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Three randomized studies of dentine hypersensitivity reduction after short-term SnF$_2$ toothpaste use

Jonathan Creeth[1] 🆔 | Robert Maclure[2] | Joon Seong[3] | Paola Gomez-Pereira[1] | Chandrashekhar Budhawant[4] | Farzana Sufi[1] | Jonathan Holt[2] | Nicholas Chapman[3] | Nicola West[3] 🆔

[1]GSK Consumer Healthcare, Surrey, UK

[2]Intertek Clinical Research Services, Hooton, UK

[3]Clinical Trials Unit (Periodontology), Bristol Dental School and Hospital, Bristol, UK

[4]Syneos Health, Hyderabad, India

Correspondence
Jonathan Creeth, GSK Consumer Healthcare, St George's Avenue, Weybridge, Surrey, KT13 0DE, UK.
Email: jonathan.e.creeth@gsk.com

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Abstract

Aim: To evaluate effects of a 0.454% stannous fluoride test toothpaste on dentine hypersensitivity (DH) applied by fingertip, then 3 days' brushing, versus a sodium monofluorophosphate-based control.

Materials and Methods: In three randomized clinical studies, DH was assessed using evaporative (Schiff scale) and tactile (Yeaple probe) stimuli. Participants applied toothpaste to two sensitive teeth by fingertip (60 s each); DH was re-assessed, prior to brushing. Test treatment participants brushed their sensitive teeth, with all participants then brushing all teeth for ≥60 s, twice daily for 3 days. DH was re-assessed. Data were analysed by study and then pooled.

Results: In two studies, test treatment significantly reduced DH versus control treatment after fingertip application and 3 days' brushing (both measures). In one study, both treatments significantly reduced DH without between-treatment differences. Mean Schiff differences (95% confidence intervals) for fingertip/3d were as follows: Study 1: −0.09 (−0.280, 0.092)/ −0.18 (−0.442, 0.072); Study 2: −0.72 (−0.839, −0.610)/ −1.02 (−1.150, −0.882); and Study 3: −0.26 (−0.387, −0.123)/ −0.92 (−1.055, −0.793). Pooled analysis indicated test treatment significantly reduced DH versus control (both timepoints, both measures). Toothpastes were generally well-tolerated.

Conclusion: Studies indicated that single, fingertip application of a SnF$_2$ toothpaste reduced DH versus a control. DH relief increased over 3 days.

KEYWORDS
clinical study, controls, dentin sensitivity, tin fluoride

1 | INTRODUCTION

Dentine hypersensitivity (DH) is defined as 'pain derived from exposed dentine in response to chemical, thermal, tactile or osmotic stimuli' (Addy, 1990). DH occurs when dentine tubules are patent following dentine exposure, most frequently from gingival recession or enamel wear (Rimondini, Baroni, & Carrassi, 1995; West, Lussi, Seong, & Hellwig, 2013), and stimuli cause fluid movement within tubules leading to pulpal nerve excitation and subsequent pain (Brännström, 1963). Dentine hypersensitivity can negatively impact oral health-related quality of life due to frequent pain insults (Gibson et al., 2010).

Dentine hypersensitivity treatment focuses on two approaches: occluding dentine tubules or blocking impulse transmission in dentinal nerves. The former relies on ingredients that form solid deposits which occlude/partially occlude dentine tubules so external stimuli do not cause substantial shifts in fluid movement (Earl & Langford, 2013; Earl, Ward, & Langford, 2010). Such agents include strontium or stannous salts (Makin, 2013; Markowitz, 2009; Mason et al., 2010; West, Seong, & Davis, 2015), arginine plus insoluble calcium salts (Bae, Kim, & Myung, 2015; Hughes et al., 2010) or bioglasses (Gendreau, Barlow, & Mason, 2011; Pradeep & Sharma, 2010). This approach has potential to work from first application (Ayad et al., 2009; Creeth, Gallob, et al., 2017; Creeth, Goyal, et al., 2017; Fu et al., 2010; He, Barker, Qaqish, & Sharma, 2011; He, Chang, et al., 2011; He, Cheng, Biesbrock, Chang, & Sun, 2011; Mason et al., 2010; Nathoo et al., 2009; Parkinson et al., 2013; Sharma, Roy, Kakar, Greenspan, & Scott, 2011; West, Newcombe, et al., 2013). Blocking of impulse transmission has been achieved by potassium ions (Bae et al., 2015; Markowitz, 2009); however, repeated administration appears to be required before symptomatic relief occurs (West, Seong, & Davies, 2014).

Directly applying an occluding desensitizing toothpaste to reduce DH can be achieved through focused brushing or fingertip application. In the former, sensitive teeth are brushed first, followed by whole-mouth brushing (Creeth, Gallob, et al., 2017; Creeth, Goyal, et al., 2017; He, Barker, et al., 2011; He, Chang, et al., 2011; He, Cheng, et al., 2011; Parkinson et al., 2013; Sharma et al., 2011). In the latter, toothpaste is gently massaged into sensitive teeth (Ayad et al., 2009; Fu et al., 2010; Mason et al., 2010; Nathoo et al., 2009; Schiff et al., 2009; West, Newcombe, et al., 2013), a technique frequently recommended by oral healthcare professionals for immediate DH symptom relief.

Stannous ions, most commonly used in toothpastes as stannous fluoride (SnF_2), have been demonstrated to occlude dentine tubules in vitro (Burnett, 2013; Burnett, Wilson, & Lucas, 2013; Earl & Langford, 2013; Khan & Wilson, 2017). SnF_2 toothpaste formulations have been used for several decades (Makin, 2013; Schiff, He, Sagel, & Baker, 2006) and are widely accepted as an effective DH treatment (Bae et al., 2015; West et al., 2015). Short-term studies (up to 3 days) have overall been positive for SnF_2 toothpastes applied using the focused brushing technique, with many demonstrating clinical efficacy versus a control toothpaste (Creeth, Gallob, et al., 2017; Creeth, Goyal, et al., 2017; He, Barker, et al., 2011; He, Chang, et al., 2011; He, Cheng, et al., 2011; Parkinson et al., 2016; Sharma et al., 2011). However, some DH studies with a SnF_2 (Parkinson et al., 2016) or stannous chloride (Cepeda-Bravo et al., 2014) toothpaste have not shown differences.

There appears to be no published assessment of DH relief from SnF_2 toothpastes applied using a fingertip technique. The three clinical studies presented here addressed this question using an experimental SnF_2 toothpaste incorporating an anhydrous base (to stabilize stannous ions against oxidation and hydrolysis) and the polyphosphate pentasodium triphosphate (to control stannous ions' propensity to stain enamel (Addy, Moran, Griffiths, & Wills-Wood, 1985). The objective was to determine whether this formulation could provide rapid, effective, symptomatic DH relief when applied

Clinical Relevance

Scientific rationale for study: Stannous fluoride (SnF_2) toothpastes have been shown in long-term studies to reduce dentine hypersensitivity (DH). This investigation explored whether a SnF_2 toothpaste applied by two focused methods—fingertip application alone or with focused brushing prior to whole-mouth brushing—could reduce DH immediately and after short-term use.

Principal findings: Across the three studies, the evidence showed the SnF_2 toothpaste applied directly by fingertip reduced DH after a single use and, when applied by focused brushing, following 3 days' use, versus a non-sensitivity toothpaste.

Practical implications: When applied directly to affected teeth, toothpastes containing SnF_2 can reduce DH immediately and with continued use.

by the fingertip technique after a single application, and also after 3 days' twice-daily application by focused brushing, compared to a conventional fluoride toothpaste. An exploratory, post hoc, pooled analysis was carried out combining all results to estimate overall efficacy across the three studies.

2 | MATERIALS AND METHODS

These randomized, examiner-blind, two-treatment arm, parallel design studies were stratified by maximum baseline Schiff sensitivity score. Study 1 was conducted at two centres of a UK clinical research facility; Studies 2 and 3 were conducted at a UK dental school. The third study was performed after the first two studies had been completed. All studies were conducted in accordance with the Declaration of Helsinki, approved by independent research ethics committees before initiation and registered at ClinicalTrials.org: Study 1 (NCT02612064): North-West Lancaster REC, #15/NW/0784; Study 2 (NCT02751450): NRES South West—Exeter REC, 16/SW/0006; and Study 3 (NCT02924350): NRES West Midlands—South Birmingham REC, 16/WM/0407.

2.1 | Participants

Studies enrolled healthy participants aged 18–55 (Study 1) or 18–65 (Studies 2/3) years with no clinically significant or relevant abnormalities on oral examination. Participants had ≥20 natural teeth and a self-reported history of DH between 6 months and 10 years. At screening, eligible participants had at least two non-adjacent accessible teeth (incisors, canines or premolars) with dentine exposure at the cervical margin, a Modified Gingival Index (MGI) (Lobene, Weatherford, Ross, Lamm, & Menaker, 1986) score of 0 adjacent to the test area, no mobility, and a positive response to a qualifying

evaporative (air) assessment. At baseline (Day 0), eligible participants had a minimum of two accessible, non-adjacent teeth with signs of DH, determined by a qualifying tactile stimulus threshold of ≤20 g and a Schiff sensitivity score ≥2 (Schiff et al., 1994).

Exclusion criteria included pregnancy; breastfeeding; allergy/intolerance to study materials; any chronic debilitating disease that could affect study outcome; xerostomia; medication affecting pain perception; dental prophylaxis within 4 weeks, vital tooth bleaching within 8 weeks or scaling within 3 months of screening; periodontal disease; dental implants (test teeth only for Study 3); full coverage restorations; orthodontic brackets; caries; and sensitive teeth not expected to respond to treatment with over-the-counter toothpastes. Study 2 participants were ineligible for Study 3.

2.2 | Procedures

At the screening visit, each participant provided written informed consent before their demographic characteristics, medical history and medication use were recorded. An oral soft tissue (OST) examination was conducted. Participants' dentition was assessed sequentially for missing teeth and teeth excluded as per the criteria; evidence of dentine exposure; gingival health status (MGI); tooth mobility; sensitivity to an evaporative (air) stimulus (where a 'yes' response indicated sensitivity). Eligible participants were supplied with an acclimatization toothpaste (Signal® Family Protection, Unilever) and toothbrush (Aquafresh® Clean Control [Everyday Clean], GSK Consumer Healthcare) to use twice daily for 4–8 weeks between screening and baseline visits (acclimatization period). First toothpaste use was carried out under supervision.

Before subsequent study visits, participants refrained from brushing their teeth and using any other oral hygiene aids, and from taking analgesics for ≥8 hr, from eating and drinking for ≥4 hr and from excessive alcohol consumption for 24 hr. Sips of water were permitted, but not within 1 hr of the study visit. During the study, participants could not use any other dental products, apart from dental floss for impacted food removal, and refrained from any non-emergency dental treatment.

At the baseline visit (Day 0), ongoing eligibility was assessed, any adverse events and changes to concomitant medications were recorded, and acclimatization toothpaste compliance was confirmed. Following an OST examination, sensitivity of eligible teeth identified at screening was evaluated. The examiner selected two non-adjacent teeth, designated 'test teeth', from those that met the qualifying sensitivity assessments to be evaluated throughout the study.

Eligible participants were randomized to one of two toothpastes according to a schedule provided by the study sponsor's biostatistics department. Randomization was stratified by test teeth maximum baseline Schiff sensitivity score (2/3). The test toothpaste contained 0.454% SnF_2 (1,100 ppm fluoride) and 5% pentasodium triphosphate in an anhydrous glycerin-based formulation. The control toothpaste contained 0.76% sodium monofluorophosphate (1,000 ppm fluoride) (Colgate® Cavity Protection; Colgate-Palmolive) in a conventional aqueous formulation. Study products were overwrapped to

blind participants to identity. The dental examiner, study statistician, data management staff and other sponsor employees were blinded to toothpaste allocation.

To assess the effect of a single fingertip application of toothpaste, participants (under supervision) applied a pea-sized amount of assigned study product to their fingertip and gently rubbed the toothpaste onto exposed dentine at the cervical margin of one of the two test teeth for 60 s. They repeated the procedure on the other test tooth. No rinsing was permitted. DH was then measured using evaporative (air) and tactile stimuli.

Prior to leaving the study centre, participants brushed (under supervision) with their assigned toothpaste. Test group participants used a focused brushing technique where they first brushed each of the two test teeth with a full ribbon of toothpaste on the toothbrush and then brushed their whole mouth for at least 60 s. Control group participants brushed their whole mouth with a full ribbon of toothpaste in their usual manner for at least 60 s. Participants could rinse with 5 ml tap water for up to 5 s. At home, participants followed their assigned brushing regimen for 3 days, twice daily and then returned to the study centre. Following confirmation of ongoing study compliance and an OST examination, final DH assessments were undertaken.

2.3 | Assessments

In accordance with consensus guidelines (Holland, Narhi, Addy, Gangarosa, & Orchardson, 1997), two independent, stimulus-based clinical measures were used to assess DH. Firstly, a tactile stimulus was administered using a constant-pressure (Yeaple) probe (Polson, Caton, Yeaple, & Zander, 1980) to the exposed sensitive dentine. Testing began at 10 g of pressure and then increased in 10 g increments for each successive challenge until the tactile threshold was reached where the participant gave two consecutive 'yes' responses, indicating the stimulus caused pain/discomfort, at the same pressure setting. At baseline, a maximum force of 20 g was used. At subsequent visits, if no response was given by 80 g, the reading was recorded as >80 g.

After a minimum 5 min recovery period, evaporative sensitivity was assessed by directing air from 1 cm for 1 s from a dental air syringe onto the exposed dentine surface, with the test tooth surface isolated to prevent exposure of adjacent teeth or surrounding soft tissue. The examiner's assessment of the participant's response to the evaporative (air) stimulus was recorded using the Schiff sensitivity scale (0 = participant does not respond to air stimulus; 1 = participant responds to air stimulus but does not request discontinuation; 2 = participant responds to air stimulus and requests discontinuation or moves from stimulus; 3 = participant responds to air stimulus, considers stimulus to be painful and requests discontinuation of the stimulus) (Schiff et al., 1994). For logistical reasons, in Study 1, separate examiners performed the two assessments, and in Studies 2 and 3, the same examiner performed both assessments.

2.4 | Safety

Spontaneously reported adverse events (AEs) and OST examination abnormalities were recorded from first use of acclimatization

toothpaste until 5 days after last use of study toothpaste. The investigator graded each AE (mild, moderate, severe) and assessed whether they were treatment-related. Treatment-emergent AEs (TEAEs) were reported for the safety population, which included all randomized participants.

2.5 | Data analysis

2.5.1 | Sample size determination

Based on outcomes from previous studies (Goyal, Sufi, Qaqish, & Creeth, 2017; Parkinson et al., 2016), for Studies 1 and 2, sufficient participants were screened to ensure approximately 107 per group completed the study to give 80% power to detect a mean difference of 0.25 (standard deviation [SD] 0.6487) between treatment groups in change from baseline in Schiff sensitivity score after 3 days' use using a two-sided t test of significance level 0.05. This represents a potentially clinically meaningful difference. Study 3 was powered based on Studies 1 and 2 outcomes; sufficient participants were screened to ensure approximately 92 evaluable participants per group completed the study to give 90% power to detect a mean between-treatment difference of 0.25 units in Schiff sensitivity score (SD 0.5198) after 3 days' use.

2.5.2 | Efficacy analyses

All statistical analyses were conducted using SAS version 9.2 (SAS Institute Inc.).

2.5.3 | Individual study analysis

The primary objective was to investigate the ability of the test treatment to reduce DH as elicited by evaporative (air) stimulus after 3 days' use, compared to the control treatment. Secondary objectives included this comparison after a tactile stimulus and comparison between treatments with both efficacy measures after a single fingertip application. Efficacy endpoints were change from baseline (mean of the two selected test teeth) for each efficacy measure at each timepoint. Efficacy analyses were performed on the intent-to-treat (ITT) population, defined as all randomized participants who provided at least one post-baseline assessment of efficacy.

Change from baseline was evaluated by analysis of covariance (ANCOVA). For Study 1 Schiff sensitivity score data, treatment group and study site were factors and baseline Schiff sensitivity score was a covariate. For Study 1 tactile threshold data, treatment group, study site and baseline Schiff sensitivity score stratification value were factors with baseline tactile threshold as a covariate. Similar analyses were performed for Studies 2 and 3 without study site as a factor.

2.5.4 | Pooled analysis

As an exploratory, post hoc analysis, data from all three studies were pooled and analysed based on the individual study ITT populations. Change from baseline in Schiff sensitivity scores at each timepoint was analysed using an ANCOVA with factors for treatment and study with baseline (Schiff sensitivity score) as a covariate. Tactile threshold data

FIGURE 1 Participant disposition throughout study

Enrolment		Study 1	Study 2	Study 3
	Screened (n)	488	263	246
	Not randomised (n)	258	30	42
	Not eligible	189	22	41
	Withdrew consent	7	5	0
	Lost to follow-up	7	1	0
	Adverse event	3	1	1
	Other	52	1	0
Allocation	Randomised	230	233	204

		Test	Cont	Test	Cont	Test	Cont
	Allocated to treatment (n)	115	115	117	116	102	102
Follow-up	Completed (n)	114	112	116	116	102	100
	Withdrew consent	1	1	0	0	0	0
	Adverse event	0	0	1	0	0	1
	Other	0	2	0	0	0	1
Analysis	Safety population	115	115	117	116	102	102
	ITT population	115	115	117	116	102	102
	PP population	115	115	117	116	102	100

were analysed similarly except baseline Schiff stratification score was included as a factor and the covariate was baseline tactile threshold. The effects of age (median age ≤30 years/>30 years) and gender (male/female) were investigated by introducing these as factors in the model.

An experimental 'responder' analysis was performed on change in Schiff sensitivity score, whereby an individual with a Schiff sensitivity score reduction of ≥1 was considered a 'responder', otherwise a 'non-responder'. This was repeated for a Schiff sensitivity score reduction of ≥0.5. Analyses were conducted separately for each timepoint using logistic regression via PROC LOGISTIC. Factors were the same as for the ANCOVA model.

3 | RESULTS

Details of participant study flow are shown in Figure 1. Treatment group demographic characteristics were similar across groups for the safety and ITT populations of all studies (Table 1). There were differences in baseline Schiff score distribution and mean participant age between studies, with Study 1 having both the highest proportion of those with baseline Schiff score 3, and the highest mean age. Study times (first participant enrolled/last participant completed) were as follows: Study 1: November 2015/June 2016; Study 2: February 2016/June 2016; and Study 3: November 2016/March 2017.

3.1 | Efficacy

In Study 1, treatment efficacy was not influenced by study centre, so this interaction term was not included in the model.

In all studies, for Schiff sensitivity scores, both test and control groups showed a statistically significant decrease from baseline after both single fingertip application ('immediate' use) and 3 days'

brushing (Table 2, Figure 2a). In Studies 2 and 3, at both timepoints, the test treatment reduced Schiff scores significantly more than did the control (Table 2). Differences at all timepoints were considered clinically relevant (above 0.25 units). However, differences in Schiff scores between test and control did not reach significance at either timepoint in Study 1.

There was a statistically significant increase from baseline in tactile threshold scores for both treatments in Studies 2 and 3 at both timepoints (Table 2, Figure 2b). For Study 1 tactile threshold data, evidence of departure from model assumptions meant a nonparametric van Elteren test was performed; differences from baseline were not significant. For Studies 2 and 3, the test treatment gave statistically significantly higher tactile threshold scores versus control following both immediate and 3 days' use. As for the Schiff data, there were no significant differences between treatments in Study 1 (Table 2).

In all studies, for both treatments and measures, DH relief increased over time.

3.2 | Pooled analysis

The post hoc pooled analysis demonstrated a statistically significantly greater decrease in Schiff sensitivity score and increase in tactile threshold for the test versus control treatment after both a single fingertip application and 3 days' use (Table 3; Figure 3), with degree of difference increasing over time (both measures). Allowing for the between-study differences in efficacy as a function of age or gender showed almost identical results (Figure 3), indicating these did not meaningfully influence overall outcome.

The experimental responder analysis (Table 4) found that after a single fingertip application, the odds ratio for likelihood of experiencing a decrease in Schiff sensitivity score of at least 1 for the

TABLE 1 Summary of baseline characteristics (safety population)

Characteristic	Study 1		Study 2		Study 3	
	Test (*n* = 115)	Control (*n* = 115)	Test (*n* = 117)	Control (*n* = 116)	Test (*n* = 102)	Control (*n* = 102)
Sex, *n* (%)						
Male	24 (20.9)	23 (20.0)	36 (30.8)	31 (26.7)	37 (36.3)	28 (27.5)
Female	91 (79.1)	92 (80.0)	81 (69.2)	85 (73.3)	65 (63.7)	74 (72.5)
Age, years						
Mean (*SD*)	40.7 (8.62)	39.9 (9.18)	34.3 (12.92)	32.8 (11.52)	22.8 (6.61)	22.2 (5.12)
Range	20–55	18–55	18–64	18–64	18–55	18–51
Race, *n* (%)						
White	112 (97.4)	112 (97.4)	93 (79.5)	102 (87.9)	85 (83.3)	90 (88.2)
Black	2 (1.7)	0	4 (3.4)	3 (2.6)	5 (4.9)	4 (3.9)
Asian	1 (0.9)	1 (0.9)	20 (17.1)	8 (6.9)	11 (10.8)	5 (4.9)
Other	0	2 (1.7)	0	3 (2.6)	1 (1.0)	3 (2.9)
Schiff strata 2, *n* (%)	12 (10.4)	11 (9.6)	98 (83.8)	98 (84.5)	75 (73.5)	76 (74.5)
Schiff strata 3, *n* (%)	103 (89.6)	104 (90.4)	19 (16.2)	18 (15.5)	27 (26.5)	26 (25.5)

TABLE 2 Change from baseline and between-treatment comparisons for change in Schiff sensitivity score and tactile threshold (intent-to-treat population)

	Test	Control	Test versus control[c]
Schiff sensitivity score[a]			
Study 1			
Baseline	2.82 (0.031)	2.80 (0.031)	
Immediate	−0.41 (−0.54, −0.27) p < .0001	−0.31 (−0.44, −0.18) p < .0001	−0.09 (−0.280, 0.092) p = .3226
Day 3	−0.96 (−1.14, −0.78) p < .0001	−0.77 (−0.95, −0.59) p < .0001	−0.18 (−0.442, 0.072) p = .1575
Study 2			
Baseline	2.12 (0.028)	2.12 (0.028)	
Immediate	−0.89 (−0.97, −0.81) p < .0001	−0.17 (−0.25, −0.09) p < .0001	−0.72 (−0.839, −0.610) p < .0001
Day 3	−1.40 (−1.49, −1.30) p < .0001	−0.38 (−0.48, 0.28) p < .0001	−1.02 (−1.150, −0.882) p < .0001
Study 3			
Baseline	2.18 (0.033)	2.18 (0.033)	
Immediate	−0.63 (−0.73, −0.54) p < .0001	−0.38 (−0.47, 0.28) p < .0001	−0.26 (−0.387, −0.123) p = .0002
Day 3	−1.37 (−1.46, −1.28) p < .0001	−0.45 (−0.54, 0.35) p < .0001	−0.92 (−1.055, −0.793) p < .0001
Tactile threshold (g)[b]			
Study 1			
Baseline	10 (10, 20)	10 (10, 20)	
Immediate	0 (−5, 65)[d]	0 (−10, 40)[d]	p = .3372
Day 3	10 (−10, 80)[d]	5 (−10, 80)[d]	p = .3719
Study 2			
Baseline	10.85 (0.229)	10.69 (0.193)	
Immediate	19.42 (17.16, 21.68) p < .0001	3.74 (1.47, 6.01) p = .0014	15.68 (12.476, 18.883) p < .0001
Day 3	35.48 (32.40, 38.55) p < .0001	6.55 (3.47, 9.62) p < .0001	28.93 (24.576, 33.277) p < .0001
Study 3			
Baseline	12.35 (0.373)	11.76 (0.346)	
Immediate	15.19 (12.81, 17.56) p < .0001	8.05 (5.67, 10.43) p < .0001	7.14 (3.768, 10.506) p < .0001
Day 3	32.87 (30.03, 35.71) p < .0001	10.37 (7.50, 13.24) p < .0001	22.50 (18.458, 26.541) p < .0001

[a]Baseline values are raw mean scores (± standard error); post-baseline values are adjusted mean changes from baseline (± 95% confidence interval).
[b]Baseline values are raw median scores (minimum, maximum) for Study 1, raw mean scores (± standard error) for Studies 2 and 3; post-baseline values are adjusted median change from baseline scores (minimum, maximum) for Study 1, adjusted mean change from baseline scores (± 95% confidence interval) for Studies 2 and 3.
[c]Difference (95% confidence) p-value from ANCOVA model: first-named minus second-named group. For Schiff sensitivity score, a negative difference favours the first-named group. For Study 1 tactile threshold, p-value is from a van Elteren nonparametric test. For tactile threshold (Studies 2 and 3 only), a positive difference favours the first-named group.
[d]The analysis of the statistical significance of change from baseline in Tactile threshold was not performed for Study 1.

test group versus the control was 4.4. The equivalent odds ratio for a 0.5-point decrease was 3.2. After 3 days' use, odds ratios were 8.7 and 4.8, respectively. Differences were statistically significant at both timepoints, for both Schiff-score changes.

3.3 | Safety

No TEAE was considered treatment-related. In Study 1, three test group participants reported four TEAEs; five control group

participants reported six TEAEs. Four TEAEs were oral, in two test group participants and one control group participant. All TEAEs were mild (none serious) and resolved by study end. In Study 2, two test group participants reported two TEAEs; three control group participants reported three TEAEs. None were oral; four were mild and resolved by study end, one severe TEAE (prostate cancer) led to participant withdrew. In Study 3, nine test group participants reported nine TEAEs (one oral) and 11 control group participants reported 11 TEAEs (none oral); all were mild (none serious). One TEAE led to participant withdrawal (nasopharyngitis), all but one TEAE (gastric haemorrhage) resolved by study end.

4 | DISCUSSION

This is the first known report of a SnF$_2$-based toothpaste reducing DH when applied directly by fingertip to hypersensitive teeth. This is important because it enables individuals with DH to achieve immediate relief using a gentle, controllable product-application method. Using this technique, two of the three studies showed the experimental SnF$_2$ toothpaste reduced DH after single application significantly more than the control toothpaste on both evaporative (air) and tactile assessments.

The post hoc pooled analysis of the three studies indicated that there were overall treatment differences, with the pooled benefit in Schiff score across the three studies of 0.36 units. This is considered clinically significant relief. A complementary perspective on the data was provided by the experimental responder analysis, which concluded the test group participants had an odds ratio of measurable DH relief several times higher than control group participants.

The fingertip application approach has been reported to be effective in clinical studies for two occlusion technologies: strontium acetate and arginine-calcium carbonate (Ayad et al., 2009; Fu et al., 2010; Mason et al., 2010; Nathoo et al., 2009; Schiff et al., 2009). The current studies confirm that the test SnF$_2$ toothpaste applied by fingertip can also provide immediate DH relief. The control toothpaste was not designed for DH treatment; however, the reduction in DH scores suggests that this toothpaste base can also provide some relief when massaged onto sensitive dentine. It is likely that abrasive particles and thickening agents within the formulation lodge at least temporarily in the tubule openings (West, Addy, & Hughes, 1998). The massaging action itself may also provide some minor relief (Ayad et al., 2009).

The fingertip application was followed by 3 days' twice-daily brushing to gauge efficacy in a more conventional oral hygiene regimen. The test group used a focused-brushing technique on
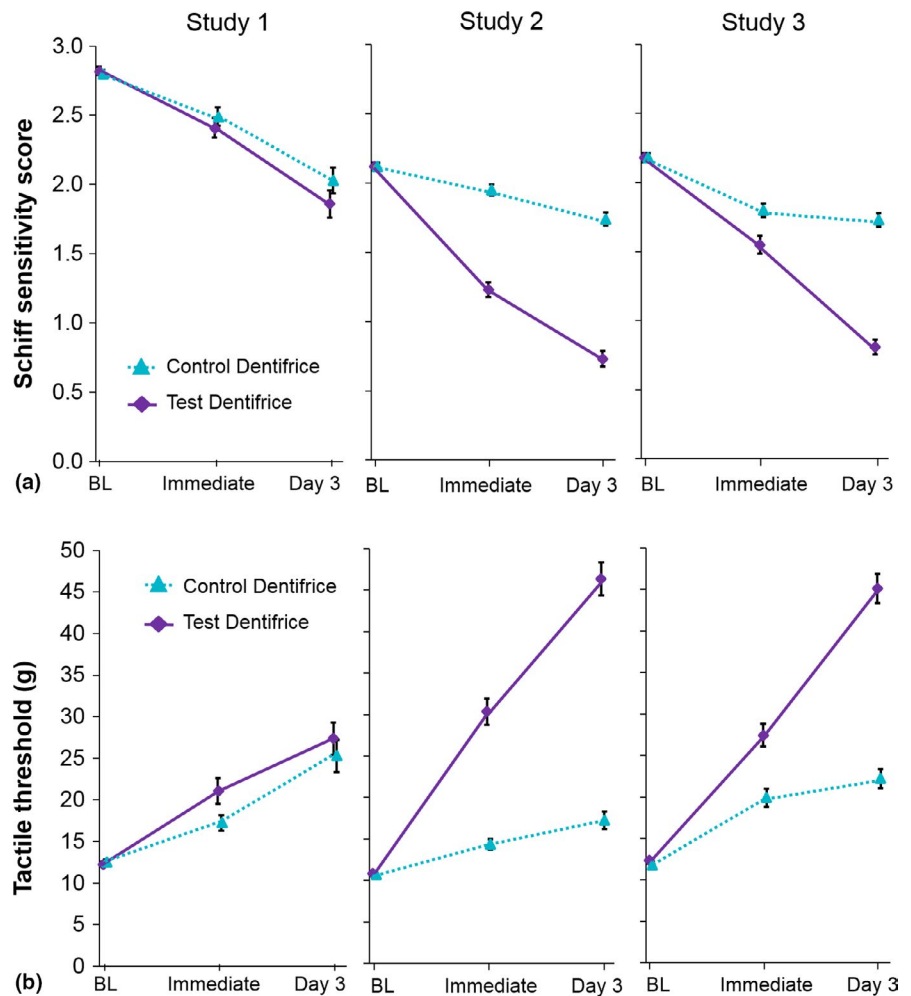

FIGURE 2 Mean (± standard error) a) Schiff sensitivity scores and b) tactile threshold (intent-to-treat population). Data offset for clarity; BL, baseline; tactile threshold values range from 0 to 80 g

	Test (n = 334)	Control (n = 333)	Test versus control[b]
Schiff sensitivity score[a]			
Immediate	−0.65 (−0.71, −0.58) p <.0001	−0.28 (−0.34, −0.22) p <.0001	−0.36 (−0.45, −0.28) p <.0001
Day 3	−1.24 (−1.32, −1.16) p <.0001	−0.53 (−0.61, −0.46) p <.0001	−0.70 (−0.81, −0.59) p <.0001
Tactile threshold (g)[a]			
Immediate	14.47 (13.07, 15.87) p <.0001	5.41 (4.01, 6.81) p <.0001	9.06 (7.08, 11.04) p <.0001
Day 3	27.66 (25.69, 29.63) p <.0001	9.85 (7.87, 11.83) p <.0001	17.81 (15.01, 20.60) p <.0001

TABLE 3 Exploratory pooled analysis of Schiff sensitivity and tactile threshold scores (post hoc, intent-to-treat population)

[a]Adjusted mean change from baseline, 95% confidence intervals and p-value from ANCOVA model with treatment and study as factors (and Schiff sensitivity score for tactile threshold) and baseline Schiff sensitivity score or tactile threshold, as appropriate, as covariate
[b]Negative difference favours the test toothpaste for the Schiff sensitivity score; positive difference favours the test toothpaste for the tactile threshold score
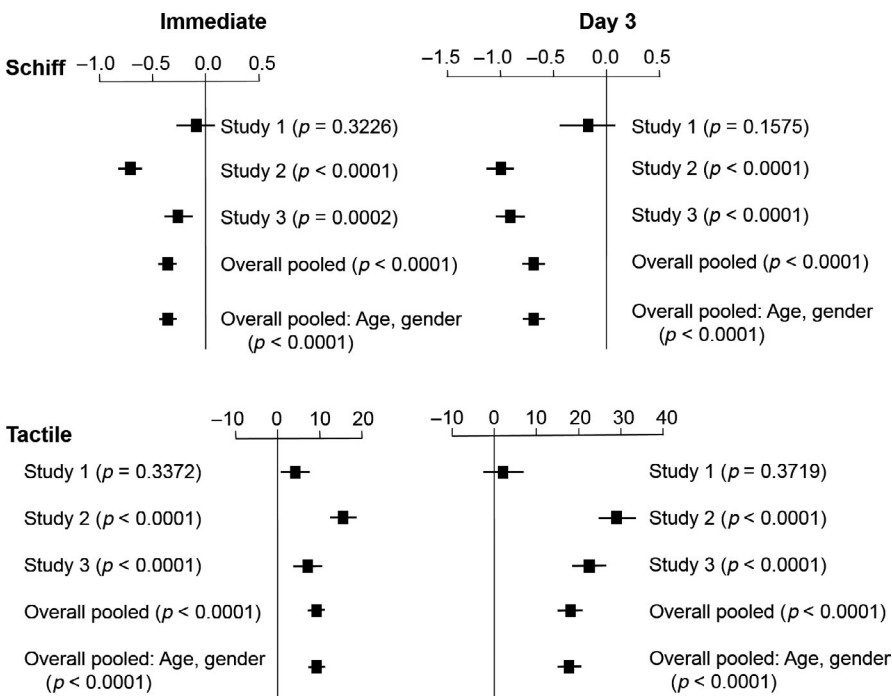

FIGURE 3 Schiff sensitivity score and tactile threshold mean between-treatment difference and 95% CIs for each individual study and pooled analysis including age, gender and baseline score as factors (intent-to-treat population), immediately after fingertip application and on Day 3. In Study 1, mean and 95% CIs from ANCOVA, p-value from nonparametric analysis

the test teeth; those in the control group brushed without specifically treating sensitive areas. This approach was taken to follow previous studies (He, Barker, et al., 2011; He, Chang, et al., 2011; He, Cheng, et al., 2011; Sharma et al., 2011) on the premise that individuals follow manufacturers' instructions for a product. This treatment reduced DH relative to baseline after 3 days in all three studies, across both treatment groups. The post hoc pooled analysis showed DH relief was greater in the test group than the control, continuing to build over the 3 days to reach a Schiff score difference of 0.70, considered clinically significant relief. The experimental responder analysis reflected this conclusion, indicating a several-fold higher odds ratio for experiencing relief among test group participants. This degree of effect is consistent with

previous studies of this toothpaste when applied solely by toothbrushing: benefits were demonstrated after first use, increasing after 3 days (Creeth, Gallob, et al., 2017; Creeth, Goyal, et al., 2017).

The three different studies performed here gave a range of results. The third study, performed after the first two (which gave contrasting results), is helpful in reaching an overall conclusion regarding efficacy. Of potential relevance to the different results observed were differences in participant characteristics: in Study 1, almost all participants were in the higher Schiff stratum, while in Studies 2 and 3, the majority were in the lower stratum. Study 3 participants were generally younger than in Study 2, who in turn were generally younger than in Study 1.

TABLE 4 Exploratory responder analysis for Schiff sensitivity score: pooled data (post hoc, intent-to-treat population)

	Responder rates		Odds ratio (95% CI)[a]	
	Test	Control	Log odds (95%CI)[b]	*p*-value
1-point change in Schiff sensitivity score				
Immediate	41.6%	14.1%	4.41 (3.02, 6.45) 1.48 (1.10, 1.86)	*p* < .0001
Day 3	75.9%	27.1%	8.69 (6.10, 12.38) 2.16 (1.80, 2.51)	*p* < .0001
0.5-point change in Schiff sensitivity score				
Immediate	65.3%	39.3%	3.20 (2.29, 4.47) 1.16 (0.82, 1.49)	*p* < .0001
Day 3	84.9%	56.4%	4.78 (3.25, 7.04) 1.56 (1.17, 1.95)	*p* < .0001

[a]From logistic regression with factors for treatment and study with baseline Schiff sensitivity score as a covariate

[b]Exponential (natural log odds and 95% confidence intervals)

The difference in average baseline Schiff score between studies is of particular interest, raising the question whether the lack of treatment difference observed in Study 1 is linked to the high proportion of participants with Schiff score 3 in that study. However, assessing the effect of baseline DH severity is confounded by the fact that this difference cannot be disentangled from other study-to-study differences. The pooled analysis considered differences in baseline DH severity, as well as differences in age and gender, and found none of these factors meaningfully affected the overall outcome.

The questions raised by these population differences regarding their influence on the analysis cannot be fully answered with available information; however, the authors believe the conclusion from the pooled analysis, indicating that clear differences exist between the effects of test and reference treatments, is appropriate.

To clarify whether baseline Schiff score influences the difference in efficacy between the test and control treatments, a further, separate study would be required, with sufficient participants in each baseline Schiff score stratum to permit a valid analysis.

Other factors may explain differences in results between studies. It is well known in pain studies that response to an inactive treatment can occur due to expectation of a treatment benefit (placebo effects) (Kirsch, 2013), to behavioural changes due to study participation (Hawthorne effects) (Benedetti, Carlino, & Piedimonte, 2016), or to the intrinsically episodic nature of DH, which may peak then resolve without intervention (West, Addy, Jackson, & Ridge, 1997). In addition, due to normal biological variation, between-treatment differences shown in a single study are estimates that may be above or below the true difference. Although a range of control steps were taken to reduce their potential impact, including acclimatization and inclusion criteria specifying DH duration, all these factors could have influenced results.

In conclusion, the evidence from the three studies presented in this report shows that 0.454% SnF_2 formulated into an anhydrous, polyphosphate-containing base can reduce DH pain when applied once directly by fingertip to hypersensitive teeth, relative to a conventional fluoride toothpaste. DH relief increased over 3 days of twice-daily brushing. This conclusion supports and extends previous studies of such toothpastes (Creeth, Gallob, et al., 2017; Creeth, Goyal, et al., 2017; Parkinson et al., 2013, 2016), which, taken together, demonstrate the experimental formulation's ability to provide short- and long-term DH reduction.

CONFLICT OF INTEREST

J Creeth, P Gomez-Pereira and F Sufi are employees of GSK Consumer Healthcare. Intertek Clinical Research Services (of whom R Maclure was an employee at the time, J Holt), the Clinical Trials Unit of Bristol Dental School and Hospital (J Seong, N Chapman, N West) and Syneos Health (of whom C Budhawant was an employee at the time) have all received funding from GSK Consumer Healthcare.

ORCID

Jonathan Creeth https://orcid.org/0000-0001-5119-9222

Nicola West https://orcid.org/0000-0002-9127-5530

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