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: Chlorhexidine Digluconate

Study Number: RH01561

Title: Clinical study to evaluate the efficacy of Chlorhexidine Mouthwashes

Rationale: Good oral hygiene which includes regular tooth brushing with a toothpaste and cleaning between teeth (e.g. by flossing) can affect the formation and control the build-up of plaque and as a result prevent gum disease. Antibacterial mouth-rinses like chlorhexidine can be added to the regimen for additional control of plaque related to gingivitis.

Phase: IV

Study Period: 15 Oct 2012 – 01 Mar 2013

Study Design: Single centre, multi-site, examiner blind, three treatment, parallel group, stratified (by site, baseline number of bleeding sites and smoking status), randomized study

Centres: Two clinical sites in UK

Indication: Dry Mouth

Treatment:

Test Product:

1. Chlorhexidine digluconate (0.2% w/v) mouthwash containing alcohol (0.2% CHX-Alc), for one minute twice a day (morning and evening) for 6 weeks, after brushing teeth with the standard toothpaste
2. Chlorhexidine digluconate (0.2% w/v) mouthwash without alcohol (0.2% CHX-Alc free) for one minute twice a day (morning and evening) for 6 weeks, after brushing teeth with the standard toothpaste

Reference Product:

Brushing alone with the standard toothpaste for one minute twice daily for 6 weeks

Objective: To evaluate and compare Gingival Bleeding (assessed by the gingival severity component of the Gingival Index [GI]) following twice daily use of an alcohol containing 0.2% chlorhexidine mouthwash plus brushing and a non-alcohol 0.2% chlorhexidine mouthwash plus brushing, to brushing only.

Primary Outcome: Mean Change from baseline to week 6 in Gingival Severity Index (GSI)

Secondary Outcome:

1. Mean change from baseline to week 6 in Gingival Index (GI)
2. Mean change from baseline to week 6 in overall plaque scores
3. Mean change from baseline to week 6 in interproximal plaque
4. Mean number of tooth sites at week 6 that increased, showed no change and decreased in GSI score
5. Chlorhexidine levels in saliva at each time point (Area Under the Curve (AUC) $_{0\text{-}4}$; $AUC_{0.5\text{-}4hr}$; Initial Retention Concentration (A_0); and Elimination Rate Constant (K_{el})

Statistical Methods: All variables were analyzed using Analysis of Covariance (ANCOVA). The ANCOVA model included treatment group, site, smoking status (yes/no), strata level of number of bleeding sites and the appropriate baseline (GSI, GI, overall plaque or interproximal plaque) as a covariate. All subjects who were dispensed the study treatment were included in safety population. Efficacy analysis was conducted on the Intent-to-Treat (ITT) population, defined as subjects who received study treatment and had at least one post-baseline efficacy measurement.

Study Population:

	0.2% CHX-Alc	**0.2% CHX-Alc free**	**Brushing Alone**
Number of Subjects Screened:		775	
Planned, N (for randomization)	120	120	120
Randomised, N	108	109	107
Completed, n (%)	105 (97.2)	109 (100.0)	105 (98.1)
Total Number Subjects Withdrawn, n (%)	3 (2.8)	0	2 (1.9)
Withdrawn due to Adverse Events n (%)	2 (1.9)	0	0
Withdrawn due to Lack of Efficacy n (%)	0	0	0
Withdrawn for other reasons n (%)	1 (0.9)	0	2 (1.9)
Demographics (Safety Population)			
N	108	109	107
Females: Males	85:23	79:30	75:32
Mean Age, years (SD)	37.8 (10.89)	36.2 (11.31)	36.5 (10.48)
Race, n (%)			
White	93 (86.1)	94 (86.2)	93 (86.9)
Black or African American	3 (2.8)	7 (6.4)	3 (2.8)
Asian	8 (7.4)	6 (5.5)	6 (5.6)
Multiple	4 (3.7)	2 (1.8)	5 (4.7)

Primary Efficacy Results: Mean Change from baseline to Week 6 in GSI

	0.2% CHX-Alc (N=105)	0.2% CHX-Alc free (N=109)	Brushing Alone (N=105)
Mean GSI at Baseline (SE)	0.250 (0.0081)	0.250 (0.0079)	0.250 (0.0091)
Mean GSI at Week 6 (SE)	0.152 (0.0085)	0.143 (0.0072)	0.212 (0.0121)
Adjusted mean[1] GSI at Week 6	0.152	0.142	0.212
Difference between treatments (95% Confidence Interval)[2]		**% Difference[3]**	**p-value[1]**
0.2% CHX-Alc vs Brushing Alone	-0.061 (-0.081, -0.041)	-28.61	<.0001
0.2% CHX-Alc free vs Brushing Alone	-0.070 (-0.090, -0.050)	-32.97	<.0001

[1]From ANCOVA with factors for treatment group, site, smoking status, number of bleeding sites strata and the baseline GSI as a covariate.
[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 calculation of % difference [(Difference/Reference)*100%].

Secondary Outcome Results:

1. Mean change from baseline to week 6 in GI

	0.2% CHX-Alc (N=105)	0.2% CHX-Alc free (N=109)	Brushing Alone (N=105)
Mean GI at Baseline (SE)	1.24 (0.009)	1.24 (0.009)	1.24 (0.010)
Mean GI at Week 6 (SE)	1.12 (0.012)	1.11 (0.010)	1.19 (0.014)
Adjusted mean[1] GI at Week 6	1.12	1.11	1.19
Difference between treatments (95% Confidence Interval)[2]		**% Difference[3]**	**p-value[1]**
0.2% CHX-Alc vs Brushing Alone	-0.08 (-0.10, -0.05)	-6.43	<.0001
0.2% CHX-Alc free vs Brushing Alone	-0.08 (-0.11, -0.06)	-7.02	<.0001

[1]From ANCOVA with factors for treatment group, site, smoking status, number of bleeding sites strata and the baseline GI as a covariate.
[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 calculation of % difference [(Difference/Reference)*100%].

2. Mean change from baseline to week 6 in overall plaque scores

	0.2% CHX-Alc (N=105)	0.2% CHX-Alc free (N=109)	Brushing Alone (N=105)
Mean Overall Plaque Scores at Baseline (SE)	3.56 (0.044)	3.51 (0.042)	3.60 (0.047)
Mean Overall Plaque Scores at Week 6 (SE)	2.50 (0.082)	2.40 (0.084)	3.34 (0.062)
Adjusted mean[1] Overall Plaque Scores at Week 6	2.50	2.44	3.30
Difference between treatments (95% Confidence Interval)[2]		**% Difference[3]**	**p-value[1]**
0.2% CHX-Alc vs Brushing Alone	-0.80 (-0.98, -0.62)	-24.33	<.0001
0.2% CHX-Alc free vs Brushing Alone	-0.86 (-1.04, -0.68)	-26.13	<.0001

[1]From ANCOVA with factors for treatment group, site, smoking status, number of bleeding sites strata and the baseline plaque as a covariate.
[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 calculation of % difference [(Difference/Reference)*100%].

3. Mean change from baseline to week 6 in interproximal plaque

	0.2% CHX-Alc (N=105)	0.2% CHX-Alc free (N=109)	Brushing Alone (N=105)
Mean Interproximal Plaque Scores at Baseline (SE)	3.92 (0.049)	3.86 (0.048)	3.96 (0.052)
Mean Interproximal Plaque Scores at Week 6 (SE)	2.77 (0.090)	2.63 (0.091)	3.69 (0.065)
Adjusted mean[1] Interproximal Plaque Scores at Week 6	2.77	2.68	3.65
Difference between treatments (95% Confidence Interval)[2]		**% Difference[3]**	**p-value[1]**
0.2% CHX-Alc vs Brushing Alone	-0.88 (-1.07, -0.69)	-24.13	<.0001
0.2% CHX-Alc free vs Brushing Alone	-0.97 (-1.16, -0.78)	-26.59	<.0001

[1]From ANCOVA with factors for treatment group, site, smoking status, number of bleeding sites strata and the baseline plaque as a covariate.
[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 calculation of % difference [(Difference/Reference)*100%].

4. Mean number of tooth sites at week 6 that increased, showed no change and decreased in GSI score

	0.2% CHX-Alc (N=105)			0.2% CHX-Alc free (N=109)			Brushing Alone (N=105)		
	Increased	*No Change*	*Decreased*	*Increased*	*No Change*	*Decreased*	*Increased*	*No Change*	*Decreased*
Mean (SE)	10.8 (0.70)	116.3 (1.39)	25.7 (0.79)	9.1 (0.52)	117.6 (1.44)	25.2 (0.73)	15.2 (1.01)	115.0 (1.32)	20.7 (0.66)

5. Chlorhexidine levels in saliva at each time point				
Variable: Mean (SD)	**Single Dose**		**Repeat Dose**	
	0.2% CHX-Alc (N=16)	**0.2% CHX-Alc free (N=19)**	**0.2% CHX-Alc (N=16)**	**0.2% CHX-Alc free (N=18)**
AUC $_{0\text{-}4hr}$ (ng.hr/ml)	127437.50 (69466.901)	148287.60 (79243.508)	171607.04 (62953.034)	180892.90 (68794.417)
AUC$_{0.5\text{-}4hr}$ (ng.hr/ml)	111840.63 (60705.980)	133826.58 (73213.071)	145801.25 (54245.267)	159712.36 (61203.096)
A0 (ng/ml)	59284.32 (34718.275)	59348.41 (32517.654)	84010.90 (30357.917)	68208.62 (30095.826)
Kel (1/hr)	-0.12 (0.049)	-0.10 (0.063)	-0.15 (0.043)	-0.08 (0.067)

Safety Results: Adverse Events (AEs) and serious AEs were collected from the start of the washout product at visit 1, and until five days following last administration of the investigational product.

	0.2% CHX-Alc (N=108)	**0.2% CHX-Alc free (N=109)**	**Brushing Alone (N=107)**
***Most Frequent AEs – On-Therapy**			
Subjects with any AE(s), n(%)	67 (62.0)	60 (55.0)	47 (43.9)
Oral AEs			
Subjects with any Oral AE(s), n(%)	47 (43.5)	37 (33.9)	23 (21.5)
Tongue coated	13 (12.0)	8 (7.3)	2 (1.9)
Glossodynia	5 (4.6)	9 (8.3)	0
Paraesthesia oral	5 (4.6)	6 (5.5)	0
Ageusia	3 (2.8)	6 (5.5)	0
Mouth ulceration	3 (2.8)	2 (1.8)	3 (2.8)
Dry mouth	4 (3.7)	5 (4.6)	0
Hypoaesthesia oral	2 (1.9)	5 (4.6)	0
Oral herpes	1 (0.9)	2 (1.8)	5 (4.7)
Dysgeusia	6 (5.6)	1 (0.9)	0
Mouth injury	4 (3.7)	1 (0.9)	2 (1.9)
Non-oral AEs			
Subjects with any Non-oral AE(s), n(%)	38 (35.2)	39 (35.8)	34 (31.8)
Headache	19 (17.6)	14 (12.8)	13 (12.1)
Upper respiratory tract infection	11 (10.2)	9 (8.3)	9 (8.4)
Back pain	2 (1.9)	3 (2.8)	2 (1.9)
Dysmenorrhoea	1 (0.9)	1 (0.9)	4 (3.7)
Vomiting	1 (0.9)	4 (3.7)	1 (0.9)
Cough	1 (0.9)	1 (0.9)	3 (2.8)
Oropharyngeal pain	3 (2.8)	1 (0.9)	1 (0.9)
Diarrhoea	1 (0.9)	2 (1.8)	1 (0.9)
Pyrexia	0	0	2 (1.9)
Otorrhoea	1 (0.9)	0	0

*Most frequent 10 events experienced in any group.

Serious Adverse Events - On-Therapy
n (%) [n considered by the investigator to be related to study medication]

	0.2% CHX-Alc (N=108)	**0.2% CHX-Alc free (N=109)**	**Brushing Alone (N=107)**
Subjects with non-fatal SAEs, n (%)	0	1 (0.9) [0]	0
Cellulitis left thigh	0	1 (0.9) [0]	0
Subjects with fatal SAEs, n (%)	0	0	0