Datatrial

CALCIVIS LTD
NINE, EDINBURGH BIOQUARTER
LITTLE FRANCE ROAD EDINBURGH
EH16 4UX

STATISTICAL ANALYSIS PLAN

CONFIDENTIAL

Calcivis® Caries Activity Imaging System
CAL-02-2014

Clinical Study to Evaluate the Safety and Performance of the Calcivis® System for Identifying Active Demineralization on Tooth Surfaces

Version: Final 3.0

Datatrial

APPROVAL SIGNATURES

Study title: Clinical Study to Evaluate the Safety and Performance of the Calcivis® System for Identifying Active Demineralization on Tooth Surfaces

Study Number: CAL-02-2014

Author

Signature: _____ Date: 11 Apr 2017

Barbara Collins
Statistician

Reviewer:

Signature: _____ Date: 11 Apr 2017

John Breddy
Consultant Statistician

Sponsor:

Signature: _____ Date: 13 April 2017

Adam Christie
CEO, Calcivis

Table of Contents

1.0 Version Control

This Statistical Analysis Plan (SAP) is based on the Post Approval Clinical Study Plan version 4 dated 03 May 2016 and CRF version final 1.0.

This SAP refers to the final analysis of the data.

2.0 Study Rationale

The technology underlying the Calcivis System was developed to help address the unmet need in relation to the determination of caries lesion activity status. The Calcivis System combines a sensitive custom intra-oral imaging device and a bioluminescent marker which produces light in the presence of free calcium ions as they are released from actively demineralising areas of a tooth surface. The images produced by the system are effectively maps of demineralisation activity across that surface.

The International Caries Detection and Assessment System (ICDAS) concept is that the use of a standardised system, based on best available evidence for detecting early and later stage caries severity, should lead to the acquisition of better quality information which could then be used to inform decisions about appropriate diagnosis, prognosis, and clinical management of dental caries at both the individual and public health levels.

The potential benefits from using the Calcivis System relate to the clinician being able to make a more informed decision about lesion activity status – the more accurate the information relating to lesion activity status, the more likely an appropriate treatment decision will be made. The potential risks from using the device relate to the device providing a false positive signal with the consequent increased potential for the clinician deciding the lesion requires either non-operative preventive therapy or a restoration / filling i.e. drilling, (the latter being unlikely since, if there is no cavitation present, the current guidelines indicate a restoration is not required).

Previous laboratory research on recently extracted teeth has demonstrated that there is strong correlation between positive light signals generated by the early Calcivis technology and caries lesion activity status, as assessed by a clinician, as well as the physical characteristics of the surface of active lesions.

The results of the previous clinical study on the advanced prototype of the Calcivis System confirmed the device to be safe in clinical use, and provided an acceptable level of “correlation” between the Investigator’s rating of sound and unsound teeth using ICDAS coding and the Calcivis System. In particular the results showed a higher level of correlation for the sound teeth, (83.9%) meaning the chances of false positives are low. It may be that some of the teeth considered sound had sub-clinical but actively demineralizing lesions.

The feedback from both user and patient questionnaires provided useful information on some of the design features, which have now been incorporated in to the commercial device which will be easier to use.

Therefore the purpose of this clinical study is to evaluate both the clinical safety and performance of the next generation Calcivis System for identifying active demineralisation on the surfaces of teeth on a patient population ≥ 6 years old.

3.0 Objectives

This is a prospective, multi-site, non-randomised, post-approval clinical study to assess the performance, safety of the Calcivis System for identifying demineralisation on the surfaces of teeth on a patient population ≥ 6 years old and the usefulness of the Calcivis System as a communication tool between dentist and patient.

3.1 Primary Objectives

3.1.1 Performance

Performance of the Calcivis System, as measured by the presence or absence of elevated luminescence on the surface of the tooth determined from intra-oral image mapping of the surfaces of teeth (with or without a visible lesion).

3.1.2 Safety

Safety of the Calcivis System, as measured by the collection of all adverse events.

3.2 Secondary Objective

To assess the usefulness of the Calcivis System images, as a communication tool between patient and dentist, as measured by Questionnaires and / or Patient Visual Analogue Scales.

4.0 Study Design

This is a prospective, multi-site, non-randomised, post-approval clinical study to assess the use of the Calcivis System for assessing active demineralization on tooth surfaces of teeth in patients 6 years and older. This post-approval clinical study will be conducted under the controlled conditions of this clinical study plan, on eligible patients, in a general dental practice setting.

The prevalence of active lesions found on the occlusal surfaces of erupting teeth is affected by the erupting stage status of the teeth – with the prevalence of active lesions greater in the earlier eruption stages.

As a result of these and similar findings the choice of teeth for identifying visible lesions which are potentially ‘active’ has been limited to erupting and erupted molars and premolars.

To ensure poolability of the data from each Investigator, up to 36 patients may be recruited to the study (to obtain a minimum of 17 evaluable images of each tooth population) by five Investigators from four general dental practices. All patients and / or parent or guardian must provide written informed consent and be willing to adhere to the study schedule, before being entered in to the study.

Patients will be encouraged to complete two Study Visits, however, patients are free to withdraw consent at any time, irrespective of their initial consent. Patients may also be withdrawn from the study by the Investigator on the grounds of safety. Any patients who withdraw or are withdrawn from the study will be replaced.

The overall study period is expected to take 10 months - 3 months for Ethics Committee and National Health Service Research and Development approval, 2 to 3 months for recruitment and study procedures, and 4 months for final follow up, data collection and analysis.

5.0 Study Procedures

5.1 Screening and Follow-up Telephone Call

Patients attending routine dental appointments who are identified by the Investigator as meeting all the inclusion / exclusion criteria, will be approached to discuss their possible participation in the study.

If the patient and / or parent or guardian is willing for the patient to participate in the study, they will be asked to return to the dental practice for Study Visit 1, when written Informed Consent will be taken by the Investigator. Patient availability for Study Visit 2 (7 to 14 days post-imaging) will also be checked.

The Site will document all patients and / or parent or guardian provided with the Patient Information Sheet and the outcome, (whether or not recruited to the study) on a Patient Screening / Recruitment Log.

5.2 Study Visit 1

At this visit, written Informed Consent will be taken by the Investigator and the following information collected: –

Pre-Imaging Information
Demographics – date of birth, ethnicity, relevant medical history and medications.

Oral hygiene information – brushing regimen, toothpaste and any other dental products used.

Preparation of the Calcivis System
The Calcivis System will be prepared following the manufacturer's Instructions for Use. The Disclosing Solution should not be reconstituted more than 2 hours before the first tooth is imaged.

Preparation Procedures for Teeth
Relevant teeth will be identified and recorded for assessment using the Calcivis System as per Inclusion / Exclusion criteria.

All teeth surfaces to be imaged will be cleaned by the Dentist, by brushing with water or dental paste and rinsing with water and an air-water spray from a conventional dental 3-in-1 device, according to the Tooth Cleaning Protocol (Appendix 2 of the Clinical Study Plan). Patients will be asked to rinse out thoroughly with tap water.

Immediately following thorough air-drying of each tooth surface to be imaged, the Investigator will take a colour photograph with a standard intra-oral camera and record the ICDAS score /activity status.

Preparation Procedures for imaging with the Calcivis device
Care must be taken to ensure the surface of the tooth and surrounding area are free from saliva before imaging by the use of appropriate moisture control aids.

Each tooth will be air-dried for 5 to 10 seconds immediately before application of the disclosing solution and Calcivis System imaging.

Imaging with the Calcivis System

For teeth from each category (no lesions, and active lesions) a maximum of one tooth per patient can be imaged.

If a patient has more than one tooth of a particular category (sound tooth [no visible lesion], or tooth with active lesion) the investigator will use best clinical judgement to choose a tooth that most clearly fits the criteria of that particular population tooth type, for example if there is the choice of 2 teeth displaying lesions considered active, each identical except one of the teeth has a lesion in a plaque stagnation area (e.g. pits and fissures) and one more distant from plaque stagnation area, the tooth with the lesion in a plaque stagnation area will be chosen.

If the first image of a selected tooth is not clear for interpretation, it is acceptable to take a second image of that tooth, however no more than two images of any one tooth can be taken.

Recruitment will be stopped for each Investigator when a minimum of 17 evaluable images (as determined by the Investigators) from each tooth population have been obtained.

After all imaging has been completed, patients will be asked to rinse out with tap water.

Any adverse events observed or volunteered by the patient will be recorded. If appropriate a colour photograph will be taken of the adverse event with a standard intra-oral camera.

The images generated with the Calcivis System will be stored digitally on the laptop provided. The software will allow overlay of the two sets of images (before and after application of the disclosing solution) and interpretation of the resulting demineralization map of each imaged tooth will be carried out by the Investigator at the end of imaging.

At the end of the imaging procedures, the Investigator will share the images of the teeth with the patient.

The Calcivis System will be dismantled and cleaned according to the Instructions for Use. All consumables will be disposed according to the Instructions for Use.

Representatives of the Sponsor, Calcivis Ltd, will be available throughout Visit 1 to provide technical support for the use of the Calcivis System, as and when required. Consent will be sought from the patient and / or parent or guardian.

Post-Imaging Questionnaires / Visual Analogue Scales

At the end of the imaging procedures, patients will be asked to remain at the dental practice to complete a Patient Questionnaire / Visual Analogue Scale. Visit 1 is then complete.

In addition, at the end of each imaging study visit, the Investigator and Dental Nurse will each complete relevant sections of a User Questionnaire.

5.3 Study Visit 2 – 7-14 days post-imaging

At this visit, a final oral examination will be performed by the Investigator and any adverse events observed or volunteered by the patient will be recorded. If appropriate, a colour photograph will be taken of the adverse event with a standard intra-oral camera.

5.4 Future Dental Care

Depending on the results, the Investigator may provide caries preventive advice to the patient and / or parent or guardian. The Investigator will not suggest further dental treatment based on the result of the images alone.

5.5 Independent Investigator Image Review

After all the images have been taken and verified as acceptable by the originating Investigator, and the CRFs collected, an independent review of the Calcivis images will be undertaken to assess the presence or absence of elevated luminescence on the surface to the teeth imaged with the Calcivis System.

This will be carried out by one of the other Investigators.

The independent reviewer will be provided with evidence of both the original investigator's decision on tooth classification (i.e. no lesion, or active lesion, based on ICDAS coding / activity status) along with documented evidence of the clinician's intended location for assessment (this is all documented by the original Investigator prior to imaging using the Calcivis System). In addition, photographic evidence of the actual location of the luminescence will be provided. The determination by the independent reviewer will be made off-site, using the visible and Calcivis images along with copies of the original Investigator's documentation. The data from the independent reviewer will be used for the primary analysis.

6.0 Sample Size

The study will assess the agreement between the Calcivis System and dentist rating of suitable teeth in two teeth populations: 'no visible lesions', and 'active lesions'. Based on previous study data and expert opinion, 'No visible lesions' are expected to correspond to 'no luminescence' according to the Calcivis system in at least 70% of cases. Similarly, 'active lesions' are also expected to correspond to 'luminescence' in at least 70% of cases.

Subjects will provide no more than one tooth of each tooth population. The study sample size is calculated in terms of the number of teeth of each tooth population required. The number of subjects required is then *at most* the total number of teeth required.

For the purpose of sample size calculations, the percentage agreement for each of the two tooth populations are jointly considered as measures of agreement. That is, the study will be deemed a success if the percentage agreement in both of the tooth status populations is statistically significant at the 2.5% level when compared to chance agreement (50%).

Expressed in terms of hypothesis tests, the null and alternative hypotheses are:

$$H0: p_{a,i}=0.5 \text{ vs. } H1: p_{a,i}>0.5 \text{ for each tooth status population } i$$

where $p_{a,i}$ is the percentage agreement in tooth status population i.

To achieve at least 90% power overall, a power of 94.9% has been used for each tooth status population individually. The planned method of analysis is an exact binomial test

and this has been used to derive a required sample size of 81 for each of the tooth status populations. This is the first sample size after which all subsequent sample sizes provide at least 94.9% power.

7.0 Deviations

A Deviation is a failure to comply with the requirements specified within the Clinical Study Plan without adequate justification.

All deviations will be documented on the appropriate forms and reported to the Sponsor. All deviations will be reviewed and assessed for their impact on patient safety and validity for analysis by Calcivis Ltd.

8.0 Analysis Populations

8.1 Safety Population

All patients on whom the Calcivis System is used will be included in the Safety Population.

8.2 Agreement Population

The Agreement Population will include all teeth on which there is a dentist ICDAS score. The Agreement Population will be used for all analyses of agreement.

9.0 Data Reporting Conventions

9.1 Descriptive Statistics

Unless otherwise stated, all continuous parameters will be summarized using standard summary statistics as appropriate (n, mean, standard deviation, minimum, median and maximum). Summary statistics for categorical variables will include frequency counts and percentages.

In the presentation of descriptive summary statistics, the minimum and maximum will be presented to the same number of decimal places as the variable being reported. If differing levels of precision are recorded then the most frequently recorded precision will be used as the basis for reporting precision. In the event of a tie, the higher level of precision will be used for summarising data. The mean and median will be reported to one extra decimal place; the standard deviation (SD) to two extra decimal places.

Frequency counts will be provided for categorical variables (e.g., gender). Unless otherwise stated, this will consist of the number of patients in a particular category and the percentage of the total number of patients, presented to one decimal place.

Analyses will be performed using the validated statistical software Statistical Analysis System (SAS) version 9.2 (or higher).

9.2 Missing Data

Missing data arising from teeth where the Calcivis System assessment is uninterpretable for reasons that are thought unrelated to the assessment outcome (image out of focus, ambient light ingress) will not be imputed. Otherwise missing data will be considered as a disagreement in the calculation of agreement. Secondary analyses based on imputing all missing data as a disagreement will be conducted, if appropriate.

Otherwise missing data will not be imputed.

10.0 Subject Disposition and Pre-Imaging Information

10.1 Subject Disposition

Study completion and discontinuation details, inclusion/exclusion criteria, population assignment, and protocol deviations will be listed.

The number of subjects attending each study visit, completing the study, withdrawing from the study and the primary reason for withdrawal will be tabulated.

The number and percentage of subjects in each analysis population will be tabulated. In the case of the agreement population, this includes the number of subjects with a tooth with no visible lesion, with a tooth with an active lesion or with either.

The number and percentage of subjects with deviations and reason for deviation will be tabulated.

10.2 Demographic Characteristics

Demographic parameters will include date of birth, age, gender and ethnicity. Demographics will be listed and tabulated using descriptive statistics.

Age = ((Date of informed consent) – (Date of Birth) + 1) / 365.25

10.3 Relevant Medical History

Details of relevant medical history and medications (known sensitivities or allergies to photoproteins, and use of calcium supplements and antacids) will be listed.

10.4 Oral Hygiene

Details of oral hygiene will be listed and the number and percentage of subjects within each oral hygiene category (frequency that teeth are brushed, use of mouthwash, frequency of mouthwash use and whether any other products are used) will be tabulated.

10.5 Calcivis System

Details of Calcivis System preparation and imaging set-up will be listed. Details of the independent review will also be listed.

The post-imaging checklist from each study visit will also be listed.

11.0 Agreement

The ICDAS defined tooth status (no visible lesions/active lesions) by the original Dentist, and the independent dentist assessment using the Calcivis System (no luminescence/luminescence) will be listed for each tooth.

A table will be presented cross-tabulating the original dentist ICDAS defined tooth status with the independent reviewer Calcivis finding.

Agreement between the ICDAS defined tooth status and Calcivis finding will be summarised using the negative and positive percent agreement as follows:

- The percentage of teeth with no visible lesion that are assessed as showing no luminescence by the Calcivis System (negative percent agreement);
- The percentage of teeth with an ‘active lesion’ that are assessed as showing

luminescence by the Calcivis System (positive percent agreement).

The hypothesis that agreement is greater than 0.5 will be tested using an exact binomial test and an exact one-sided 97.5% Clopper-Pearson confidence interval will be presented.

Secondary analyses based on imputing all missing data as a disagreement will be conducted, if appropriate.

12.0 Patient and User Questionnaires

Details of Patient and User Questionnaires will be listed and responses to each question will be summarised using frequency counts and percentages.

13.0 Safety

Safety will be assessed from records of Adverse Events.

13.1 Adverse Events

AEs will be collected from the point of informed consent.

A procedure emergent AE (PEAE) is defined as an AE with start date on or after the start of the Calcavis system procedure. AEs with unknown start date will be assumed to be procedure emergent unless the end date is known to be before the procedure commenced.

All adverse events and serious adverse events will be listed. PEAEs will be flagged in the listings.

14.0 Table Mock Ups

Table 1	Patient Disposition	Safety Population
Table 2	Protocol Deviations	Safety Population
Table 3	Demography	Safety Population
Table 4	Oral Hygiene	Safety Population
Table 5	Original Dentist Assessment of ICDAS Score and Independent Dentist Interpretation of Calcivis System Assessment	Agreement Population
Table 6	Agreement between Original Dentist ICDAS Assessment and Independent Dentist Interpretation of Calcivis System Assessment	Agreement Population
Table 7	Agreement between Original Dentist ICDAS Assessment and Independent Dentist Interpretation of Calcivis System Assessment – Secondary Analysis (if required)	Agreement Population
Table 8	Patient Questionnaires	Safety Population
Table 9	User Questionnaires	Safety Population

15.0 Figure Mock Ups

No Figures are required for this study.

16.0 Data Listing Mock Ups

Each listing will include all patients that provide any data relevant to the listing. Listings will be ordered by patient number.

Listing 1	Patient Disposition	Safety Population
Listing 2	Inclusion and Exclusion Criteria	Safety Population
Listing 3	Population Assignment	Safety Population
Listing 4	Protocol Deviations	Safety Population
Listing 5	Demography	Safety Population
Listing 6	Relevant Medical History and Medications	Safety Population
Listing 7	Oral Hygiene	Safety Population
Listing 8	Calcivis System Preparation	Safety Population
Listing 9	Calcivis System Imaging	Safety Population
Listing 10	Post-Imaging Checklist	Safety Population
Listing 11	Independent Imaging Interpretation and Analysis	Safety Population
Listing 12	Patient Questionnaires	Safety Population
Listing 13	User Questionnaires	Safety Population
Listing 14	Adverse Events	Safety Population
Listing 15	Serious Adverse Events	Safety Population

Table 1 Patient
Disposition Safety

Population

	Overall (N=XX)
Attended Visit 1	X (xx.x %)
Attended Visit 2	X (xx.x %)
Completed Study	X (xx.x %)
Withdrew from Study	X (xx.x %)
Reason for Withdrawal	
Consent withdrawn by patient	X (xx.x %)
Investigator withdrew patient	X (xx.x %)
Lost to follow-up	X (xx.x %)
Adverse Event	X (xx.x %)
Death	X (xx.x %)
Other	X (xx.x %)
Population	
Safety	X (xx.x %)
Agreement[1]	X (xx.x %)
Tooth with no visible lesion	X (xx.x %)
Tooth with active lesion	X (xx.x %)

Produced : xxxxxxxxx xx:xx (Page xx of yy)

[1] Subjects with a tooth with no visible lesion or a tooth with an active lesion or both. Table supported by Listings 1 & 3

Table 2 Protocol

Deviations Safety
Population

	Overall (N=XX)
Any Protocol Deviations	X (xx.x %)
Informed Consent Process	X (xx.x %)
Inclusion/Exclusion	X (xx.x %)
Study Procedure	X (xx.x %)
Other	X (xx.x %)

Produced : xxxxxxxxx xx:xx (Page xx of yy)
Table supported by Listing 4

Table 3 Demography

Safety Population

		Overall (N=XX)
Age (years)	n	X
	Mean	XX.X
	SD	XX.XX
	Minimum	XX
	Median	XX.X
	Maximum	XX
Gender	Male	X (xx.x %)
	Female	X (xx.x %)
Ethnic Group	Hispanic or Latino	X (xx.x %)
	Asian	X (xx.x %)
	Black	X (xx.x %)
	White	X (xx.x %)
	Other	X (xx.x %)

Produced : xxxxxxxxx xx:xx (Page xx of yy)

Table supported by Listing 5

Safety Population

		Overall (N=XX)
Teeth Brushed	Once per day	X (xx.x %)
	Twice per day	X (xx.x %)
	Three times per day	X (xx.x %)
	Other	X (xx.x %)
Use Mouthwash	Yes	X (xx.x %)
	No	X (xx.x %)
Mouthwash Used	Once per day	X (xx.x %)
	Twice per day	X (xx.x %)
	Three times per day	X (xx.x %)
	Other	X (xx.x %)
Other Products	Yes	X (xx.x %)
	No	X (xx.x %)

Produced : xxxxxxxxx xx:xx (Page xx of yy)
Table supported by Listing 7

Table 5

Original Dentist Assessment of ICDAS Score and Independent Dentist Interpretation of Calcivis System Assessment

Agreement Population

As Assessed by Original Dentist using ICDAS	As Interpreted by Calcivis System			
	No Luminescence	Luminescence	Missing	Total
ICDAS 0	X (xx.x %)	X (xx.x %)	X (xx.x %)	X (xx.x %)
ICDAS 2	X (xx.x %)	X (xx.x %)	X (xx.x %)	X (xx.x %)
ICDAS 3	X (xx.x %)	X (xx.x %)	X (xx.x %)	X (xx.x %)
Total	X (xx.x %)	X (xx.x %)	X (xx.x %)	X (xx.x %)

Produced : xxxxxxxxx xx:xx (Page xx of yy)

Table supported by Listings 9 & 11

Percentages are calculated from total number of teeth assessed by Calcivis system

Table 6

Agreement between Original Dentist ICDAS Assessment and Independent Dentist Interpretation of Calcivis System Assessment

Agreement Population

Original Dentist ICDAS Assessment	N	Agreement n (%)	P-value	1 – sided 97.5% CI
No visible lesion	X	xx (xx.x%)	x.xxx	x.xx
Active lesion	X	xx (xx.x%)	x.xxx	x.xx
All teeth	X	xx (xx.x%)		

Produced : xxxxxxxxx xx:xx (Page xx of yy)

N = Number of teeth with no visible lesion or active lesion respectively; n (%) = Number (%) of teeth with no luminescence or luminescence out of the number of teeth with no visible lesion or active lesion respectively.

Table supported by Listings 9 & 11

Programmers note: Repeat table for

Table 7 Agreement between Original Dentist ICDAS Assessment and Independent Dentist interpretation of Calcivis System Assessment - Secondary Analysis - Agreement Population

Question	Response	Overall (N=XX)
How would you rate your overall experience with the Calcivis System?[1]	Good	X (xx.x %)
	Neither good nor bad	X (xx.x %)
	Bad	X (xx.x %)
Did you find seeing the images of your teeth and having the dentist explain your situation helpful?[2]	Helpful	X (xx.x %)
	Neither helpful nor unhelpful	X (xx.x %)
	Unhelpful	X (xx.x %)

Produced : xxxxxxxxx xx:xx (Page xx of yy)

[1] 6-11 year olds were asked “How do you feel about your dentist using the Calcivis system?”

[2] 6-11 year olds were asked “Did you find seeing the pictures of your teeth and having the dentist explain them to you helpful?”

Table supported by Listing 12

Question	Response	Overall (N=XX)
How easy was it to prepare the Calcivis System?	Easy	X (xx.x %)
	Neither easy nor difficult	X (xx.x %)
	Difficult	X (xx.x %)
How easy was it to use the device?	Easy	X (xx.x %)
	Neither easy nor difficult	X (xx.x %)
	Difficult	X (xx.x %)
How would you rate your overall experience with the Calcivis System?	Good	X (xx.x %)
	Neither good nor bad	X (xx.x %)
	Bad	X (xx.x %)
Were the instructions provided sufficient for you to understand how to use the Calcivis System?	Easy	X (xx.x %)
	Neither easy nor difficult	X (xx.x %)
	Difficult	X (xx.x %)

Produced : xxxxxxxxx xx:xx (Page xx of yy)
Table supported by Listing 13

Listing 1

Patient
Disposition

Safety
Population

Site	Patient	Informed Consent	Did the		Patient	Date of Completion/

Number	Number	Date	Time	Complete the Study	Withdrawal	Reason for Withdrawal
XX	YY	DDMMMYYYY	hh:mm	Yes	DDMMMYYYY	
	YY	DDMMMYYYY	hh:mm	No	DDMMMYYYY	Consent withdrawn by patient
	YY	DDMMMYYYY	hh:mm	No	DDMMMYYYY	Investigator withdrew patient
	YY	DDMMMYYYY	hh:mm	No	DDMMMYYYY	Lost to follow-up
	YY	DDMMMYYYY	hh:mm	No	DDMMMYYYY	Adverse event
	YY	DDMMMYYYY	hh:mm	No	DDMMMYYYY	Death
	YY	DDMMMYYYY	hh:mm	No	DDMMMYYYY	Other: XXXXXXXXXX

Listing 2

Inclusion and Exclusion Criteria
Safety Population

Site Number	Patient Number	Criterion Type	Criterion Number	Criterion Text	Criterion Response
XX	YY	Inclusion	1	Patient must be ≥6 years old	Yes
			2	Patient must have one unrestored, accessible, free smooth buccal surface on a canine or incisor, away from the gingival surface identified with no visible lesion (coded ICDAS 0) and/or	Yes
			3	Patient must have one unrestored, accessible, erupting or erupted molar or pre-molar with a visible lesion identified (coded ICDAS 2 or 3) in a plaque stagnation area	No
			4	Patient and/or parent or guardian must be willing and able to give written informed consent	Yes
			5	Patient and/or parent or guardian must be willing and able to adhere to study schedule	Yes
		Exclusion	1	Any patient with recent tooth bleaching (within previous two weeks of treatment with the Calcivis System)	No
			2	Any patient having on-going re-mineralisation treatment including, but not limited to high concentration prescription fluoride toothpaste	No
			3	Any patient with a fixed orthodontic appliance	Yes
			4	Any patient currently taking part in a clinical research study, or has taken part in a clinical research study in the previous three months	No
			5	Pregnant and/or nursing mothers	No

Site Number	Patient Number	Population		
		Safety	Agreement	Lesion
XX	YY	Yes	Yes	No visible lesion
	YY	Yes	No	Active lesion

Site Number	Patient Number	Date of Protocol Deviation	Details of Protocol Deviation	Reason for Protocol Deviation	Date Reported to Calcivis	Action Taken
XX	YY	DDMMMYYY	XXXXXXXXXX	Informed Consent Process	DDMMMYYY	XXXXXXXXXX
	YY	DDMMMYYY	XXXXXXXXXX	Inclusion/Exclusion	DDMMMYYY	XXXXXXXXXX
	YY	DDMMMYYY	XXXXXXXXXX	Study Procedure	DDMMMYYY	XXXXXXXXXX
	YY	DDMMMYYY	XXXXXXXXXX	Other: XXXXXXX	DDMMMYYY	XXXXXXXXXX

Listing 5
Demography
Safety Population

Site Number	Patient Number	Date of Birth	Age[1]	Gender	Race
XX	YY	DDMMMYYYY	xx	Male	Hispanic or Latino
	YY	DDMMMYYYY	xx	Female	Asian
	YY	DDMMMYYYY	xx		Black
	YY	DDMMMYYYY	xx		White
	YY	DDMMMYYYY	xx		Other: XXXXXXXXX

[1]Age = (Date of informed consent–Date of Birth+1)/365.25.

Produced : xxxxxxxxx xx:xx (Page xx of yy)

Site Number	Patient Number	Question	Response	Name	Frequency	Date of Last Dose	Time of Last Dose
XX	YY	Any known sensitivities or allergies to photoproteins?	No				
		Do you take any calcium supplements?	Yes	XXXXXXXX	XXXXXX	DDMMMYYYY	HH:MM
		Do you take any antacid tablets?	Yes	XXXXXXXX	XXXXXX	DDMMMYYYY	HH:MM

Listing 7 Oral

Hygiene
Safety Population

Site Number	Patient Number	Question	Response	Details
XX	YY	Which toothpaste do you use most often?	XXXXXXXXX	
		How many times per day do you brush your teeth?	Once per day	
			Twice per day	
			Three times per day	
			Other	XXXXXXXXX
		Do you use mouthwash?	Yes	XXXXXXXXX
			No	
		On average, how many times per day do you use mouthwash?	Once per day	
			Twice per day	
			Three times per day	
			Other	XXXXXXXXX
		Do you use any other dental products?	Yes	XXXXXXXXX
			No	

Produced : xxxxxxxxx xx:xx (Page xx of yy)

Site Number	Patient Number	Visit	Question	Response	Time Procedures Started
XX	YY HH:MM	Visit 1	Has the Calcavis System been set up according to the manufacturers Instructions for Use?	Yes	
				No	
			Were teeth cleaned according to teeth cleaning protocol?	Yes	
				No	
			Was patient rinsed out thoroughly with tap water?	Yes	
				No	
			Have colour photographs been taken of each selected tooth surface?	Yes	
				No	

Produced : xxxxxxxxx xx:xx (Page xx of yy)

Site Number	Patient Number	Visit	Visit Date	Tooth	Tooth ID	Surface to be Imaged	ICDAS code	Inactive or Active	Number of Images	Image to be used
XX	YY	Visit 1	DDMMMYYYY	1	xx	Buccal	0	Inactive	1	1
				2	xx	Occlusal	2 or 3	Active	2: XXXXXXX	1

Listing 10
Safety Population

Datatrial

Post-Imaging Checklist

Site Number	Patient Number	Visit	Visit Date	Were images reviewed with the patient?	Did any Adverse Events occur?	Has the patient been given a Patient Questionnaire / Visual Analogue Scale to complete?	Is the visit 7-14 days after visit 1?	Has final oral exam been carried out?
XX	YY	Visit 1	DDMMMYYYY	Yes	Yes	Yes		
				Yes	Yes	No		
				Yes	No	Yes		
				No	Yes	Yes		
				Yes	No	No		
				No	Yes	No		
				No	No	Yes		
				No	No	No		
		Visit 2			Yes		Yes	Yes
					Yes		Yes	No
					Yes		No	Yes
					No		Yes	Yes
					Yes		No	No
					No		Yes	No
					No		No	Yes
					No		No	No

Produced : Produced : xxxxxxxxx xx:xx (Page xx of yy)

Listing 11

Independent Imaging Interpretation and Analysis

Safety Population

Site Calcivis Number	Patient Number	Visit	Date	Original Dentist Tooth ID	ICDAS Rating	ICDAS Activity	Luminescence Detected from System - Independent Dentist
XX	YY	Visit 1	DDMMMYYYY	Xx	Xx	No visible lesion - inactive	Yes
				xx	xx	Active lesion	No

Produced : xxxxxxxxx xx:xx (Page xx of yy)

Site Number	Patient Number	Visit	Question Number	Question Text	Response	Comments
XX	YY	Visit 1	1	How would you rate your overall experience with the Calcivis System?	Good	xxxxxx
					Neither good nor bad	
					Bad	
			2	Did you find seeing the images of your teeth and having the dentist explain your situation helpful?	Helpful	
					Neither helpful nor unhelpful	
					Unhelpful	

Programming note: Questions may differ based on the age of the patient. Please output the relevant question for the patient age.

Site Number	Investigator	Dental Nurse	Number of Procedures	Date Completed	Question Number	Question Text	Response	Comments
XX	xxxxxxxx	xxxxxxxx	xx	DDMMMYYYY	1	How easy was it to prepare the Calcivis System?	Easy Neither easy nor difficult Difficult	XXXXXXXXXX
					2	How easy was it to use the device?	Easy Neither easy nor difficult Difficult	XXXXXXXXXX
					3	How would you rate your overall experience with the Calcivis System?	Good Neither good nor bad Bad	XXXXXXXXXX
					4	Were the instructions provided sufficient for you to understand how to use the Calcivis system?	Easy Neither easy nor difficult Difficult	XXXXXXXXXX

Listing 14

Datatrial

Adverse Events
Safety Population

Inv Name/ Site Number	Patient Number	No.	Verbatim Term	Date of Procedure	Device(s) - Code/ Lot Number	Onset Date/ Stop Date	Status/ Outcome	Severity	Action Taken	Relationship to Procedure	Relationship to Device	Did AE arise from insufficiencies in the Instructions for use?	Did the AE arise due from user error?	SAE?
XXXXX/ XX	YY	1*	xxxxxxxxxxx	DDMMMYYYY	xxxxx	DDMMMYYYY/ DDMMMYYYY	Continued/ ongoing	Mild Moderate	None Medical	Unrelated Possible	Unrelated Possible	Yes No	Yes No	Yes No
						DMMMYYYY/ Ongoing	Recovered Recovered with sequelae Death	Severe	Therapies Procedural Other: XXXXXX	Probable Definite	Probable Definite			

Produced : xxxxxxxxx xx:xx (Page xx of yy)* Procedure emergent adverse event.

Listing 15

Serious Adverse Events
Safety Population

Inv Name/ Site Number	Patient Number	No.	Verbatim Term	Onset Date/ Stop Date	Date Became Serious	Date Reported to Sponsor	Reason for Serious	Is the AE Anticipated?
XXXXXXX/ YY	1*		xxxxxxxxxxx	DDMMMYYYY/	DDMMMYYYY	DDMMMYYYY	Death	Yes
XX				DDMMMYYYY			Life-threatening illness or injury	No
				DMMMYYYY/ Ongoing			Resulted in a permanent impairment of a body structure or a body function	
							In-patient hospitalization required	
							In-patient hospitalization prolonged	
							Resulted in a medical or surgical intervention to prevent a permanent impairment of a body structure or a body function	
							Foetal distress, foetal death or congenital anomaly or birth defect	

Produced : xxxxxxxxx xx:xx (Page xx of yy)
* Procedure emergent adverse event.