The study listed may include approved and non-approved uses, formulations or treatment regimens. The results reported in any single study may not reflect the overall results obtained on studies of a product. Before prescribing any product mentioned in this Register, healthcare professionals should consult prescribing information for the product approved in their country.

GSK Medicine: 4-Isopropyl-3-methyl phenol (IPMP) and sodium fluoride (NaF)

Study Number: T3450515

Title: Clinical Efficacy of an Experimental Toothpaste

**Rationale:** To investigate the ability of an IPMP containing toothpaste to control dental plaque and maintain gingival health following professional dental cleaning.

Phase: I

Study Period: 13<sup>th</sup> January 2010 to 18<sup>th</sup> May 2010

**Study Design:** This was a single centre, examiner blind, two arm, parallel group, randomised study in healthy adult volunteers. Subjects with overnight plaque attended the Pre-Prophylaxis Baseline Visit and underwent baseline oral soft tissue (OST) assessment, plaque sampling (sub-set of subjects only), Modified Gingival Index (MGI) inflammation and Bleeding Index (BI) assessment and then dental plaque assessment. A sub-set of approximately 50 subjects per group had a plaque sample collected for plaque bacteria assessment.

A dental prophylaxis was performed on each subject's teeth followed by flossing to ensure complete removal of all plaque. Subjects were provided with oral hygiene instructions on how to brush correctly and provided with a washout toothpaste and toothbrush to use at home for 1 week.

Subjects returned to the site after 1 week for an additional oral hygiene instruction visit where they underwent a gross OST assessment and brushed their teeth with the washout toothpaste and toothbrush under supervision in order for study staff to observe their brushing procedure. They then had their plaque disclosed and the study staff highlighted any areas missed during brushing before removing any residual plaque by polishing using the washout toothpaste. Subjects were then reminded of the oral hygiene instruction. The purpose of this visit was to bring the subjects to their optimum achievable gingival health over this period.

Subjects returned to site after a further 2 weeks and only those subjects who had demonstrated an improvement in their gingival health (decrease in MGI from pre prophylaxis Baseline Visit) as a result of the dental prophylaxis and oral hygiene instruction were allowed to proceed with the study. Subjects went through the same assessments as were carried out at the Pre Prophylaxis Baseline Visit. They were stratified according to their MGI score from the Pre-Prophylaxis Baseline Visit and randomised into one of two treatment groups. Subjects were instructed to brush their teeth at home with the assigned study treatment twice a day for one timed minute. Study site staff then removed any residual plaque by dental polishing with the subjects' assigned treatment to bring the subject to zero plaque prior to commencing the treatment phase of the study.

Subjects returned to the site with overnight plaque after 4, 8 and 12 weeks. At each visit subjects underwent a full OST examination and any adverse events (AEs) were recorded. This was followed by plaque sampling (sub-set of subjects only at 4 and 12 week visits only), MGI inflammation and BI assessment and then dental plaque assessment.

An evaluation of the AE profiles from the test and reference treatments were used to monitor the tolerability of the test treatments with a focus on oral related AEs.

Centre: 1, UK

Indication: Dental plaque

## Treatments:

Test product: Experimental toothpaste containing 0.1w/w IPMP (923 parts per million [ppm] Fluoride [F]),

**Reference product**: Sodium Fluoride Silica toothpaste (923 ppm F)

For both, test and reference products, subjects brushed their teeth for one timed minute twice each day (morning and evening) for 12 weeks at home.

Objectives:

## Primary objective:

To evaluate and compare gingivitis as measured by MGI and BI following twice daily use of experimental toothpaste compared to reference toothpaste after 12 weeks.

### Secondary objectives:

- 1. To evaluate and compare gingivitis as measured by MGI and BI following twice daily use of experimental toothpaste compared to reference toothpaste after 4 and 8 weeks.
- 2. To evaluate and compare dental plaque scores (overall and interproximal) following twice daily use of experimental toothpaste compared to reference toothpaste after 4, 8 and 12 weeks.
- 3. To evaluate and compare changes in cultivable plaque bacterial groups in plaque samples, following twice daily use of experimental toothpaste compared to reference toothpaste after 4 and 12 weeks.

#### Primary Endpoints:

- 1. MGI at 12 weeks:
- 2. BI at 12 weeks:

## Secondary Endpoints:

- 1. MGI at 4 and 8 weeks
- 2. BI at 4 and 8 weeks
- 3. Dental plaque scores after 4,8, and 12 weeks
- 4. Proportion of sites that worsen in MGI,
- 5. Proportion of sites that worsen in their BI score,
- 6. Plaque,
- 7. Gingival MGI,
- 8. Papillae MGI,
- 9. Gingival BI,
- 10. Papillae BI,
- 11. Interproximal Plaque and
- 12. Bacterial count data (total anaerobic, total aerobic, Streptococcus mutans, total Volatile Sulfur Compounds [VSC]).

# Statistical Methods:

All efficacy variables were analysed under a null hypothesis of no difference between experimental and regular toothpaste against an alternate hypothesis of a difference between experimental and regular toothpaste. The MGI and BI were calculated taking the average over all tooth sites for a subject. The MGI was compared between treatments using an analysis of covariance. The Analysis of covariance (ANCOVA) model included factors for treatment group, bacteria sampling and the baseline level (Pre Prophy and Randomisation) of MGI as a covariate. The gingival strata level was not included as the actual baseline level was included as a covariate. The BI was compared between treatments using ANCOVA. The ANCOVA model included treatment group, bacteria sampling and strata level of gingival index as factors and the baseline (Pre Prophy and Randomisation) (BI) as a covariate. Treatment differences and 95% confidence intervals were presented. All tests were two sided and performed at the 5% significance level. The BI and MGI were analysed at 4, 8 and 12 weeks after treatment. The primary timepoint for analysis was 12 weeks. The two primary variables (MGI and BI) were required to show statistical significance between treatments so that no adjustment for multiplicity was required.

The proportion of sites that worsen for MGI and BI was compared between treatments using Analysis of variance (ANOVA) at each visit. The ANOVA model included factors for treatment group, bacteria sampling and strata level of gingival index. The MGI (for gingival and papillae regions separately) was compared between treatments using ANCOVA at each visit. The ANCOVA model included factors for treatment group, bacteria sampling and the baseline level (Pre Prophy and Randomisation) of MGI as a covariate. The gingival strata level will not be included as the actual baseline level is included as a covariate. The BI (for gingival and papillae regions separately), plaque and interproximal plaque were compared between treatments using ANCOVA at each visit. The ANCOVA model included treatment group, bacteria sampling and strata level of gingival index as factors and the baseline (Pre Prophy and Randomisation) (BI or interproximal plaque as appropriate) as a covariate. The bacterial count data was compared between treatments using ANCOVA. The ANCOVA model included treatment group and strata level of gingival index as factors and the baseline (Pre

Prophy and Randomisation) bacterial count as a covariate. The bacterial count data (including baselines) was log transformed prior to analysis. For each analysis, treatment differences and 95% confidence intervals were presented. All tests were two sided and performed at the 5% significance level.

Study Population					
Treatment Sequence	0.1%	IPMP / 0.5%		Sodium Fl	uoride /Silica
	Sodiu	m Fluoride /		Toot	hpaste
	Zinc Toothpaste				
Randomised, N (%)		95	_	95	
Completed, n (%)	8	8 (92.6)		82 (86.3)	
Subjects not completing the study, n (%)		/ (/.4)		13	(13.7)
Due to adverse event					(1.1)
Protocol Violation		5 (5.3) 2 (2.1)		8	(8.4)
Intent To Treat (ITT) Deputation	0	2 (2.1) 2(06 9)		4	(4. <i>Z)</i>
Demographics (All Randomized Subjects)	7	2(90.0)		70	(74.7)
Sex n (%)	0 1% IPMP / 0 5% Sodium Eluoride /Silic			ioride /Silica	
	Sodium	Fluoride /7inc		Toot	hpaste
	То	othpaste			
Males	2	3 (24.2)		21	(22.1)
Females	7.	2 (75.8)		74	(77.9)
Race, n (%)		· · ·			. ,
White	95	(100.0)		93 (	97.9)
Multiple		0		2 (2	2.1)
Mean Age, years	41.7	' (10.56)		41.5 (	12.50)
(Standard Deviation [SD])					
Primary Efficacy Results					
Table 1 Modified Gingival Index Score					
Baseline	0.1% IPI	MP / 0.5% Sodiu	JM	Sodium	Fluoride /Silica
	Fluoride	Dandomizati	sie	Drophy Dondomizatio	
Ν					
Mean (SD)	1 97	1 61 (0 226	)	1 96	1 58 (0 218)
	(0 199)	1.01 (0.220	')	(0 197)	1.50 (0.210)
Treatments (Week 12)	0.1% IPN	/IP / 0.5% Sodiu	ım	Sodium I	luoride /Silica
	Fluoride	/Zinc Toothpas	ste	То	othpaste
n		88			82
Mean (SD)	1	.80 (0.236)		1.8	4 (0.205)
Adjusted means [1]		1.80			1.84
Treatment comparison (IPMP/zinc toothpas	ste vs. Sodi	um fluoride/sili	ica too	othpaste)	
Difference <sup>[2]</sup>			-0.0	)4	
95% CI		(-	-0.09,	0.01)	
% Difference <sup>[3]</sup>			-2.2	24	
p-Value [1]	atorio commina	(unalma) with mean	0.09	27 d randomination	haadina aa
(1) From ANCOVA with factors for treatment group and bac covariates.	ciena sampling	(yes/no) with pre pr	opny ar	ia randomization	Daseline as
[2] Difference is first named treatment minus second name	d treatment suc	ch that a negative di	fference	e favours the firs	t named treatment.
[3] Second named treatment is taken as reference for calcu	ulation of % diff	erence [(Difference/	Referer	nce)*100%].	
Table 2 Analysis of Bleeding Score	0 10/ 10			Codless	Fluorido /Ciliaa
Daseiine	U. 1% IPI Eluorido	VIP / U.5% SOOIL	ulli sto	Soaium	riuoriue /Silica
	Dronby		ole Izati	Drophy	Dandomizatio
	FIOPHY	n	12011	порну	n
n	92	92		90	90
 Mean (SD)	0.48	0.25		0.47	0.24
	(0.190)	( 0.113	3)	(0.191)	(0.113)
Treatments (Week 12)	0.1% IPN	AP / 0.5% Sodiu	Im	Sodium I	- Iuoride /Silica

	Fluoride	e /Zinc Toothpaste	Too	Toothpaste		
n		88		82		
Mean (SD)		0.14(0.084)	0.15	0.15 (0.090)		
Adjusted means 11		0.35		0.37		
Back Transformed Mean [2]		0.13		0.14		
Treatment comparison (IPMP/zinc toothpas	ste vs. Sod	ium fluoride/silica	toothpaste)			
Difference <sup>[2]</sup>		-	0.01			
Difference <sup>[3]</sup>		-	0.02			
95% CI		(-0.0	5. 0.01)			
% Difference <sup>[4]</sup>			0.64			
p-Value 11		0.	1502			
<ol> <li>From ANCOVA (square root transformation) with factor. with pre prophy and randomisation baseline as covariates.</li> <li>Based on back transformed values (value squared).</li> <li>Difference is first named treatment minus second name [4] Second named treatment is taken as reference for calcuvalues.</li> </ol>	nation) with factors for treatment group, bacteria sampling (yes/no) and gingival strata (low, high) ine as covariates. alue squared). nus second named treatment such that a negative difference favours the first named treatment. reference for calculation of % difference [(Difference/Reference)*100%] using back transformed					
Secondary Efficacy Results						
Table 3 Analysis of Modified Gingival Index	Score – W	leek 4 and 8				
	0.1% IP	MP / 0.5% Sodium	Sodium F	luoride /Silica		
Bacalina	Fluoride	Pandomization	Dranhu	Dandomizatio		
Baseline	Propny	Randomization	Propny	Randomizatio		
N	00	00	00	00		
N Moon (SD)	92	92	90	90 1 E 0		
iviean (SD)	1.97	1.01	1.90	1.00		
	(0.199) (0.220) (0.197) (0.210)					
Tractmente (Meak A)	0.10/ ID	MD / 0 EV/ Sodium	Codium F	luorido /Silioo		
Treatments (week 4)	0.1% IPMP / 0.5% Sodium Sodium Fluoride /Silica					
	FIUOTIO		100			
II Maan (CD)		9Z	1 71	90		
Mean (SD)		1.08 (0.191)	1.71	(0.104)		
Aujusteu means		1.0/		1.71		
	sie vs. 500	ium nuoride/silica				
		-	0.05			
95% CI		(-0.0	8, -0.01)			
% Difference <sup>(3)</sup>		-	2.64			
	0.40/ 101/	0.	0242			
Treatments (week 8)	0.1% IPIV	IP / 0.5% Sodium	Sodium Fil	Ioride /Silica		
-	Fluoride		1001	npaste		
n Marca (CD)	1	88	1 75	35		
Mean (SD)	Ι.	/3 (0.200)	1./5	(0.184)		
		1./Z	. 	.75		
I reatment comparison (IPMP/ZINC toothpa	ste vs. 500	ium fluoride/silica	tootnpaste)			
		-0.03 (-	0.07, 0.01)			
	4.74					
% Dillerence <sup>(3)</sup>	-1./1					
p-Value II	atorio complin	U.	1421	hacalina aa		
<ul> <li>[1] From ANCOVA with factors for treatment group and bac covariates.</li> <li>[2] Difference is first named treatment minus second name</li> <li>[3] Second named treatment is taken as reference for calculation</li> </ul>	d treatment su	ich that a negative differe fference [(Difference/Refe	nce favours the first prence)*100%].	named treatment.		
Table 4 Analysis of Bleeding Score – Week	4 and 8					
	0.1% IPN	IP / 0.5% Sodium /Zinc Toothpasto	Sodium Flu	uoride /Silica		
Basolino	Drophy	Dandomization	Drophy	Dandomizatio		
	FIOPITY	Nanuomization	гторну	n		

N	92	92	90	90	
Mean (SD)	0.48	0.25	0.47	0.24	
	(0.190)	(0.113)	(0.191)	(0.113)	
Treatments (Week 4)	0.1% IPN	IP / 0.5% Sodium	I Sodium Flu	uoride /Silica	
	Fluoride	/Zinc Toothpaste	e Tootl	npaste	
n		92	(	90	
Mean (SD)	0.	.21 (0.121)	0.23	(0.119)	
Adjusted means 11		0.44	0	.47	
Back Transformed Mean [2]		0.19	0	.22	
Treatment comparison (IPMP/zinc toothpas	ste vs. Sod	lium fluoride/silio	a toothpaste)		
Difference <sup>[2]</sup>	-0.03				
Difference <sup>[3]</sup>			-0.03		
95% CI		(-(	).06, 0.00)		
% Difference <sup>14]</sup>			-11.96		
p-Value 11			0.0513		
Treatments (Week 8)	0.1%	PMP / 0.5%	Sodium Fluc	oride /Silica	
	Sodium	Fluoride /Zinc	Tooth	oaste	
	То	othpaste			
n		88	85	)	
Mean (SD)	0.1	6 (0.101)	0.16 (0	.087)	
Adjusted means 11		0.38	0.3	9	
Back Transformed Mean [2]		0.15	0.16		
Treatment comparison (IPMP/zinc toothpas	oaste vs. Sodium fluoride/silica toothpaste)				
Difference <sup>[2]</sup>	-0.01				
Difference <sup>[3]</sup>	-0.01 (-0.04, 0.02)				
95% CI					
% Difference <sup>[4]</sup>			-6.25		
p-Value 🗉			0.4029		
<ol> <li>From ANCOVA (square root transformation) with factor with pre prophy and randomisation baseline as covariates.</li> <li>Based on back transformed values (value squared).</li> <li>Difference is first named treatment minus second name [4] Second named treatment is taken as reference for calcuvalues.</li> </ol>	s for treatment d treatment su ulation of % di	group, bacteria samp Ich that a negative diff fference [(Difference/R	ling (yes/no) and gingiva erence favours the first reference)*100%] using	al strata (low, high) named treatment. back transformed	
Table 5 Analysis of Plaque Score – Week 4,	8, and 12	(ITT Population)			
	0.1%	PMP / 0.5%	Sodium Fluc	oride /Silica	
	Sodium	Fluoride /Zinc	Tooth	oaste	
	То	othpaste			
Baseline	Prophy	Randomizati	Prophy	Randomizatio	
		on		n	
N	92	92	90	90	
Mean (SD)	2.78	2.42 (0.315)	2.71	2.43	
	(0.465)		(0.522)	(0.347)	
Treatments (Week 4)	0.1%	PMP / 0.5%	Sodium Fluc	ride /Silica	
	Sodium	Fluoride /Zinc	looth	baste	
	10	othpaste			
n (05)		92	9(	)	
Mean (SD)	2.3	0 (0.352)	2.31(0	.393)	
		2.28	2.3	0	
Ireatment comparison (IPMP/zinc toothpa:	ste vs. Sod	lium fluoride/silic	ca toothpaste)		
			-0.02		
95% UI	(-0.10, 0.06)				
	-1.00				
	0.10		0.5/61		
Treatments (Week 8)	0.1% IPMP / 0.5% Sodium Fluoride /Silica				

	Sodium Fluoride /Zinc Toothpaste			paste	
	Toothpaste				
n	88 85			5	
Mean (SD)	2.34 (0.363) 2.42 (0.426)			.426)	
Adjusted mean [1]		2.33	2.4	.3	
Treatment comparison (IPMP/zinc toothpas	ste vs. Sod	lium fluoride/silic	a toothpaste)		
Difference <sup>[2]</sup> 95% CI		(-0	-0.10 18 -0.01)		
% Difference <sup>[3]</sup>		( 0	-4 04		
n-Value [1]			0 0242		
Treatments (Week 12)	0.1%	PMP / 0.5%	Sodium Fluc	oride /Silica	
	Sodium	Fluoride /7inc	Tooth	paste	
	То	othpaste			
n		87	82	2	
Mean (SD)	2.1	5 (0.433)	2.31 (0	.505)	
Adjusted mean <sup>[1]</sup>		2.15	2.5	30	
Treatment comparison (IPMP/zinc toothpas	ste vs. Sod	lium fluoride/silic	a toothpaste)	-	
Difference <sup>[2]</sup>		-0.15	(-0.26, -0.05)		
95% CI					
% Difference <sup>[3]</sup>			-6.59		
p-Value <sup>[1]</sup>			0.0047		
[1] From ANCOVA with factors for treatment group, bacteri	a sampling (ye	es/no) and gingival stra	ta (low, high) with pre p	prophy and	
randomisation baseline as covariates.					
[2] Difference is first named treatment minus second name [3] Second named treatment is taken as reference for calcu	for calculation of % difference [(Difference/Reference)*100%]				
Table 6 Analysis of Interproximal Plaque So	ore-Week	(4, 8, and 12 ( IT)	Population)		
	0.1% IPM	IP / 0.5% Sodium	Sodium Flu	uoride /Silica	
	Fluoride /Zinc Toothpaste Toothpaste				
Baseline	Prophy	Randomization	Prophy	Randomizatio	
	. ,			n	
N	92	92	90	90	
Mean (SD)	2.94	2.51 (0.353)	2.85	2.51	
	(0.532)		(0.599)	(0.392)	
Treatments (Week 4)	0.1% IPN	IP / 0.5% Sodium	Sodium Flu	uoride /Silica	
	Fluoride	/Zinc Toothpaste	Toot	hpaste	
n		92	90		
Mean (SD)	2.	.39 (0.374)	2.41	(0.436)	
Adjusted mean [1]		2.37	2	2.41	
Treatment comparison (IPMP/zinc toothpas	ste vs. Sod	lium fluoride/silic	a toothpaste)		
		<i>.</i>	-0.04		
95% CI		(-(	0.13, 0.05)		
% Difference <sup>[3]</sup>			-1.70		
p-Value <sup>[1]</sup>			0.3522		
Treatments (Week 8)	0.1% IPN	IP / 0.5% Sodium	Sodium Flu	uoride /Silica	
	Fluoride /Zinc Toothpaste Toothpaste				
n N (0D)	88 85			85	
Mean (SD)	2.	.43 (0.397)	2.51	(0.469)	
		2.42	2	.53	
Treatment comparison (IPMP/zinc toothpas	ste vs. Sod	lium fluoride/silic	a toothpaste)		
			-0.11		
95% CI		(-(	<u>J.20, -0.02)</u>		
			-4.3/		
	0.40/ 151		0.0200		
Treatments (Week 12)	0.1% IPN	1P / 0.5% Sodium	Sodium Flu	Joride /Silica	

	Fluoride /Zinc Toothpaste	Toothpaste				
n	87	82				
Mean (SD)	2.24 (0.458)	2.41 (0.538)				
Adjusted mean <sup>[1]</sup>	2.23	2.39				
Treatment comparison (IPMP/zinc toothpa	ste vs. Sodium fluoride/silica t	oothpaste)				
Difference <sup>[2]</sup>	-(	).16				
95% CI	(-0.27	7, -0.06)				
% Difference <sup>[3]</sup>	-6	5.89				
p-Value <sup>[1]</sup>	0.0	0034				
[1] From ANCOVA with factors for treatment group, bacter	ia sampling (yes/no) and gingival strata (	low, high) with pre prophy and				
randomization baseline as covariates.	d tractor and such that a parative differen	and for your the first named to almost				
[2] Difference is first named treatment is taken as reference for calc	ulation of % difference [(Difference/Refe	rence)*1001				
Table 7 Analysis of Proportion of Sites With Increase in MGI Score Compared to Pre Prophy Visit (ITT						
Population)	·					
Baseline	0.1% IPMP / 0.5% Zinc	Sodium Fluoride / Silica				
	Toothpaste	Toothpaste				
	•					
N	92	90				
Mean (SD)	0.05 (0.039)	0.05 ( 0.041)				
Treatments (Week 4)	0.1% IPMP / 0.5% Zinc	Sodium Fluoride / Silica				
	Toothpaste	Toothpaste				
n	92 90					
Mean (SD)	0.05 (0.043)	0.07 (0.056)				
Adjusted mean <sup>[1]</sup>	0.19 0.22					
Back Transformed Mean <sup>[2]</sup>	0.04 0.05					
Treatment comparison (IPMP/zinc toothpa:	ste vs. Sodium fluoride/silica t	oothpaste)				
Difference <sup>[2]</sup>	-(	).01				
Difference <sup>[3]</sup>	-(	0.03				
95% CI	(-0.0	6, 0.00)				
% Difference <sup>[4]</sup>	-2	6.89				
p-Value <sup>[1]</sup>	0.0	0211				
Treatments (Week 8)	0.1% IPMP / 0.5% Zinc	Sodium Fluoride / Silica				
	Toothpaste	Toothpaste				
n	88	85				
Mean (SD)	0.07 (0.056)	0.08 (0.061)				
Adjusted mean <sup>[1]</sup>	0.23	0.24				
Back Transformed Mean <sup>[2]</sup>	0.05	0.06				
Treatment comparison (IPMP/zinc toothpa:	ste vs. Sodium fluoride/silica t	oothpaste)				
Difference <sup>[2]</sup>	0	.00				
Difference <sup>[3]</sup>	-(	).01				
95% CI	(-0.0-	4, 0.02)				
% Difference <sup>[4]</sup>	-6.05					
p-Value <sup>[1]</sup>	0.0	5164				
Treatments (Week 12)	0.1% IPMP / 0.5% Zinc   Sodium Fluoride / Silica					
	Toothpaste Toothpaste					
n (az)	88	82				
Mean (SD)	0.09 (0.074)	0.10 (0.067)				
Adjusted mean <sup>[1]</sup>	0.27	0.29				
Back Transformed Mean <sup>[2]</sup>	0.07	0.09				
Treatment comparison (IPMP/zinc toothpaste vs. Sodium fluoride/silica toothpaste)						

Difference <sup>[2]</sup>	-0.01					
Difference <sup>[3]</sup>	-0.03					
95% CI	(-0.06)	0.01)				
% Difference <sup>[4]</sup>	-17	.31				
p-Value [1]	0.14	102				
[1] From ANOVA (square root transformation) with factors for treat	ment group, bacteria sampling (yes/no) and ging	ival strata (low, high).				
[2] Based on back transformed values (value squared). [3] Difference is first named treatment minus second named treatm	ent such that a negative difference favours the t	irst named treatment				
[4] Second named treatment is taken as reference for calculation of	f % difference [(Difference/Reference)*100] usin	g back transformed values.				
Table 8 Analysis of Proportion of Sites With	Increase in MGI Score Compar	ed to Baseline				
Treatments (Week 4)	0.1% IPMP / 0.5% Zinc	Sodium Fluoride / Silica				
	Toothpaste	Toothpaste				
N	92	90				
Mean (SD)	0.19 (0.113)	0.22 (0.115)				
Adjusted mean [1]	0.41	0.45				
Back Transformed Mean <sup>[2]</sup>	0.16	0.20				
Treatment comparison (IPMP/zinc toothpa	ste vs. Sodium fluoride/silica to	othpaste)				
Difference <sup>[2]</sup>	-0.	04				
Difference <sup>[3]</sup>	-0.04 (-0.0	08, -0.01)				
95% CI						
% Difference <sup>[4]</sup>	-18	.82				
p-Value <sup>[1]</sup>	0.0	150				
Treatments (Week 8)	0.1% IPMP / 0.5% Zinc	Sodium Fluoride / Silica				
	Toothpaste	Toothpaste				
n	88	85				
Mean (SD)	0.23 (0.112)	0.25 (0.108)				
Adjusted mean <sup>[1]</sup>	0.46	0.48				
Back Transformed Mean <sup>[2]</sup>	0.21	0.23				
Treatment comparison (IPMP/zinc toothpa	ste vs. Sodium fluoride/silica to	othpaste)				
Difference <sup>[2]</sup>	-0.	03				
Difference <sup>[3]</sup>	-0.03 (-0.	06, 0.01)				
95% CI						
% Difference <sup>[4]</sup>	-11	.03				
p-Value <sup>[1]</sup>	0.04	993				
Treatments (Week 12)	0.1% IPMP / 0.5% Zinc	Sodium Fluoride / Silica				
	loothpaste	loothpaste				
	00	82				
() Maan (CD)	88	82				
Mean (SD)	0.28 (0.134)	0.31 (0.126)				
	0.51	0.54				
Back Iransformed Mean <sup>[2]</sup>	U.20	U.29				
	ste vs. Sodium fluoride/silica to	otnpaste)				
	-0.	03				
	-0.03 (-0.07, 0.00)					
95% CI	41.00					
	-11	.28				
p-value III						
I able 9 Analysis of Proportion of Sites With	increase in Bleeding Index Sco	ore compared to Pre Prophy				
VISIL Pacolino	0.1% IDMD / 0.5% 7:20	Sodium Eluorida / Silica				
Daseillie	U. 1% IPIVIP / U.5% ZINC	Souluili Fluoride / Silica				
	rootripaste	rounpasie				
N	92	90				
1	12	/ 0				

Mean (SD)	0.10 (0.045)	0.09 (0.040)		
Treatments (Week 4)	0.1% IPMP / 0.5% Zinc	Sodium Fluoride / Silica		
	Toothpaste	Toothpaste		
n	92	90		
Mean (SD)	0.08 (0.047)	0.09 (0.043)		
Adjusted mean <sup>[1]</sup>	0.27	0.28		
Back Transformed Mean <sup>[2]</sup>	0.07	0.08		
Treatment comparison (IPMP/zinc toothpas	ste vs. Sodium fluoride/silica to	othpaste)		
Difference <sup>[2]</sup>	-0.	01		
Difference <sup>[3]</sup>	-0.	01		
95% CI	(-0.04)	0.01)		
% Difference <sup>[4]</sup>	-8.	71		
p-Value [1]	0.28	331		
Treatments (Week 8)	0.1% IPMP / 0.5% Zinc Toothpaste	Sodium Fluoride / Silica Toothpaste		
n	88	85		
Mean (SD)	0.06 (0.038)	0.06 (0.032)		
Adjusted mean [1]	0.23	0.23		
Back Transformed Mean <sup>[2]</sup>	0.05	0.05		
Treatment comparison (IPMP/zinc toothpas	ste vs. Sodium fluoride/silica to	othpaste)		
Difference <sup>[2]</sup>	0.0	00		
Difference <sup>[3]</sup>	0.00 (-0.0	02, 0.02)		
95% CI				
% Difference <sup>[4]</sup>	-1.	11		
P-Value <sup>[1]</sup>	0.9	151		
Treatments (Week 12)	0.1% IPMP / 0.5% Zinc Toothpaste	Sodium Fluoride / Silica Toothpaste		
n	88	82		
Mean (SD)	0.05 (0.027)	0.05 (0.035)		
Adjusted mean <sup>[1]</sup>	0.22	0.22		
Back Transformed Mean <sup>[2]</sup>	0.05	0.05		
Treatment comparison (IPMP/zinc toothpas	ste vs. Sodium fluoride/silica to	othpaste)		
Difference <sup>[2]</sup>	0.0	00		
Difference <sup>[3]</sup>	0.00 (-0.0	02, 0.02)		
95% CI				
% Difference <sup>[4]</sup>	-1.	26		
p-Value <sup>[1]</sup>	0.90	020		
<ul> <li>[1] From ANOVA (square root transformation) with factors for treatment group, bacteria sampling (yes/no) and gingival strata (low, high).</li> <li>[2] Based on back transformed values (value squared).</li> <li>[3] Difference is first named treatment minus second named treatment such that a negative difference favours the first named treatment.</li> <li>[4] Second named treatment is taken as reference for calculation of % difference [(Difference/Reference)*100] using back transformed values</li> </ul>				
Table 10 Analysis of Proportion of Sites Wi	th Increase in Bleeding Index S	core Compared to Baseline		
Treatments (Week 4)	0.1% IPMP / 0.5% Zinc Toothpaste	Sodium Fluoride / Silica Toothpaste		
N	92 90			
Maam (CD)	0.10 (0.050) 0.11 (0.055)			
Mean (SD)	0.10 (0.050)	0.11 (0.055)		
Adjusted mean <sup>[1]</sup>	0.10 (0.050) 0.30	0.11 (0.055) 0.32		
Adjusted mean <sup>[1]</sup> Back Transformed Mean <sup>[2]</sup>	0.10 (0.050) 0.30 0.09	0.11 (0.055) 0.32 0.10		
Adjusted mean <sup>[1]</sup> Back Transformed Mean <sup>[2]</sup> Treatment comparison (IPMP/zinc toothpa:	0.10 (0.050) 0.30 0.09 ste vs. Sodium fluoride/silica to	0.11 (0.055) 0.32 0.10 othpaste)		

Difference <sup>[3]</sup>	-0.02 (-0.04, 0.01)				
95% CI					
% Difference <sup>[4]</sup>		-10	.46		
p-Value <sup>[1]</sup>		0.1	542		
Treatments (Week 8)	0.1% IPMP / Toothpaste	0.5% Zinc	Sodium Flue Toothpaste	Sodium Fluoride / Silica Toothpaste	
n		88		85	
Mean (SD)	0.07	(0.042)	80.0	3 (0.043)	
Adjusted mean [1]	0.07	1 26	0.00	0 27	
Back Transformed Mean <sup>[2]</sup>		0.20		0.07	
Treatment comparison (IPMP/zinc toothna	naste vs. Sodium fluoride/silica toothnaste)				
Difference [2]		-0	01		
Difference [3]					
		-0.01 (-0.	04, 0.01)		
% Difforonco <sup>[4]</sup>		0	72		
n Valuo [1]		- 7.	75 415		
Trootmonts (Mook 12)	0.1% IDMD /	0.20	Sodium Elui	orido / Silica	
	Toothpaste	0.5 % ZINC	Toothpaste		
n		88		82	
Mean (SD)	0.06	(0.036)	0.07	′ (0.040)	
Adjusted mean [1]	0.24			0.26	
Back Transformed Mean <sup>[2]</sup>	0.06 0.07			0.07	
Treatment comparison (IPMP/zinc toothpa:	hpaste vs. Sodium fluoride/silica toothpaste)				
	-0.01				
Difference <sup>[3]</sup>	-0.02 (-0.04, 0.00)				
95% CI	0.02 ( 0.01, 0.00)				
% Difference <sup>[4]</sup>		-13	.81		
p-Value <sup>[1]</sup>		0.00	972		
<ol> <li>From ANOVA (square root transformation) with factors</li> <li>Based on back transformed values (value squared).</li> <li>Difference is first named treatment minus second name</li> <li>Second named treatment is taken as reference for calc values.</li> </ol>	for treatment group d treatment such ti ulation of % differe.	n, bacteria sampling (ye nat a negative differenc nce [(Difference/Refere	es/no) and gingival re favours the first nce)*100] using b	l strata (low, high). named treatment. ack transformed	
Table 11 Analysis of Modified Gingival Inde	x - Margin Sco	re (ITT Populatio	n)		
	0.1% IPMP / Toothpaste	0.5% Zinc	Sodium Flue Toothpaste	oride / Silica	
Baseline	Prophy	Randomisation	Prophy	Randomisation	
N	92	92	90	90	
Mean (SD)	1.87	1.47	1.85	1.44	
	(0.205)	(0.217)	(0.197)	(0.209)	
Treatments (Week 4)	0.1% IPMP /	0.5% Zinc	Sodium Flue	oride / Silica	
	Toothpaste     Toothpaste				
n		92		90	
Mean (SD)	1.52	( 0.216)	1.55	( 0.196)	
Adjusted mean <sup>[1]</sup>		1.51		1.56	
Treatment comparison (IPMP/zinc toothpa	ste vs. Sodiun	n fluoride/silica to	othpaste)		
Difference <sup>[2]</sup>		-0.	05		
95% CI	(-0.10, 0.00)				
% Difference <sup>[3]</sup>		-3.	13		
p-Value [1]	0.0401				

Treatments (Week 8)	0.1% IPMP / 0.5% Zinc Toothpaste		Sodium Fluoride / Silica Toothpaste	
n		88		85
Mean (SD)	1.56	<u>(0.218)</u>	1.59	9 (0.205)
Adjusted mean [1]		1.55		1.59
Difference [9]	ste vs. Sodiun	n fluoride/silica to	otnpaste)	
		-U. ( 0 09	0.00)	
% Difference <sup>[3]</sup>	(-0.09, 0.00)			
p-Value [1]		0.0	738	
Treatments (Week 12)	0.1% IPMP /	0.5% Zinc	Sodium Flu	oride / Silica
	Toothpaste		Toothpaste	
	_			
n		88		82
Mean (SD)	1.63	8 (0.237)	1.68	3 (0.225)
Adjusted mean [1]		1.63		1.68
I reatment comparison (IPMP/zinc toothpa	ste vs. Sodiun	n fluoride/silica to	othpaste)	
		-U. ( 0 10	05	
% Difference[3]		(-0.10)	, 0.00)	
n-Value [1]		-3.	501 501	
[1] From ANCOVA with factors for treatment group and ba	cteria sampling (ye	s/no) with pre prophy a	nd randomisation	
baseline as covariates. [2] Difference is first named treatment minus second named treatment such that a negative difference favours the first named treatment.				
[3] Second named treatment is taken as reference for calc	ulation of % differe	nce [(Difference/Refere	ence)^100].	
	0.1% IPMP / 0.5% Zinc Sodium Eluoride / Silica			
	Toothpaste Toothpaste			
Baseline	Prophy	Randomisation	Prophy	Randomisation
Ν	92	92	90	90
Mean (SD)	2.09	1.77 (0.255)	2.08	1.73 (0.252)
	(0.215)		(0.225)	
Treatments (Week 4)	0.1% IPMP / Toothpaste	0.5% Zinc	Sodium Flu Toothpaste	oride / Silica
n		02		90
Mean (SD)	1.85	<u>72</u> 5 (0 182)	1.8	70 7 (0 155)
Adjusted mean [1]	1.00	1.84	1.07	1.88
Treatment comparison (IPMP/zinc toothpa	ste vs. Sodiun	n fluoride/silica to	othpaste)	
Difference <sup>[2]</sup> 95% Cl		-0.04 (-0.	08, 0.00)	
% Difference <sup>[3]</sup>		-2.	17	
p-Value [1]		0.02	296	
Treatments (Week 8)	0.1% IPMP /	0.5% Zinc	Sodium Flu	oride / Silica
	Toothpaste		Toothpaste	
n		88		85
Mean (SD)	1.91	(0.199)	1.92	2 (0.183)
Adjusted mean [1]		1.90		1.92
Treatment comparison (IPMP/zinc toothpa	ste vs. Sodiun	n fluoride/silica to	othpaste)	
Difference <sup>[2]</sup> 95% Cl		-0.02 (-0.	06, 0.02)	
% Difference <sup>[3]</sup>		-0.	83	

p-Value <sup>[1]</sup>	0.4300				
Treatments (Week 12)	0.1% IPM	IP / 0.5% Zinc	Sodium Flu	Sodium Fluoride / Silica	
	Toothpas	ste	Toothpaste		
	_		-		
n		88		82	
Mean (SD)	_	1.98 (0.248)	2.01	(0.199)	
Adjusted mean <sup>[1]</sup>		1.98		2.01	
Treatment comparison (IPMP/zinc toothpas	ste vs. Sod	lium fluoride/silica	toothpaste)		
Difference <sup>[2]</sup>		-	0.03		
95% CI		(-0.0	08, 0.02)		
% Difference <sup>[3]</sup>		-	1.53		
p-Value <sup>[1]</sup>		0.	.2123		
[1] From ANCOVA with factors for treatment group and bac baseline as covariates	cteria sampling	g (yes/no) with pre prophy	y and randomisation		
[2] Difference is first named treatment minus second name	d treatment su	ich that a negative differe	ence favours the first	named treatment.	
[3] Second named treatment is taken as reference for calcu	ulation of % di	fference [(Difference/Refe	erence)*100].		
Table 13 Analysis of Bleeding Index - Margi	n Score				
	0.1% IPM	IP / 0.5% Zinc	Sodium Fluor	ide / Silica	
	Tootnpas	ste	Tootnpaste		
Pasalina	Drophy	Dandomisation	Drophy	Dandomisatio	
Dasenne	Propiny	Ranuomisation	горну	n	
N	92	92	90	90	
Mean (SD)	0.57	0.27	0.57 (0.269)	0.25	
	(0.266)	(0.143)	0.07 (0.207)	(0.158)	
Treatments (Week 4)	0.1% IPMP / 0.5% Zinc Sodium F			ide / Silica	
	Toothpas	ste	Toothpaste		
			•		
n		92		90	
Mean (SD)	0.	.21 (0.127)	0.26	(0.163)	
Adjusted mean <sup>[1]</sup>		0.43	0	.48	
Back Transformed Mean <sup>[2]</sup>		0.19		0.23	
Treatment comparison (IPMP/zinc toothpa	ste vs. Sod	lium fluoride/silica	toothpaste)		
		-	0.04		
		-0.05 (-	0.09, -0.01)		
95% CI			10 10		
		- 0	0156		
Treatments (Meek 8)	0.1% IDM	U.	Sodium Elui	orido / Silica	
Treatments (week b)	Toothpas	ste	Toothnaste		
	roompu		roompuoto		
n		88		85	
Mean (SD)	0.17 (0.132)		0.18	3(0.124)	
Adjusted mean [1]	0.38 0.40			0.40	
Back Transformed Mean <sup>[2]</sup>	0.14 0.16			0.16	
Treatment comparison (IPMP/zinc toothpas	ste vs. Sod	lium fluoride/silica	toothpaste)		
Difference <sup>[2]</sup>			0.01		
Difference <sup>[3]</sup>		-0.02 (-	0.06, 0.03)		
95% CI					
% Difference <sup>[4]</sup>		-	8.96		
	0.404 100	0.	4106		
Treatments (Week 12)	0.1% IPM	IP / 0.5% Zinc	Sodium Flue	oride / Silica	
	Toothpas	ste	Toothpaste		
		00		00	
- 11		бð		ŏΖ	

	1				
Mean (SD)	0.13 (0.091)		0.15 (0.114)		
Adjusted mean <sup>[1]</sup>		0.34	0.36		
Back Transformed Mean <sup>[2]</sup>		0.11		0.13	
Treatment comparison (IPMP/zinc toothpa:	ste vs. Sod	lium fluoride/silica to	oothpaste)		
Difference <sup>[2]</sup>		-0.	.02		
Difference <sup>[3]</sup>		-0.02 (-0.	.06, 0.01)		
95% CI					
% Difference <sup>[4]</sup>	-13.19				
p-Value <sup>[1]</sup>		0.1	757		
<ol> <li>[1] From ANCOVA (square root transformation) with factors for treatment group, bacteria sampling (yes/no) and gingival strata (low, high) with pre prophy and randomisation baseline as covariates.</li> <li>[2] Based on back transformed values (value squared).</li> <li>[3] Difference is first named treatment minus second named treatment such that a negative difference favours the first named treatment.</li> <li>[4] Second named treatment is taken as reference for calculation of % difference [(Difference/Reference)*100] using back transformed values.</li> </ol>					
Table 14 Analysis of Bleeding Index - Papil	lae Score		•		
	0.1% IPM	IP / 0.5% Zinc	Sodium Fl	uoride / Silica	
	Toothpas	ste	Toothpaste	6	
Baseline	Prophy	Randomisation	Prophy	Randomisation	
Ν	92	92	90	90	
Mean (SD)	0.40	0.24	0.36	0.22	
	(0.189)	(0.141)	(0.188)	(0.123)	
Treatments (Week 4)	0.1% IPMP / 0.5% Zinc Sodium Fluoride / Si Toothpaste Toothpaste			uoride / Silica e	
n	92 90				
Mean (SD)	(	0.22 (0.196)	0.20 (0.146)		
Adjusted mean [1]		0.42	0.42		
Back Transformed Mean <sup>[2]</sup>		0.17		0.18	
Treatment comparison (IPMP/zinc toothpas	ste vs. Sod	lium fluoride/silica to	oothpaste)		
Difference <sup>[2]</sup>		0.	00		
Difference <sup>[3]</sup>		0.00 (-0.	05, 0.04)		
95% CI					
% Difference <sup>[4]</sup>		-1.	.17		
p-Value <sup>[1]</sup>		0.9	117		
Treatments (Week 8)	0.1% IPM	IP / 0.5% Zinc	Sodium Fluoride / Silica		
	Toothpas	ste	Toothpaste	e	
n		88		85	
Mean (SD)	(	0.15 (0.130)	0.1	14 (0.106)	
Adjusted mean <sup>[1]</sup>	0.35			0.36	
Back Transformed Mean <sup>[2]</sup>		0.12		0.13	
Treatment comparison (IPMP/zinc toothpa	ste vs. Sod	lium fluoride/silica to	oothpaste)		
Difference <sup>[2]</sup>		-0.	.01		
Difference <sup>[3]</sup> 95% CI		-0.01 (-0.	.05, 0.03)		
% Difference <sup>[4]</sup>		-7.	00		
p-Value [1]		0.5	371		
Treatments (Week 12)	0.1% IPM Toothpas	IP / 0.5% Zinc ste	Sodium Flu Toothpaste	uoride / Silica e	
n		88		82	
Mean (SD)	(	0.15 (0.119)	0.1	15 (0.125)	
Adjusted mean [1]	0.35 0.36				

Back Transformed Mean <sup>[2]</sup>		0.12		0.13		
Treatment comparison (IPMP/zinc toothpasi	te vs. Sodiı	um fluoride/silica to	othpaste)			
Difference <sup>[2]</sup>		-0	.01			
Difference <sup>[3]</sup>		-0.01 (-0.06, 0.03)				
95% CI						
% Difference <sup>[4]</sup>		-7	.75			
p-Value <sup>[1]</sup>		0.5	5134			
<ul> <li>[1] Hom Arcova (square tool transformation) with factor with pre prophy and randomisation baseline as covariates.</li> <li>[2] Based on back transformed values (value squared).</li> <li>[3] Difference is first named treatment minus second name [4] Second named treatment is taken as reference for calc values.</li> <li>Table 15. Applysis of Plague Bactoria Count</li> </ul>	ed treatment su ulation of % dif	ch that a negative differen ference [(Difference/Refer	ce favours the fi ence)*100] using	rst named treatment. g back transformed		
Table 15 Analysis of Plaque Bacteria Court		MD / 0.5% Zinc	Sodium I	Fluorido / Silica		
	Toothpaste Toothpaste					
			10			
Baseline	Prophy	Randomisation	Prophy	Randomisation		
N	34	34	33	33		
Mean (SD)	7.30	7.34	7.34	7.25		
	(0.368)	(0.298)	(0.349)	(0.292)		
Treatments (Week 4)	0.1% IP	MP / 0.5% Zinc	Sodium I	Fluoride / Silica		
	To	oothpaste	То	othpaste		
	Log <sup>[1]</sup> Log <sup>[1]</sup>					
n M (OD)		34		33		
Mean (SD)	1.	30 (0.464)	7.4	5 (0.304)		
Adjusted mean <sup>[2]</sup>	o NoE to oth	/.29		/.46		
Difference [3]	S NAF LOOLI	ipasie)	10			
		-U (_N 3/	.10 _0.01)			
Ratio <sup>[4]</sup>		<u>(-0.34</u> 0	<u>, -0.01)</u> 67			
p-Value <sup>[2]</sup>		0.0	397			
Treatments (Week 12)	0.1%	PMP / 0.5% Zinc	Sodium	Fluoride / Silica		
. , ,	T	oothpaste	T	oothpaste		
		Log <sup>[1]</sup>		Log <sup>[1]</sup>		
n		33		32		
Mean (SD)	7	'.15 (0.443)	7.	19 (0.528)		
Adjusted mean <sup>[2]</sup>		7.14		7.21		
Treatment comparison (IPMP/zinc toothpa:	ste vs. Sod	ium fluoride/silica t	oothpaste)			
		-()	.07			
		(-0.29	0, U. 10)			
		0.6	.00			
[1] Log values are to the base 10. [2] From ANCOVA with factors for treatment group and gir	i gival strata wit	h pre prophy and randomi	zation baseline l	bacterial counts as		
covariates. [3] Difference in adjusted mean based on log-values of firs difference favours the first named treatment.	t named treatm	nent minus second named	treatment such	that a negative		
[4] Second named treatment is taken as reference for calc	ulation of ratio	10**Difference. (ie Anti log	of difference)			
Table 16 Analysis of Plaque Bacteria Coun	t Data - Tol	al Aerobic	- C "	Flooring Collin		
	0.1%	PMP/0.5% Zinc	Sodium	Fluoride / Silica		
Baseline	Pronhy	Randomisation	Pronhy	Randomisation		
N	34	34	22	22		
Mean (SD)	7.10	7.11	7.00	6.93		

	(0.325)	(0.324)	(0.369)	(0.376)		
Treatments (Week 4)	0.1% IP	MP / 0.5% Zinc	Sodium	Fluoride / Silica		
	To	othpaste	Т	oothpaste		
		Log <sup>[1]</sup>		Log <sup>[1]</sup>		
n	34			33		
Mean (SD)	7.28 (0.352)		7.31 (0.375)			
Adjusted mean <sup>[2]</sup>	7.27		7.32			
Treatment comparison (IPMP/zinc toothpas	ste vs. Sodiu	m fluoride/silica too	othpaste)			
Difference <sup>[3]</sup>		-0.05				
95% CI		(-0.22, 0.13)				
Ratio <sup>[4]</sup>		0.9	0			
p-Value <sup>[2]</sup>		0.5890				
Treatments (Week 12)	0.1% IP	MP / 0.5% Zinc	Sodium	Fluoride / Silica		
	Тс	othpaste	T	oothpaste		
		Log <sup>[1]</sup>				
n		33		32		
Mean (SD)	6.8	36 (0.519)	6	.93 (0.608)		
Adjusted mean <sup>[2]</sup>		6.81		6.98		
Ireatment comparison (IPMP/zinc toothpa:	ste vs. Sodiu	m fluoride/silica too	othpaste)			
		-0.1	( 0 07)			
		(-0.42,	0.07)			
		0.0	1			
P-Value <sup>[2]</sup>		0.1644				
[2] From ANCOVA with factors for treatment group and gin	iqival strata with p	ore prophy and randomiza	tion baseline b	pacterial counts as		
covariates.	5	1 1 3				
[3] Difference in adjusted mean based on log-values of firs	t named treatmer	nt minus second named tr	eatment such	that a negative		
[4] Second named treatment is taken as reference for calcu	ulation of ratio 10	**Difference. (ie Anti log c	of difference).			
Table 17 Analysis of Plaque Bacteria Count	t Data - Strep	tococcus Mutans	,			
,	0.1% IPMP / 0.5% Zinc		Sodium Fluoride / Silica			
	To	Toothpaste		Toothpaste		
		Log <sup>[1]</sup>				
Baseline	Prophy	Randomisation	Prophy	Randomisation		
N	34	34	33	33		
Mean (SD)	1.71	1.70	1.70	1.70		
	(0.052)	( 0.000)	(0.000)	(0.000)		
Treatments (Week 4)	0.1% IPMP toothpaste		NaF toothpaste			
			Log <sup>[1]</sup>			
n M (OD)	34		33			
Mean (SD)	1./0 (0.000)					
Treatments (week 12)	0.1% IPMP toothpaste					
Moon (SD)	33		32			
IVICALL (SU)	1.70 (0.000)					
An analysis was not carried out on this variable as nearly a	[1] Log values are to the base TU. An analysis was not carried out on this variable as nearly all values were < 50					
Table 18 Analysis of Plaque Bacteria Count Data - Total VSC						
Table to Allalysis of Flaque Dacletta Court	all values were < t Data - Tota	50. I <b>VSC</b>				
	t Data - Tota 0.1% IP	<sup>50.</sup> I VSC MP / 0.5% Zinc	Sodium	Fluoride / Silica		
	t Data - Tota t Data - Tota 0.1% IP To	50. I VSC MP / 0.5% Zinc pothpaste	Sodium T	Fluoride / Silica oothpaste		
	all values were < t Data - Tota 0.1% IP To	50. I VSC MP / 0.5% Zinc pothpaste Log <sup>[1]</sup>	Sodium T	Fluoride / Silica oothpaste Log <sup>[1]</sup>		
Baseline	<u>ill values were &lt;</u> t Data - Tota 0.1% IP Tc Prophy	50. VSC MP / 0.5% Zinc oothpaste Log <sup>[1]</sup> Randomisation	Sodium T Prophy	Fluoride / Silica oothpaste Log <sup>[1]</sup> Randomisation		
Baseline N	Ill values were < t Data - Tota 0.1% IP Tc Prophy 22	50. VSC MP / 0.5% Zinc bothpaste Log <sup>[1]</sup> Randomisation 34	Sodium T Prophy 23	Fluoride / Silica oothpaste Log <sup>[1]</sup> Randomisation 33		
Baseline N Mean (SD)	Ill values were < t Data - Tota 0.1% IP Tc Prophy 22 6.80	50. VSC MP / 0.5% Zinc oothpaste Log <sup>[1]</sup> Randomisation 34 6.72	Sodium T Prophy 23 6.61	Fluoride / Silica oothpaste Log <sup>[1]</sup> Randomisation <u>33</u> 6.59		

Treatments (Week 4)	0.1% IPMP / 0.5% Zinc	Sodium Eluoride / Silica		
	Toothpaste	Toothpaste		
	Log <sup>[1]</sup>			
n	34	33		
Mean (SD)	6.87 (0.531)	6.82 (0.533)		
Adjusted mean <sup>[2]</sup>	6.78	6.90		
Treatment comparison (IPMP/zinc toothpa	ste vs. Sodium fluoride/silica toothpaste)			
Difference <sup>[3]</sup>	-0.12			
95% CI	(-0.	(-0.41, 0.18)		
Ratio <sup>[4]</sup>	0.77			
p-Value <sup>[2]</sup>	0.4287			
Treatments (Week 12)	0.1% IPMP / 0.5% Zinc	Sodium Fluoride / Silica		
	Toothpaste	Toothpaste		
n	33	32		
Mean (SD)	6.56 (0.645)	6.71 (0.692)		
Adjusted mean [2]	6.56	6.95		
Treatment comparison (IPMP/zinc toothpa	ste vs. Sodium fluoride/silica	i toothpaste)		
Difference <sup>[3]</sup>		-0.39		
95% CI	(-0.	71, -0.06)		
Ratio <sup>[4]</sup>		0.41		
p-Value <sup>[2]</sup>	(	).0208		
[1] Log values are to the base 10.				
[2] From AINCOVA with factors for treatment group and gir covariates	igival strata with pre prophy and rando	mization daseline dacterial counts as		
[3] Difference in adjusted mean based on log-values of firs	t named treatment minus second nam	ed treatment such that a negative		
difference favours the first named treatment.				
[4] Second named treatment is taken as reference for calc	ulation of ratio 10**Difference. (ie Anti	log of difference)		
Cofety Deculto (Cofety negulation)				
Salety Results (Salety population)	nto			
Treatmente		Sodium Eluorido/Silico		
Treatments	0.1% FMF/0.5% ZINC	Toothnaste		
N	95	05		
Number of Subjects With at Least one AF n	70 (73 7)	63 (66 3)		
(%)	10 (13.1)	03 (00.3)		
Oral	l			
Anhthous stomatitis	4 (4 2)			
Gingiyal injury	6 (6 3)	3 (3 2)		
Orophanyngeal nain		3 (3.2)		
	9 (9.5)	3 (3.2) 7 (7.4) 3 (3.2)		
Oral hernes	9 (9.5)	3 (3.2) 7 (7.4) 3 (3.2) 3 (3.2)		
Oral herpes Gingiyal bleeding	9 (9.5) 6 (6.3) 5 (5.3)	3 (3.2) 7 (7.4) 3 (3.2) 3 (3.2) 4 (4 2)		
Oral herpes Gingival bleeding Mouth ulceration	9 (9.5) 6 (6.3) 5 (5.3) 3 (3.2)	3 (3.2) 7 (7.4) 3 (3.2) 3 (3.2) 4 (4.2) 3 (3.2)		
Oral herpes Gingival bleeding Mouth ulceration Gingival pain	9 (9.5) 6 (6.3) 5 (5.3) 3 (3.2) 6 (6.3)	3 (3.2) 7 (7.4) 3 (3.2) 3 (3.2) 4 (4.2) 3 (3.2) 2 (2 1)		
Oral herpes Gingival bleeding Mouth ulceration Gingival pain Thermal burn	9 (9.5) 6 (6.3) 5 (5.3) 3 (3.2) 6 (6.3) 2 (2 1)	3 (3.2) 7 (7.4) 3 (3.2) 4 (4.2) 3 (3.2) 2 (2.1) 5 (5.3)		
Oral herpes Gingival bleeding Mouth ulceration Gingival pain Thermal burn Mouth injury	$\begin{array}{c} 9 (9.5) \\ 6 (6.3) \\ 5 (5.3) \\ 3 (3.2) \\ 6 (6.3) \\ 2 (2.1) \\ 6 (6.3) \end{array}$	3 (3.2) 7 (7.4) 3 (3.2) 3 (3.2) 4 (4.2) 3 (3.2) 2 (2.1) 5 (5.3) 1 (1 1)		
Oral herpes Gingival bleeding Mouth ulceration Gingival pain Thermal burn Mouth injury Sensitivity of teeth	$\begin{array}{c} 9 \ (9.5) \\ 6 \ (6.3) \\ \hline 5 \ (5.3) \\ \hline 3 \ (3.2) \\ \hline 6 \ (6.3) \\ \hline 2 \ (2.1) \\ \hline 6 \ (6.3) \\ \hline 3 \ (3.2) \\ \end{array}$	3 (3.2) 7 (7.4) 3 (3.2) 3 (3.2) 4 (4.2) 3 (3.2) 2 (2.1) 5 (5.3) 1 (1.1) 3 (3.2)		
Oral herpes Gingival bleeding Mouth ulceration Gingival pain Thermal burn Mouth injury Sensitivity of teeth Tooth fracture	$\begin{array}{c} 9 (9.5) \\ \hline 6 (6.3) \\ \hline 5 (5.3) \\ \hline 3 (3.2) \\ \hline 6 (6.3) \\ \hline 2 (2.1) \\ \hline 6 (6.3) \\ \hline 3 (3.2) \\ \hline 3 (3.2) \\ \hline 3 (3.2) \\ \hline 3 (3.2) \\ \hline \end{array}$	$\begin{array}{c} 3 (3.2) \\ \hline 7 (7.4) \\ \hline 3 (3.2) \\ \hline 3 (3.2) \\ \hline 4 (4.2) \\ \hline 3 (3.2) \\ \hline 2 (2.1) \\ \hline 5 (5.3) \\ \hline 1 (1.1) \\ \hline 3 (3.2) \\ \hline 2 (2.1) \\ \hline \end{array}$		
Oral herpes         Gingival bleeding         Mouth ulceration         Gingival pain         Thermal burn         Mouth injury         Sensitivity of teeth         Tooth fracture         Toothach	$\begin{array}{c} 9 (9.5) \\ \hline 9 (9.5) \\ \hline 6 (6.3) \\ \hline 3 (3.2) \\ \hline 6 (6.3) \\ \hline 2 (2.1) \\ \hline 6 (6.3) \\ \hline 3 (3.2) \\ \hline 3 (3.2) \\ \hline 3 (3.2) \\ \hline 2 (2.1) \\ \hline \end{array}$	3 (3.2) 7 (7.4) 3 (3.2) 3 (3.2) 4 (4.2) 3 (3.2) 2 (2.1) 5 (5.3) 1 (1.1) 3 (3.2) 2 (2.1) 3 (3.2) 2 (2.1) 3 (3.2) 2 (2.1) 3 (3.2)		
Oral herpes         Gingival bleeding         Mouth ulceration         Gingival pain         Thermal burn         Mouth injury         Sensitivity of teeth         Tooth fracture         Toothache         Oral mucosal exfoliation	$\begin{array}{c} 9 \ (9.5) \\ \hline 6 \ (6.3) \\ \hline 5 \ (5.3) \\ \hline 3 \ (3.2) \\ \hline 6 \ (6.3) \\ \hline 2 \ (2.1) \\ \hline 6 \ (6.3) \\ \hline 3 \ (3.2) \\ \hline 3 \ (3.2) \\ \hline 2 \ (2.1) \\ \hline 0 \end{array}$	$\begin{array}{c} 3 (3.2) \\ 7 (7.4) \\ 3 (3.2) \\ 4 (4.2) \\ 3 (3.2) \\ 2 (2.1) \\ 5 (5.3) \\ 1 (1.1) \\ 3 (3.2) \\ 2 (2.1) \\ 3 (3.2) \\ 2 (2.1) \\ 3 (3.2) \\ 2 (2.1) \\ 3 (3.2) \\ 3 (3.2) \\ 3 (3.2) \end{array}$		
Oral herpes         Gingival bleeding         Mouth ulceration         Gingival pain         Thermal burn         Mouth injury         Sensitivity of teeth         Tooth fracture         Toothache         Oral mucosal exfoliation	$\begin{array}{c} 9 \ (9.5) \\ \hline 6 \ (6.3) \\ \hline 5 \ (5.3) \\ \hline 3 \ (3.2) \\ \hline 6 \ (6.3) \\ \hline 2 \ (2.1) \\ \hline 6 \ (6.3) \\ \hline 3 \ (3.2) \\ \hline 3 \ (3.2) \\ \hline 2 \ (2.1) \\ \hline 0 \\ \hline 1 \ (1 \ 1) \end{array}$	$\begin{array}{r} 3 (3.2) \\ \hline 7 (7.4) \\ \hline 3 (3.2) \\ \hline 3 (3.2) \\ \hline 4 (4.2) \\ \hline 3 (3.2) \\ \hline 2 (2.1) \\ \hline 5 (5.3) \\ \hline 1 (1.1) \\ \hline 3 (3.2) \\ \hline 2 (2.1) \\ \hline \end{array}$		
Oral herpes         Gingival bleeding         Mouth ulceration         Gingival pain         Thermal burn         Mouth injury         Sensitivity of teeth         Tooth fracture         Toothache         Oral mucosal exfoliation         Tongue ulceration         Tooth disorder	$\begin{array}{c} 9 (9.5) \\ 6 (6.3) \\ 5 (5.3) \\ 3 (3.2) \\ 6 (6.3) \\ 2 (2.1) \\ 6 (6.3) \\ 3 (3.2) \\ 3 (3.2) \\ 2 (2.1) \\ 0 \\ 1 (1.1) \\ 2 (2 1) \\ \end{array}$	$\begin{array}{r} 3 (3.2) \\ \hline 7 (7.4) \\ \hline 3 (3.2) \\ \hline 4 (4.2) \\ \hline 3 (3.2) \\ \hline 4 (4.2) \\ \hline 3 (3.2) \\ \hline 2 (2.1) \\ \hline 5 (5.3) \\ \hline 1 (1.1) \\ \hline 3 (3.2) \\ \hline 2 (2.1) \\ \hline 3 (3.2) \\ \hline 2 (2.1) \\ \hline 3 (3.2) \\ \hline 2 (2.1) \\ \hline 1 (1.1) \\ 1$		
Oral herpes         Gingival bleeding         Mouth ulceration         Gingival pain         Thermal burn         Mouth injury         Sensitivity of teeth         Tooth fracture         Toothache         Oral mucosal exfoliation         Tooth disorder         Breath odour	$\begin{array}{c} 9 \ (9.5) \\ \hline 6 \ (6.3) \\ \hline 5 \ (5.3) \\ \hline 3 \ (3.2) \\ \hline 6 \ (6.3) \\ \hline 2 \ (2.1) \\ \hline 6 \ (6.3) \\ \hline 3 \ (3.2) \\ \hline 3 \ (3.2) \\ \hline 2 \ (2.1) \\ \hline 0 \\ \hline 1 \ (1.1) \\ \hline 2 \ (2.1) \\ \hline 1 \ (1 \ 1) \\ \end{array}$	$\begin{array}{r} 3 (3.2) \\ \hline 7 (7.4) \\ \hline 3 (3.2) \\ \hline 3 (3.2) \\ \hline 4 (4.2) \\ \hline 3 (3.2) \\ \hline 2 (2.1) \\ \hline 5 (5.3) \\ \hline 1 (1.1) \\ \hline 3 (3.2) \\ \hline 2 (2.1) \\ \hline 3 (3.2) \\ \hline 2 (2.1) \\ \hline 3 (3.2) \\ \hline 3 (3.2) \\ \hline 2 (2.1) \\ \hline 1 (1.1) \\ \hline 1 (1.1) \\ \hline 1 (1.1) \\ \hline 1 (1.1) \end{array}$		
Oral herpes         Gingival bleeding         Mouth ulceration         Gingival pain         Thermal burn         Mouth injury         Sensitivity of teeth         Tooth fracture         Toothache         Oral mucosal exfoliation         Tooth disorder         Breath odour         Chapped lips	$\begin{array}{c} 9 \ (9.5) \\ \hline 6 \ (6.3) \\ \hline 5 \ (5.3) \\ \hline 3 \ (3.2) \\ \hline 6 \ (6.3) \\ \hline 2 \ (2.1) \\ \hline 6 \ (6.3) \\ \hline 3 \ (3.2) \\ \hline 2 \ (2.1) \\ \hline 0 \\ \hline 1 \ (1.1) \\ \hline 2 \ (2.1) \\ \hline 1 \ (1.1) \\ \hline 1 \ (1.1) \\ \hline 1 \ (1.1) \\ \hline \end{array}$	$\begin{array}{r} 3 (3.2) \\ \hline 7 (7.4) \\ \hline 3 (3.2) \\ \hline 3 (3.2) \\ \hline 4 (4.2) \\ \hline 3 (3.2) \\ \hline 2 (2.1) \\ \hline 5 (5.3) \\ \hline 1 (1.1) \\ \hline 3 (3.2) \\ \hline 2 (2.1) \\ \hline 1 (1.1) \end{array}$		

Dry mouth	2 (2.1)	0
Glossitis	2 (2.1)	0
Oropharyngeal plague	0	1 (1.1)
Tonsillitis	2 (2.1)	0
Gingival abscess	1 (1.1)	0
Gingival ulceration	1 (1.1)	0
Glossodynia	1 (1.1)	0
Lichen planus	0	1(1 1)
	0	1(1.1)
Mouth cyst	1 (1 1)	0
Oral mucosal ervthema	0	1 (1 1)
Oral nain	0	1 (1 1)
Oronharyngeal blistering	1 (1 1)	0
Paraesthesia oral	1 (1.1)	0
	0	1 (1 1)
Tooth abscess	0	1 (1 1)
Non Oral	0	1 (1.1)
Headache	20 (30 5)	26 (27 1)
Linner Respiratory Tract Infection	10 (10 5)	15 (15 8)
Nasopharypaitis	5 (5 2)	7 (7 4)
Migraino	2 (3.3)	2 (2 2)
Rack pain	2 (2 2)	1 (1 1)
	<u> </u>	1 (1.1)
Dysneroia		1 (1.1)
Dyspepsid	4 (4.2)	2 (2 2)
	l (1.1)	3 (3.2)
Arthroloio	2 (2.1)	2 (2.1)
Altilialyid	3 (3.2) 2 (2.1)	0
	2 (2.1)	1(1.1)
	1 (1.1) 2 (2.1)	2 (2.1)
Malaiso	2 (2.1)	1 (1.1)
Musculoskolotal pain	2 (2.1)	0
Mack pain	1 (1.1)	1 (1.1)
Skin lacoration		1 (1.1)
Urinary tract infection		1 (1.1)
Abdominal pain	1 (1.1)	1 (1.1)
	1 (1.1)	0
Abortion spontanoous	1 (1.1)	0
	1 (1.1)	0
Cough	1 (1.1)	0
Dizziness	1 (1.1)	0
Fatique	1 (1.1)	0
Hand fracture	0	1 (1 1)
Hernes virus infection	1 (1 1)	0
Hypothyroidism	0	1 (1 1)
loint sprain	1 (1 1)	0
Kidney infection	0	1 (1 1)
	0	1 (1 1)
	0	1 (1 1)
Muscle injury	0	1 (1 1)
Muscle strain	1 (1 1)	0
Pain	1 (1.1)	0
Procedural pain	1 (1.1)	0

Rash	1 (1.1)	0		
Sinus congestion	0	1(1.1)		
Skin infection	0	1(1.1)		
Transient ischaemic attack	0	1(1.1)		
Vomiting	0	1(1.1)		
Serious Adverse Events (SAEs) - On-Therapy				
No serious adverse events were reported				