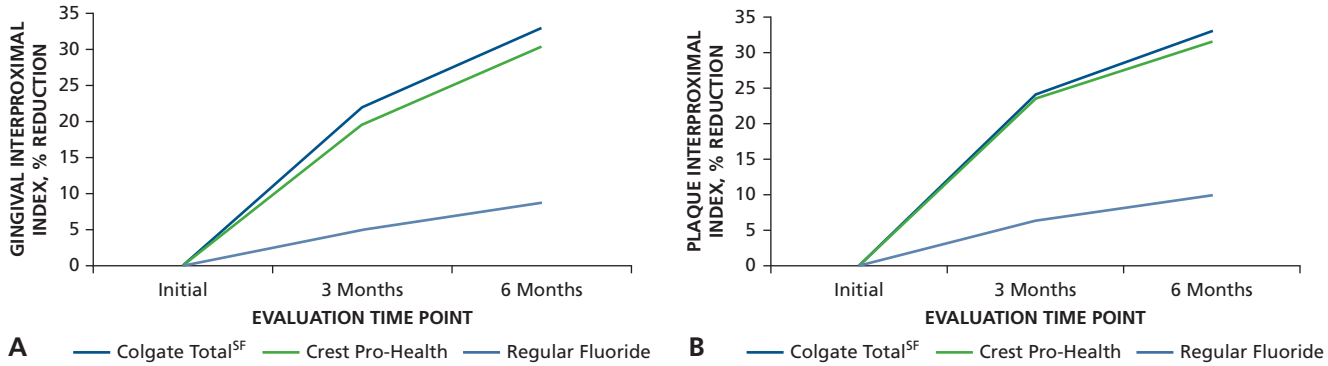

Figure 3. Graphical representation of the percentage reduction relative to baseline for the gingival interproximal index (**A**) and plaque interproximal index (**B**).

6-Month follow-up

At 6 months, gingival and plaque indexes showed a similar trend. All dentifrice groups reported significant reductions in all gingival and plaque indexes, with the exception of plaque severity index in the control group (Table 2). Graphical representation of the reductions relative to baseline are shown in Figures 2A and 2B and Figures 3A and 3B.

DISCUSSION

Periodontal disease is one of the most common chronic diseases affecting the human population.[23] The primary etiopathogenic mechanism for periodontal disease is the host response against dental biofilm.[24] Inadequate control of dental biofilm has other local manifestations, such as caries and oral malodor.[25,26] However, there are important systemic associations related to periodontal disease that may compromise overall health.[27,28] Because prevention of periodontal disease and maintenance of periodontal health rely on adequate biofilm control,[28] there are various oral hygiene aids and dentifrice formulations that have been developed.

This randomized, single-center, 3-cell, double-blind, parallel-group clinical study was conducted in a Thai cohort to compare SnF_2 stabilized with zinc phosphate against a fluoride control and an SnF_2 formulation stabilized with sodium hexametaphosphate in a low-water content silica base. The groups were compared for gingival and plaque indexes at baseline and at 3- and 6-month intervals. Participants did not differ significantly between groups for age and sex and were also comparable between groups across all gingival and plaque indexes at baseline.

All groups reported a significant reduction in plaque and gingival indexes at both 3- and 6-month intervals. The gingival severity index reduction at 3 months ($P = .598$) and plaque severity index reduction at 6 months ($P = 0.440$) were not statistically significant in the control group. As expected, both dentifrice groups (test and Crest Pro-Health) reported statistically significant reductions in all indexes compared with the control group ($P < .001$). Conversely, the comparison of test and Crest Pro-Health groups showed differences that were not statistically significant across all indexes. This indicates that SnF_2-containing dentifrices were comparable in their efficacy, as

measured for control of plaque and gingival inflammation, and the stabilization of SnF_2 through incorporation of zinc phosphate did not reduce the clinical efficacy of the test dentifrice.

The most notable difference between Colgate Total[SF] and Crest Pro-Health is in the manner in which the 2 products stabilize SnF_2. For SnF_2 to maintain efficacy against plaque and gingivitis, it is critical that tin remains in the free stannous ion oxidation state.[18] In an aqueous environment, it is difficult to prevent the free stannous ions from oxidizing to stannic ions, which are inactive. Previously, strategies to achieve this stabilization included use of nonaqueous systems, reduction of water content, including additional stannous ions in the form of stannous chloride, and the incorporation of high levels of phosphate excipients, such as hexametaphosphate.[16,29-31] These strategies may result in astringent taste, staining of teeth and dental appliances, and changes in appearance and texture of the dentifrice.[12,32-34] Crest Pro-Health uses the traditional approach, significantly lowering the water content and adding a chelating agent, in the form of sodium hexametaphosphate. In contrast, Colgate Total[SF] stabilized with zinc phosphate allows the formula to use a water content that is in a range of most commercial fluoride toothpastes. From a consumer use perspective, this is an advantage. Significantly lowering the water content of the toothpaste negatively impacts the flavor, mouth feeling, and esthetics, which can diminish the user experience and potentially impact compliance.

In this study, both Colgate Total[SF] and Crest Pro-Health delivered significant effects in controlling plaque and reducing gingivitis over a 6-month period compared with a regular fluoride toothpaste. Six parameters associated with plaque and gingivitis were measured in this study. Although no significant difference between Colgate Total[SF] and Crest Pro-Health was detected, the numerical trend favored Colgate Total[SF] in terms of an increased performance in every plaque and gingivitis parameter measured over the 6-month period. Indeed, both Figures 1 and 2 show that although indexes are statistically parity, at the 6-month point, there is evidence of further reduction in gingival and plaque parameters in benefit to Colgate Total[SF]. Such differences at 6 months may be attributed to how the 2 SnF_2 formulations are stabilized. However, just as likely, the differences at 6 months may be ascribed to important consumer parameters that influence the product's continued use, such as taste leading to improved compliance; continued adoption of a therapeutic product is just as critical to long-term benefits as is the stability of the antibacterial agent itself. Use of zinc phosphate to stabilize SnF_2 has enabled Colgate Total[SF] to provide excellent control of plaque and gingivitis without compromising on flavor, mouth feeling, and esthetics that other dentifrices using SnF_2 must make.

CONCLUSIONS

Colgate-Palmolive Company has developed a new toothpaste, Colgate Total[SF] that contains SnF_2 stabilized with zinc phosphate. This toothpaste contains traditional water content and had a pleasing taste, mouth feeling, and esthetics. Colgate Total[SF] was compared with a commercial SnF_2 toothpaste stabilized in a typical way via lowering the water content and adding high levels of excipient chelants. The new Colgate Total[SF] was shown to deliver significant benefits with respect to control of plaque and reduction in gingival inflammation that was on par with a commercial SnF_2 toothpaste stabilized in the traditional way. ■

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Disclosure. Dr. Sabharwal received an honorarium from Colgate-Palmolive.

Publication of this article was supported by Colgate-Palmolive Company.

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