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STATISTICAL ANALYSIS PLAN

CONFIDENTIAL

Calcivis® Caries Activity Imaging System
CAL-03-2015

Monitoring of Caries Lesion Activity in Orthodontic Patients with the Calcivis® System

Version: Final 1.0

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APPROVAL SIGNATURES:

Study title: Monitoring of Caries Lesion Activity in Orthodontic Patients with the Calcivis® System

Study Number: CAL-03-2015

Author:

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1.0 Version Control

This Statistical Analysis Plan (SAP) is based on the Clinical Study Plan (CSP) version 5 dated 08 November 2017 and CRF version Final 2.0.

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 intraoral 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.

The purpose of this clinical study is to assess the use of the Calcivis System for monitoring the activity levels of post-orthodontic treatment white spot lesions over time.

3.0 Objectives

3.1 Primary Objective

To assess the Calcivis System for monitoring the activity levels of post-orthodontic treatment white spot lesions as an indicator of either 1) gradual arrest of lesion activity (remineralization/repair) or 2) continuing lesion activity (on-going demineralization) of the Calcivis system. This will be measured by bioluminescent output over time from baseline (de-bond) to 12 weeks post de-bond (presence or absence of bioluminescence).

3.2 Secondary Objectives

To assess the safety of the Calcivis system, as measured by the collection of all adverse events.

To assess the value of feedback and/or communication with patients after using the Calcivis System, as measured by questionnaires for both the patient and the user.

4.0 Study Design

This is a prospective, single-site, non-randomised, post-approval clinical study to assess the use of the Calcivis System for monitoring the activity levels of post-orthodontic treatment white spot caries lesions over time, from baseline (de-bond) to 12 weeks post de-bond (CSP version 4) or 8 weeks post de-bond (CSP version 5). This post-approval clinical study will be conducted under the controlled conditions of this clinical study plan, on eligible patients in a clinical setting (NHS hospital, orthodontic clinic) by three investigators.

Only patients who have active lesions on de-bond, as confirmed with the Calcivis System at the baseline visit, will be followed up in this study. If all lesions are assessed as inactive, the patient will be withdrawn from the study.

It is expected that up to 100 patients may have to be recruited and imaged with the Calcivis System at de-bond (baseline) in order to find 45 patients with active lesions. All patients (or parents or guardians where the patient is not competent to provide written informed consent) 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 all 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 21 months - 3 months for Ethics Committee and National Health Service Research and Development approval, 14 months for recruitment and study procedures, and 4 months for final follow up, data collection and analysis.

5.0 Study Procedures

5.1 Screening Procedures

Patients attending routine orthodontic appointments to have their appliances checked, and who are identified by the Investigator as meeting all the inclusion and exclusion

criteria and are ready for de-bond, 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 orthodontic clinic for Study Visit 1 (baseline).

5.2 Study Visit 1 – de-bond – baseline

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

- Demographics – date of birth and gender.
- Relevant medications – calcium supplements and antacids.
- Oral hygiene information – routine brushing regimen, toothpaste and any other dental products used.
- Orthodontic history – date braces applied, type of bracket, ligation used and any other relevant information (e.g. re-mineralization products used).

The Calcivis System will then be prepared following the manufacturer's Instructions for Use.

Immediately after the orthodontic appliances have been removed, up to a maximum of five teeth from any of the four upper incisors and two canines with visible white spot lesions on de-bond will be identified and recorded for assessment using the Calcivis System.

Each free smooth surface will be air dried before taking a colour photograph of the tooth or teeth with a digital camera for reference, and coded for ICDAS (1, 2 or 3).

All relevant teeth will then be cleaned by the Orthodontist according to the Tooth Cleaning Protocol (Appendix 2 of the Clinical Study Plan).

Images of the free smooth tooth surfaces will then be taken with the Calcivis System. If the first image of a selected tooth is not clear, it is acceptable to take a second image of the selected tooth. A maximum of five images per patient can be taken with the Calcivis System.

Any adverse events observed or volunteered by the patient will be recorded.

The images generated with the Calcivis System will be stored digitally on the laptop provided. The software overlays the two sets of images (before and after application of the disclosing solution), resulting in a demineralization map of each imaged tooth.

At the end of the imaging procedures, the Investigator will review the images on the laptop and record any 'activity' as a YES or NO, according to areas of elevated bioluminescence. If there is no area of elevated bioluminescence on a selected tooth surface, that tooth will not be followed up at future visits. Only patients with at least one tooth surface showing areas of active demineralization will be followed up.

In the event that none of the teeth imaged from a patient show any active demineralization, that patient will be withdrawn from the study and will be replaced.

At the end of Visit 1, the Investigator will share the images of the teeth with the patient and discuss the results.

At the end of the imaging procedures, patients will complete a Patient Questionnaire.

In addition, the Investigator and Dental Nurse will each complete relevant sections of a User Questionnaire.

5.3 Study Visits 2, 3, 4 and 5 – post-de-bond

Subjects recruited prior to version 5 of the CSP have visits at 2, 4, 8 and 12 weeks post-de-bond. Subjects recruited from version 5 onwards have just Visit 2 at 4 weeks and Visit 3 at 8 weeks post-de-bond.

The Calcivis System will be prepared following the manufacturer's Instructions for Use. All teeth found to be active at Visit 1 will be cleaned according to the Tooth Cleaning Protocol (Appendix 2 of the Clinical Study Plan). Each free smooth surface will be air dried before being coded for ICDAS (0, 1, 2 or 3).

Images of the free smooth tooth surfaces will then be taken with the Calcivis System. If the first image of a selected tooth is not clear, it is acceptable to take a second image of the selected tooth. A maximum of five images per patient can be taken with the Calcivis System.

Any adverse events observed or volunteered by the patient will be recorded.

At the end of the imaging procedures, the Investigator will review the images on the laptop and record any 'activity' as a YES or NO, according to areas of elevated bioluminescence.

The Investigator will share the images of the teeth with the patient at the end of each visit.

At the end of the imaging procedures, patients will complete a Patient Questionnaire.

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

6.0 Sample Size

The sample size of 45 patients (with potentially a maximum of five teeth per patient) is not based on statistical power considerations, but as a number of patients that will enable useful data to be collected on the functionality and safety of the Calcivis System for assessing the activity of post-orthodontic lesions. In addition, the data may be used to support the design of future clinical studies.

Therefore, it is intended to recruit a total of 45 patients to the study, who have at least one tooth with an active, visible caries lesion on de-bond who will be followed up for 12 weeks.

It is expected that up to 100 patients may have to be recruited and imaged with the Calcivis System at de-bond, in order to find 45 patients with active lesions.

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. This population will be used for all summaries.

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 will not be imputed.

10.0 Patient Disposition and Pre-Imaging Information

10.1 Patient Disposition

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

The number of patients 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 patients in the safety population will be tabulated.

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

10.2 Demographic Characteristics

Demographic parameters will include date of birth, age and gender. 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 Orthodontic History

Details of orthodontic history will be listed, length of time in situ (years) will be summarized and the number and percentage of patients within each oral hygiene category (type of appliances and type of ligation) will be tabulated. Details of any re-mineralisation therapies will be listed and summarised.

10.5 Oral Hygiene

Details of oral hygiene will be listed and the number and percentage of patients within each oral hygiene category (which toothpaste used most often, type of toothbrush, frequency that teeth are brushed, use of mouthwash, frequency of mouthwash use and whether any other products are used) will be tabulated. Details of oral hygiene updates will be listed.

10.6 Calcivis System

Details of Calcivis System preparation and imaging set-up will be listed.

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

11.0 Luminescence

For each patient the percentage of teeth showing luminescence using the Calcivis System will be calculated. This will then be summarised over all patients for each visit. A plot of the percentage of teeth showing luminescence will also be presented over time. Additionally, the percentage of teeth showing luminescence will be summarised for each visit by Investigator.

12.0 Patient and User Questionnaires

Details of Patient and User Questionnaires will be listed and responses to each question will be summarised by visit 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 after the start of the baseline Calcivis System procedures. 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 on the listings.

An overall summary of adverse events, including the number of patients and number of events for each of the following categories will be provided: all PEAEs, all serious PEAEs, all PEAEs related to procedure, all serious PEAEs related to procedure, all PEAEs related to device, all serious PEAEs related to device and all PEAEs with an outcome of death. Related PEAEs will be those with a relationship of possible, probable or definite.

14.0 Interim Analysis

No interim analysis will be performed for this study.

15.0 Table Mock Ups

Table 1	Patient Disposition	All Patients
Table 2	Protocol Deviations	Safety Population
Table 3	Demography	Safety Population
Table 4	Orthodontic History	Safety Population
Table 5	Oral Hygiene	Safety Population
Table 6	Percentage of Teeth with Luminescence Over Time	Safety Population
Table 7	Percentage of Teeth with Luminescence by Investigator Over Time	Safety Population
Table 8	Patient Questionnaires	Safety Population
Table 9	User Questionnaires	Safety Population
Table 10	Adverse Events	Safety Population

16.0 Figure Mock Ups

No Figures are required for this study.

17.0 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	All Patients
Listing 2	Inclusion and Exclusion Criteria	All Patients
Listing 3	Population Assignment	All Patients
Listing 4	Protocol Deviations	Safety Population
Listing 5	Demography	Safety Population
Listing 6	Relevant Medical History and Medications	Safety Population
Listing 7	Orthodontic History	Safety Population
Listing 8	Remineralization Therapies	Safety Population
Listing 9	Oral Hygiene	Safety Population
Listing 10	Oral Hygiene Update	Safety Population
Listing 11	Calcivis System Preparation	Safety Population
Listing 12	Calcivis System Imaging	Safety Population
Listing 13	Post-Imaging Checklist	Safety Population
Listing 14	Patient Questionnaires	Safety Population
Listing 15	User Questionnaires	Safety Population
Listing 16	Adverse Events	Safety Population
Listing 17	Serious Adverse Events	Safety Population

Table 1
Patient Disposition
All Patients

	Overall (N=XX)
Attended Baseline	X (xx.x %)
Attended Week 2	X (xx.x %)
Attended Week 4	X (xx.x %)
Attended Week 8	X (xx.x %)
Attended Week 12	X (xx.x %)
Completed Study	X (xx.x %)
Withdrew from Study	X (xx.x %)
Reason for Withdrawal	
No teeth show active demineralization	X (xx.x %)
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 %)

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Table supported by Listings 1 & 3

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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 %)

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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 %)

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Table supported by Listing 5

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Table 4
Orthodontic History
Safety Population

		Overall (N=XX)
Length of Time in Situ (years)	n	X
	Mean	XX.XX
	SD	XX.XXX
	Minimum	XX.X
	Median	XX.XX
	Maximum	XX.X
Type of Appliances	Ceramic	X (xx.x %)
	Metal	X (xx.x %)
Type of Ligation	Conventional	X (xx.x %)
	Self-ligation	X (xx.x %)
Re-mineralisation Therapies	XXXXXXXXXXXXX	X (xx.x %)
	XXXXXXXXXXXXX	X (xx.x %)

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Table supported by Listings 7 and 8

Table 5
Oral Hygiene
Safety Population

		Overall (N=XX)
Type of Toothpaste Used Most Often	XXXXXXXXXXXXX	X (xx.x %)
	XXXXXXXXXXXXXX	X (xx.x %)
Type of Toothbrush	Manual	X (xx.x %)
	Electric	X (xx.x %)
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 %)

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Table supported by Listing 9

Table 6
Percentage of Teeth with Luminescence Over Time
Safety Population

	Percentage of Teeth with Luminescence	Overall (N=XX)
Baseline	n	X
	Mean	XX.X
	SD	XX.XX
	Minimum	XX
	Median	XX.X
	Maximum	XX
Week 2	…….	
…….		

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Table supported by Listing 12

Programming Note: Include all visits in this table

Table 7

Percentage of Teeth with Luminescence by Investigator Over Time

Safety Population

Investigator	Visit	Percentage of Teeth with Luminescence	Overall (N=XX)
XX	Baseline	N	X
		Mean	XX.X
		SD	XX.XX
		Minimum	XX
		Median	XX.X
		Maximum	XX
XX	Week 2	N	X
		Mean	XX.X
		SD	XX.XX
		Minimum	XX
		Median	XX.X
		Maximum	XX
……..			

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Table supported by Listing 12

Programming Note: Include all visits in this table

Table 8
Patient Questionnaires
Safety Population

Visit	Question	Response	Overall (N=XX)
Baseline	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 %)
	Did you find seeing the images of your teeth and having the dentist explain your situation helpful?	Helpful	X (xx.x %)
		Neither helpful nor unhelpful	X (xx.x %)
		Unhelpful	X (xx.x %)
Final Visit	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 %)
	Did you find seeing the images of your teeth and having the dentist explain your situation helpful?	Helpful	X (xx.x %)
		Neither helpful nor unhelpful	X (xx.x %)
		Unhelpful	X (xx.x %)

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Table supported by Listing 14

Table 9
User Questionnaires
Safety Population

Visit	Question	Response	Overall (N=XX)
Baseline	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 %)
	How easy was it to understand 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 %)
Final Visit	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 %)
	How easy was it to understand 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 %)

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Table supported by Listing 15

Table 10
Adverse Events
Safety Population

Category of Adverse Event	Overall (N=XX)	
	Number (%) of Patients	Number of Events
Any procedure emergent adverse event	X (xx.x%)	X
Any serious procedure emergent adverse event	X (xx.x%)	X
Any procedure emergent adverse event related to procedure	X (xx.x%)	X
Any serious procedure emergent adverse event related to procedure	X (xx.x%)	X
Any procedure emergent adverse event related to device	X (xx.x%)	X
Any serious procedure emergent adverse event related to device	X (xx.x%)	X
Any procedure emergent adverse event with an outcome of death	X (xx.x%)	X

Related events are those considered possibly, probably or definitely related.
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Table supported by Listings 16 & 17

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Listing 1
Patient Disposition
All Patients

Investigator Number	Patient Number	Informed Consent Date	Informed Consent Time	Did the Patient Complete the Study	Reason for Withdrawal
XX	YY	DDMMMYYYY	hh:mm	Yes	
	YY	DDMMMYYYY	hh:mm	No	Patient withdrawn – no teeth show active demineralization
	YY	DDMMMYYYY	hh:mm	No	Consent withdrawn by patient
	YY	DDMMMYYYY	hh:mm	No	Investigator withdrew patient
	YY	DDMMMYYYY	hh:mm	No	Lost to follow-up
	YY	DDMMMYYYY	hh:mm	No	Adverse event
	YY	DDMMMYYYY	hh:mm	No	Death
	YY	DDMMMYYYY	hh:mm	No	Other: XXXXXXXXXX

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Listing 2
Inclusion and Exclusion Criteria
All Patients

Investigator Number	Patient Number	Criterion Type	Criterion Number	Criterion Text	Criterion Response
XX	YY	Inclusion	1	Patient must be ≥12 years old	Yes
			2	Patient must have had orthodontic appliances placed on the upper incisors and / or canines for at least 12 months, and be ready for de-bond	Yes
			3	Patient must have at least one active white spot lesion identified by the Calcivis System immediately post de-bond	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) or within the follow-up period	No
			2	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
			3	Pregnant and/or nursing mothers	No

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Listing 3
Population Assignment
All Patients

Investigator Number	Patient Number	Safety Population
XX	YY	Yes
	YY	No

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Listing 4
Protocol Deviations
Safety Population

Investigator Number	Specific to One Patient	Patient Number	Date of Protocol Deviation	Details of Protocol Deviation	Reason for Protocol Deviation	Date Reported to Calcivis	Action Taken
XX	Yes	YY	DDMMMYYY	XXXXXXXXXX	Informed Consent Process	DDMMMYYY	XXXXXXXXXX
	No	YY	DDMMMYYY	XXXXXXXXXX	Inclusion/Exclusion	DDMMMYYY	XXXXXXXXXX
		YY	DDMMMYYY	XXXXXXXXXX	Study Procedure	DDMMMYYY	XXXXXXXXXX
		YY	DDMMMYYY	XXXXXXXXXX	Other: XXXXXXX	DDMMMYYY	XXXXXXXXXX

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Listing 5
Demography
Safety Population

Investigator Number	Patient Number	Date of Birth	Age[1]	Gender
XX	YY	DDMMMYYYY	xx	Male
	YY	DDMMMYYYY	xx	Female
	YY	DDMMMYYYY	xx	
	YY	DDMMMYYYY	xx	
	YY	DDMMMYYYY	xx	

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

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Listing 6
Relevant Medical History and Medications
Safety Population

Investigator 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

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Listing 7
Orthodontic History
Safety Population

Investigator Number	Patient Number	Date Appliances First Placed	Length of Time In Situ	Type of Appliance	Type of Ligation
XX	YY	DDMMMYYYY	xx	Ceramic	Conventional
	YY	DDMMMYYYY	xx	Metal	Self-ligation
	YY	DDMMMYYYY	xx		
	YY	DDMMMYYYY	xx		
	YY	DDMMMYYYY	xx		

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Listing 8
Remineralization Therapies
Safety Population

Investigator Number	Patient Number	Name of Toothpaste/ Treatment	Dose	Frequency	Start Date	Stop Date	Ongoing
XX	YY	XXXXXXXXXXX	xx	XXXXXXXXXXX	DDMMMYYYY	DDMMMYYYY	Yes
	YY	XXXXXXXXXXX	xx	XXXXXXXXXXX	DDMMMYYYY	DDMMMYYYY	No
	YY	XXXXXXXXXXX	xx	XXXXXXXXXXX	DDMMMYYYY	DDMMMYYYY	
	YY	XXXXXXXXXXX	xx	XXXXXXXXXXX	DDMMMYYYY	DDMMMYYYY	
	YY	XXXXXXXXXXX	xx	XXXXXXXXXXX	DDMMMYYYY	DDMMMYYYY	

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Listing 9
Oral Hygiene
Safety Population

Investigator Number	Patient Number	Question	Response	Details
XX	YY	Which toothpaste do you use most often?	XXXXXXXXX	
		Which type of toothbrush do you use?	Manual	
			Electric	
		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	

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Listing 10

Oral Hygiene Update

Safety Population

Investigator Number	Patient Number	Visit	Has Your Dentist/Hygienist Recommended The Use of Any Dental Products Since Your Visit	Dental Product	Dose	Frequency
XX	YY	X	Yes	XXXXXXXXXXXXXX	XX.X	XXXXXXXX
		No				

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Programming Note: Include all visits in the listing

Listing 11
Calcivis System Preparation
Safety Population

Investigator Number	Patient Number	Visit	Question	Response	Time Procedures Started
XX	YY	Baseline	Has the Calcivis System been set up according to the manufacturer's Instructions for Use?	Yes	HH:MM
				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 the selected tooth surfaces?	Yes	
				No	

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Programming Note: Include all visits in the listing

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Listing 12
Calcivis System Imaging
Safety Population

Investigator Number	Patient Number	Visit	Visit Date	Tooth	Tooth ID	ICDAS Code	Number of Images	Image to be Used	Signal
XX	YY	Baseline	DDMMMYYYY	1	xx	1	1	1	Yes
				2	xx	2	2	2	No
				3	xx	3	NA		NA
				4	xx				
				5	xx				

Note: Based on the protocol version enrolled under, potentially up to five teeth can be imaged if only one image per tooth, and a maximum of two images per any one tooth
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Programming Note: Include all visits in the listing. Only list teeth that are imaged.

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Listing 13
Post-Imaging Checklist
Safety Population

Investigator Number	Patient Number	Visit	Visit Date	Did any Adverse Events Occur?	Were Images Reviewed with the Patient?	Has the Patient Been Given a Patient Questionnaire to Complete?	Has Final Oral Exam Been Carried Out?
XX	YY	Baseline	DDMMMYYYY	Yes	Yes	Yes	NA
				Yes	Yes	No	NA
				No	Yes	Yes	NA
				Yes	No	Yes	NA
				No	Yes	No	NA
				Yes	No	No	NA
				No	No	Yes	Na
				No	No	No	NA
		Week 2		Yes			Yes
				Yes			No
				Yes			Yes
				No			Yes
				Yes			No
				No			No
				No			Yes
				No			No

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Programming Note: Include all visits in the listing

Listing 14
Patient Questionnaires
Safety Population

Investigator Number	Patient Number	Visit	Question Number	Question Text	Response	Comments
XX	YY	Baseline	1	How would you rate your overall experience with the Calcivis System?	Good	xxxxxx
					Neither good nor bad	
					Bad	
		Final Visit			Helpful	
					Neither helpful nor unhelpful	
					Unhelpful	

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

Listing 15
User Questionnaires
Safety Population

Investigator 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	How easy was it to understand the instructions provided, sufficient for you to understand how to use the Calcivis system?	Easy Neither easy nor difficult Difficult	XXXXXXXXXX
					5	What improvements could be made to the Calcivis System, if any?		XXXXXXXXXX

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Listing 16
Adverse Events
Safety Population

Inv Name/ Inv 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 From User Error?	SAE?
XXXXX/ XX	YY	1 *	xxxxxxxxxxx	DDMMMYYYY	xxxxx	DDMMMYYYY/ DDMMMYYYY DMMMYYYY/ Ongoing	Continued/ ongoing Recovered Recovered with sequelae Death	Mild Moderate Severe	None Medical Therapies Procedural Other: XXXXXX	Unrelated Possible Probable Definite	Unrelated Possible Probable Definite	Yes No	Yes No	Yes No

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* Procedure emergent adverse event.

Listing 17
Serious Adverse Events
Safety Population

Inv Name/ Inv Number	Patient Number	No.	Verbatim Term	Onset Date/ Stop Date	Date Became Serious	Date Reported to Sponsor	Reason for Serious	Is the AE Unanticipated?
XXXXXXX/ XX	YY	1 *	xxxxxxxxxx	DDMMMYYYY/ DDMMMYYYY DMMMYYYY/ Ongoing	DDMMMYYYY	DDMMMYYYY	Death	Yes
							Life-threatening illness or injury	No
							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	

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* Procedure emergent adverse event.