SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name:	Caries detection product with drug or biologic
Device Trade Name:	CALCIVIS Imaging System
Device Procode:	QJX
Applicant's Name and Address:	CALCIVIS Limited Nine Edinburgh BioQuarter 9 Little France Road Edinburgh EH16 4UX United Kingdom
Date of Panel Recommendation:	None
Premarket Approval Application (PMA) Number:	P170029
Date of FDA Notice of Approval:	3/07/2023

II. INDICATIONS FOR USE

The CALCIVIS Imaging System is intended to be used by dental healthcare professionals on patients (6 years and older) with, or at risk of developing, demineralization associated with caries lesions, on accessible coronal tooth surfaces.

The CALCIVIS Imaging System is indicated for use to provide images of active demineralization on tooth surfaces, as an aid to the assessment, diagnosis and treatment planning of demineralization associated with caries lesions.

III. CONTRAINDICATIONS

There are no known contraindications.

IV. WARNINGS AND PRECAUTIONS

The Warnings and Precautions can be found in CALCIVIS Imaging System labeling.

V. DEVICE DESCRIPTION

A. Overview of the CALCIVIS Imaging System

The CALCIVIS Imaging System consists of two main components that are used in conjunction to enable a Dental Practitioner to obtain images of active demineralization on accessible coronal tooth surfaces: (1) CALCIVIS Imaging Device Kit and (2) CALCIVIS Imaging Kit.

The CALCIVIS Imaging Device Kit includes an intra-oral camera within the applicator main body of the Intra-oral Imaging Device and is used with associated software, which allows both video streaming of images and capture of still images. The Intra-oral Imaging Device contains a syringe applicator mechanism that dispenses a small amount (25µl) of CALCIVIS Photoprotein onto the tooth under investigation. As an accessory to the CALCIVIS Imaging Device Kit, the CALCIVIS Function Check Kit provides a gross check that the system is setup correctly to function for applicator dispensing and luminescent image capturing; it is not intended for calibration purposes.

The key component of the CALCIVIS Imaging Kit is the CALCIVIS Photoprotein that contains a non-therapeutic biologic component (recombinant photoprotein) to visualize luminescence of unbound calcium associated with active demineralization of caries lesions. When the photoprotein in the reconstituted CALCIVIS Photoprotein solution binds with free calcium ions, it emits light (in the visible spectrum) that is captured by the imaging system. The sequence of image capture and CALCIVIS Photoprotein application are controlled using the custom application software from the CALCIVIS Imaging Device Kit.

The overall CALCIVIS Imaging System comprises:

1) CALCIVIS Imaging Device Kit

Consists of:

- CALCIVIS Intra-oral Imaging Device
- CALCIVIS Device Cradle
- CALCIVIS (Imaging) Software on USB card
- CALCIVIS User Manual

a. Accessory - CALCIVIS Function Check Kit

Consists of:

- CALCIVIS Function Check Kit
- Instructions for use

2) CALCIVIS Imaging Kit

Consists of:

- CALCIVIS Photoprotein (freeze dried in vials)
- CALCIVIS Diluent for reconstitution (containing 0.9% anti-microbial preservative benzyl alcohol)
- Vial Adaptors to allow for needle-less reconstitution
- Device syringes
- Medical wipes used to clean the top of the multi-use vial adaptor
- CALCIVIS Applicator sheath single use components
- Instructions for use

Figure 1. CALCIVIS Imaging Device loading and fully assembled CALCIVIS Imaging Device on stand

Overall, the CALCIVIS Imaging System is intended to provide images of active demineralization on tooth surfaces, as an aid to the assessment, diagnosis and treatment planning of demineralization associated with caries lesions. The CALCIVIS Imaging System is for use by trained dental healthcare professionals.

B. CALCIVIS Imaging Device Kit

The CALCIVIS Imaging Device Kit incorporates an intraoral camera within the Intra-oral Imaging Device applicator main body. The intraoral camera system is also housed with an integrated syringe applicator component for dispensing the CALCIVIS Photoprotein onto the tooth surfaces. Images from the intraoral camera are viewed through the CALCIVIS (Imaging) Software that controls image processing and display, along with allowing for overlapping of visual and luminescence images. The entirety of the Intra-oral Imaging Device is available as a one-size-fits-all handheld device component. The CALCIVIS Applicator sheath (from the CALCIVIS Imaging Kit) provides single use components that will be removed and replaced after each set of assessments on individual patients have been completed.

Figure 2. Identification and locations of parts for the CALCIVIS Intra-oral Imaging Device

C. CALCIVIS Imaging Kit

The CALCIVIS Photoprotein is the main component of the CALCIVIS Imaging Kit, and it is a low bioburden, non-therapeutic biologic component (recombinant photoprotein) for exclusive use with the CALCIVIS Imaging System. The CALCIVIS Photoprotein is for use in the oral cavity only, and it is sprayed onto a tooth surface by the intraoral applicator device at approximately 3µg per tooth (in 25µl volume) with a maximum of 20 teeth examined at any one visit.

Other constituents in the CALCIVIS Photoprotein include a low concentration of EDTA (ethylenediaminetetraacetic acid) and pharmacopeia or food grade materials that provide stabilizing sugars and buffer solution.

Mechanism of Action

The CALCIVIS Photoprotein has no intended therapeutic effect. It is not dependent upon being metabolized to reach its target site nor perform its function (i.e., emission of light on contact with free calcium ions).

CALCIVIS Photoprotein is a calcium-regulated, bioluminescent photoprotein (produced in nature by marine organisms). The CALCIVIS Photoprotein tertiary structure is a compact globule containing four helix-turn-helix (HTH) motifs; the second of which does not bind Ca^{2+} ions. The other 3 HTH motifs each bind a single charged calcium ion. The cofactor of coelenterazine is non-covalently bound within the helix motifs. A clear relationship can be observed between the luminescence intensity and calcium ion concentration over a specific range that is limited by photoprotein concentration. This mechanism of action renders areas of calcium loss visible using the specialized intraoral camera system, and the luminescence images acquired provide aid for assessment of demineralization associated with caries lesions. Specifically, the system camera detects the luminescence to generate a demineralization map of the tooth and present to the healthcare professional as part of a systematic approach to caries management.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are several other alternatives used to detect tooth structure changes for clinician diagnosis of dental caries and treatment planning:

- Visual inspection with and without tactile exploration with a probe
- Radiograph images
- Caries detection dyes
- Transillumination
- Optically-based methodology (i.e., light induced fluorescence, laser induced fluorescence, near infrared)
- Use of electrical current to show existence of decay and carious lesions in a tooth

Each alternative has its own advantages and disadvantages. A patient should fully discuss these alternatives with his/her physician and/or dentist to select the method(s) that best meets expectations and lifestyle.

VII. MARKETING HISTORY

The CALCIVIS Imaging System has a CE mark, and it has been marketed in the United Kingdom since March 2018. The CALCIVIS Imaging System has never been withdrawn from marketing for any reason related to its safety or effectiveness.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Below is a list of the potential adverse effects (e.g., complications) associated with the use of the CALCIVIS Imaging System.

- Sensitivity or allergic reaction to photoprotein resulting in tissue irritation
- Sensitivity or allergic reaction to applicator plastic or Thermoplastic Elastomer (TPE) resulting in tissue irritation
- Not suitable for use if teeth cannot be accessed
- Not suitable if patient has limited ability to open their mouth or a small mouth opening that impacts the device intraoral placement and can result in risk of tissue trauma or patient discomfort
- Discomfort or jaw pain from prolonged usage
- Infection stemming from cross contamination if single use items are reused
- Choking hazard from patient biting down on applicator device components
- Unwanted shock due to malfunction of the electrical or power source components
- Risk from electromagnetic fields, which might interfere with the functions of implanted systems (such as pacemakers)

No adverse events were reported in the clinical studies; please see Section X below.

IX. SUMMARY OF NONCLINICAL STUDIES

The following nonclinical studies were performed for the CALCIVIS Imaging System:

A. CALCIVIS Photoprotein Activity Testing

The laboratory studies to support the safety and effectiveness of the CALCIVIS Imaging System for the CALCIVIS Photoprotein activity testing were performed to demonstrate calcium ion detection, diagnosis and treatment planning of demineralization, and caries activity assessment. A summary of the CALCIVIS Photoprotein activity testing and results can be found in **Table 1** below, followed by the corresponding written descriptions.

Table 1. Summary of CALCIVIS Photoprotein Activity Testing

	Test	Purpose	Acceptance Criteria	Results
1	Detection of calcium ions in solution	Assess bioluminescent emission from the photoprotein following binding of free calcium ions.	Increasing signal with increasing calcium ion concentration.	Pass
2	Detection of demineralization from acid-challenge on enamel blocks	Assess the system's ability to detect enamel demineralization from acid-challenge over time using enamel blocks.	Visual and numerical differentiation of treated and untreated enamel blocks.	Pass
3	Activity status of caries lesions on sample enamel blocks	Evaluate the activity of caries lesions developed on sample enamel blocks.	Visual increase in luminescence within the lesion area after generation of lesion.	Pass
4	Detection of demineralization from acid challenge on extracted teeth	Assess the system's ability to detect enamel demineralization from acid-challenge over time using extracted teeth.	Visual and numerical differentiation of treated and untreated teeth.	Pass

5	Detection of remineralization	Assess whether the CALCIVIS Imaging System can be used to detect enamel demineralization via the assessment of increased concentration of free calcium ions.	Little or no signal for sound surface at initial baseline. Luminescence signal detected after generation of lesion over 100 days compared to little or no signal after 100 days remineralization for the inactive control.	Pass
6	Caries activity assessment on extracted teeth	Assessment of luminescence level in extracted teeth with active / inactive lesions and sound surfaces.	Luminescence level detected in extracted teeth with active lesions compared to little or no signal detected for the control samples with either inactive lesions or sound surfaces.	Pass
7	Reproducibility of consecutive images from extracted teeth	Assess reproducibility of signal on repeated imaging of extracted teeth.	Exploratory experiment with no acceptance criteria.	The images showed reproducible and persistent pattern for up to 5 consecutive images, after which the signal started to diminish due to depletion of available calcium ions.
8	Photoprotein activity range	Assess range of photoprotein activity/protein concentration in which no false positive or false negative images are seen.	Exploratory experiment with no acceptance criteria.	A working range of 50 to 150% (equivalent to 53 – 160µg/ml photoprotein) determined to be acceptable for displaying images of active lesions and demineralization on enamel blocks.

1. ***Detection of Calcium Ions in Solution***

The primary mode of action of the CALCIVIS Imaging System is the bioluminescent emission from the photoprotein following binding of free calcium ions. The photoprotein is highly specific to calcium ions. This study demonstrated the ability of

the system to detect calcium ions in aqueous solution with increasing calcium ion concentration, following the application of photoprotein solution to stock solutions of aqueous calcium chloride.

2. ***Detection of Demineralization from Acid-Challenge on Enamel Blocks***

As the enamel surface undergoes demineralization, calcium ions are liberated from the hydroxyapatite crystal structure, which can then be detected by the CALCIVIS imaging system. This study demonstrated the ability of the system to detect enamel demineralization from applied acid-challenges over time. By exposing a single block to successive acid treatments, the gradual increase in demineralization of the enamel surface can be captured.

3. ***Activity Status of Caries Lesions on Sample Enamel Blocks***

The CALCIVIS Imaging System was used to evaluate the activity of caries lesions on sample enamel blocks. The results showed a visually discernable increase in luminescence within the lesion areas over the evaluated time points at days 7, 10, and 14, indicating progression of the carious lesions and increased demineralization of the enamel surfaces.

4. ***Detection of Demineralization from Acid Challenge on Extracted Teeth***

Extracted teeth were subjected to successive acid challenges using the replicated conditions of 30% phosphoric acid at a 10µL application for each evaluated occlusal surface. The images captured showed an increasing luminescent signal following successive acid-challenge treatments, illustrating the relationship between acid demineralization and increased detection of free calcium ions.

5. ***Detection of Remineralization***

The CALCIVIS Imaging System was used to assess the activity of *ex-vivo* caries lesions prepared using a validated multi-species bacteria model, which also incorporates the assessment of the prepared lesions over time that have been inactivated via a standardized 100 day remineralization protocol.[1,2] The active lesions evaluated showed a clear increase in luminescence in and around the area of interest, which then significantly reduced following the 100-day remineralization procedure, down to an inactive level which is comparable to that seen on sound enamel surfaces at the initial baseline measurements.

6. ***Caries Activity Assessment on Extracted Teeth***

The caries activity was assessed using the CALCIVIS Imaging System on extracted teeth samples with the following conditions: (1) active lesions, (2) inactive lesions, and (3) sound surfaces with no lesions. The *ex-vivo* teeth with active lesions were identified by a specialist cariologist according to ICDAS (International Caries Detection and

Assessment System) guidelines. The CALCIVIS Imaging System showed increased luminescence around the areas of these teeth diagnosed as active caries lesions. For the inactive lesions test group, the results showed no increased luminescence in the areas of interest. Lastly, the control baseline group evaluating sound surfaces on extracted teeth showed no spots of luminescence.

7. ***Reproducibility of Consecutive Images from Extracted Teeth***

The use of the CALCIVIS Imaging System across consecutive image sets of the same extracted tooth was shown to be reproducible and persistent. The results from repeated imaging of the same tooth surface showed reproducible persistence of low level signaling for up to 5 consecutive images, after which the signal started to diminish due to depletion of the pool of calcium ions available to the photoprotein.

8. ***Photoprotein Activity Range***

The concentration of the reconstituted photoprotein solution is approximately 130µg/ml. The photoprotein activity range studies were conducted to assess the working activity range of the photoprotein. The CALCIVIS Photoprotein displayed a wide working range, where images of active lesions and demineralization on enamel blocks were still clearly seen at activities as low as 50%. Furthermore, the untreated sections of the enamel block samples showed little variability of luminescence over the range of 50 – 150% (equivalent to 53 – 160µg/ml photoprotein).

B. Design Verification Testing

Design verification testing (DVT) was performed to confirm the design of the CALCIVIS Imaging System met the intended purpose for the end user through hands-on assessment with dental healthcare professionals. The DVT covered four areas to verify the user requirements have been met.

- Configuration and Usability
- Image Capture Characteristics
- Photoprotein Disclosing Solution Delivery and Operational Characteristics
- Applicator Characteristics

A summary of the DVT and results can be found in **Table 2**.

Table 2. Design Verification Testing

Test	Purpose	Acceptance Criteria	Results
Configuration and Usability	Assess the configuration and usability characteristics of the CALCIVIS Imaging System to confirm the design meets the user requirement specifications.	Confirm configuration and usability characteristics.	Pass
Image Capture Characteristics	Assess the image capture characteristics of the CALCIVIS Imaging System to confirm the design meets the user requirement specifications.	In focus and acceptable quality images.	Pass
Photoprotein Disclosing Solution Delivery and Operational Characteristics	Assess the delivery method and operational characteristics of the photoprotein solution supplied with the CALCIVIS Imaging System to confirm the design meets the user requirement specifications.	Correct volume dispensed with evenly applied and reproducible coverage of the area of interest.	Pass
Applicator Characteristics: Prevention of Cross – Contamination	Assess the applicator / device shield characteristics of the CALCIVIS Imaging System to confirm the design meets the user requirement specifications.	Confirm the device is not contaminated with oral fluids.	Pass
Applicator Characteristics: Photoprotein Dispensing	Demonstrate that the applicator complied with the design requirements by showing the samples under testing can successfully apply a photoprotein solution to the surface of a tooth with acceptable coverage and capture images of acceptable visual quality.	In focus and acceptable quality images.	Pass

C. Biocompatibility Studies

Biocompatibility testing of the CALCIVIS Imaging system was conducted for the patient-contacting components of the CALCIVIS Applicator as used with the CALCIVIS Intra-oral Imaging Device and the CALCIVIS Photoprotein within the CALCIVIS Imaging Kit. All biocompatibility testing was conducted in accordance with

the Biological Evaluation of Medical Devices - International Standard ISO 10993-1, United States Pharmacopoeia (USP), and American Dental Association (ADA) guidelines. All biocompatibility studies had passing results and are summarized in **Tables 3 and 4**.

1. ***CALCIVIS Applicator***

The CALCIVIS Applicator is categorized as a surface device that is direct patient contacting with limited contact duration (≤24 hours). The testing to support the biocompatibility of the CALCIVIS Applicator is found in **Table 3** below.

Table 3. Biocompatibility Testing of CALCIVIS Applicator

Test	Test Details	Material Tested	Results
MTS Cytotoxicity test (ISO 10993-5)	To determine potential for cytotoxicity of the test article extract.	Patient contact applicator components.	No evidence of cell lysis or cytotoxicity. The test article met the requirements of the test and showed no cytotoxic potential.
Oral mucosal irritation study in hamster (ISO 10993-10)	To screen test article extracts for potential to produce irritation.	Patient contact applicator components.	Considered a non-irritant to the oral mucosa.
ISO Guinea Pig Maximization Sensitization test (ISO 10993-10)	Tests for irritation and skin sensitization.	Patient contact applicator components.	No evidence of causing delayed dermal contact sensitization in the guinea pig. The test article was not considered a sensitizer.

2. ***CALCIVIS Photoprotein***

The CALCIVIS Photoprotein is categorized as a surface device that is direct patient contacting with limited contact duration (≤24 hours). The CALCIVIS Photoprotein is used in low dosage with transient application in solution (less than 1 minute) before being immediately washed from the mouth after use. The testing to support the biocompatibility of the CALCIVIS Photoprotein is found in **Table 4** below.

Table 4. Biocompatibility Testing of CALCIVIS Photoprotein

Test	Test Details	Material Tested	Results
Cytotoxicity test (USP39 – NF 34)	USP standard: Agarose overlay method	CALCIVIS Photoprotein	No evidence of cell lysis or toxicity. The test article met the requirements of the test and showed no cytotoxic potential.
Oral toxicity (ADA Specification No. 41)	Tested according to American Dental Association Specification No. 41 guidelines (using rats)	CALCIVIS Photoprotein	No mortality or significant evidence of toxicity. Not considered toxic at a dose of 2g/kg by the oral route.
Oral mucosal irritation (ISO 10993-10)	Study in hamsters was conducted based on the requirements of ISO 10993-10, Biological Evaluation of medical Devices – Part 10. Tests for irritation and skin sensitization.	CALCIVIS Photoprotein	Considered a non-irritant to the oral mucosa.
ISO Guinea Pig Maximization Sensitization test (ISO 10993-10)	Study was conducted based on the requirements of ISO 10993-10, Biological Evaluation of Medical Devices – Part 10. Tests for irritation and skin sensitization.	CALCIVIS Photoprotein	No evidence of causing delayed dermal contact sensitization in the guinea pig. The test article was not considered a sensitizer.

Based on the biocompatibility testing, combined with the potential negligible systemic exposure of the CALCIVIS Photoprotein, the additional considerations for local toxicity and systemic toxicity from the CALCIVIS Photoprotein under the expected clinical use conditions are not found to present significant risks to patients.

D. Electrical Safety Testing

The CALCIVIS Imaging Device has been tested for electrical safety in compliance to IEC 60601-1. The electrical safety for CALCIVIS Imaging Device was found sufficient based on the labeling mitigations and test results to account for power supply, creepage, clearance, leakage, and insulation for patient protections.

The equipment connected to this product must conform to IEC standards (i.e., IEC 60601-1 for Medical electrical equipment, IEC 60950-1 for Information technology equipment, IEC 60065 for Audio, video and similar electronic apparatus). In addition, equipment connected to this product should be connected to the power supply via an isolation transformer and have at least basic insulation to conform to IEC 60601-1.

E. Electromagnetic Compatibility (EMC) Testing

The CALCIVIS Imaging Device has undergone Electromagnetic Compatibility (EMC) testing for compliance to IEC 60601-1-2 and IEC 60601-2. All the EMC tests conducted for the radiated and conducted immunity and the radiated and conducted emissions were performed satisfactorily and at the correctly specified levels. All results for EMC testing were found to pass, including the summarized evaluations in **Table 5** below.

Table 5. Electromagnetic Compatibility Testing for Interference and Emissions

Immunity Against:	Compliance Level	Electromagnetic Environment	Results
Radiated RF EM fields (IEC 61000-4-3)	3V/m 80-2700MHz Plus Proximity Fields	Power frequency magnetic fields should be at levels characteristic of a typical location in a typical commercial or hospital environment.	Pass
Power Frequency Magnetic Field 50/60Hz (IEC 61000-4-8)	30A/m		Pass

F. Software Verification and Validation

The software used within the CALCIVIS Imaging system was verified and validated in accordance with the following FDA Guidance documents:

- "Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices"
- "Content of Premarket Submissions for Management of Cybersecurity in Medical Devices"

The software for the CALCIVIS Imaging system is identified to have a moderate level of concern. The software information and validation included a description of the software, Device Hazard Analysis, Software Requirements Specifications, Architecture Design Chart, Software Design Specifications, Traceability Analysis/Matrix, Software Development Environment Descript, Verification and Validation Testing, Revision level history, Unresolved anomalies, and Cybersecurity to demonstrate overall verification of the system functionality.

G. Sterilization and Shelf Life (Product Stability)

The CALCIVIS Imaging System is to be used non-sterile. The shelf life (product stability) descriptions of the components in the CALCIVIS Imaging System are discussed below.

1. ***CALCIVIS Imaging Device Kit***

Device functional testing and packaging system testing were conducted following both accelerated and real time aging to demonstrate that the CALCIVIS Applicator as used with the CALCIVIS Intra-oral Imaging Device performed within specifications for the labeled shelf life of 12 months. The shelf life claim is supported by both bioburden testing and functionality testing (i.e., leak test, function test for fluid delivery, imaging test, applicator fit test) to demonstrate maintained safe and effective use.

For the shelf life testing of the CALCIVIS Function Check Kit accessory, both accelerated and real-time age testing were conducted to support the shelf life claim of 12 months. The completed shelf life test results demonstrated the CALCIVIS Function Check Kit is stable and within specifications for imaging assessment over the shelf life duration.

2. ***CALCIVIS Photoprotein***

Finished product stability studies were developed according to International Conference for Harmonization (ICH) guidelines to establish the shelf life of 24 months for the CALCIVIS Photoprotein. The product stability testing included the following evaluations:

- Stability data to show the finished product met the potency specifications up to 24 months.
- Stability data for pH, moisture content, and reconstitution time up to 24 months at room temperature, which met the stability specifications.
- Stability program assessment to include testing for purity, specific activity, and protein concentration for supporting the shelf life duration.

The data generated from the product stability studies were found to support a shelf life of 24 months for the CALCIVIS Photoprotein.

H. Chemistry Manufacturing Control (CMC) Release Testing

Where applicable, ICH guidelines were followed for the testing routinely performed on the CALCIVIS Photoprotein as part of Chemistry Manufacturing Control (CMC).

Final Product CMC release testing is shown in **Table 6** below.

Table 6. Final Product CMC Release Testing

Description	Method	Specification
Identity		
Appearance	Visual examination	Score 3, 4 or 5 for Cake pre-reconstitution Clear liquid upon reconstitution (on reconstitution with 4.17mL Calcivis Diluent)
Specific Activity Assay (on reconstitution with 4.17ml Calcivis Diluent)	Luminescence in presence of free calcium ions. (Dilution to 1.5µg/ml)	4.39 to 8.15 Vmax/0.06µg protein (Immediately upon reconstitution)
Purity		
pH (on reconstitution with 4.17ml Calcivis Diluent)	Potentiometric USP<791>; Ph. Eur 2.2.3	7.0 ± 1.0
Residual Water	Karl Fischer method	<5%
Reconstitution time (on reconstitution with 4.17ml Calcivis Diluent)	Manual reconstitution	<20 seconds
Specific Activity Assay (on reconstitution with 4.17ml Calcivis Diluent)	Luminescence in presence of free calcium ions. (Dilution to 1.5µg/ml)	4.39 to 8.15 Vmax/0.06µg protein (Immediately upon reconstitution)
Bioburden (on reconstitution with 4.17ml WFI)	USP <61>, <62>; Ph. Eur. 2.6.12, 2.6.13	Total Aerobic microbial count ≤100cfu/ml Total yeast and molds count ≤10cfu/ml Absence of specific organisms: *Staphylococcus Aureus, Pseudomonas Aeruginosa, E. coli*
Potency		
Potency Assay (on reconstitution with 4.17ml Calcivis Diluent)	Luminescence in presence of free calcium ions. Fixed dilution (1:67)	90 – 150% reference material (Immediately upon reconstitution)
Protein Content (on reconstitution with 4.17ml Calcivis Diluent)	Total protein determination in accordance with USP <1057>, Ph. Eur. procedure (section 2.5.33) using A280 determination.	129 ± 19µg/ml (110 – 148µg/ml)

X. SUMMARY OF PRIMARY CLINICAL STUDY

The applicant performed a clinical study to establish a reasonable assurance of safety and effectiveness to provide images of active demineralization on accessible coronal tooth surfaces with the CALCIVIS Imaging System for use as an aid to the assessment, diagnosis and treatment planning of demineralization associated with caries lesions. Data from this clinical study were the basis for the PMA approval decision. A summary of the clinical study is presented below. The primary clinical study was titled "CAL-02-2014 Clinical Study to Evaluate the Safety and Performance of the Calcivis® System for Identifying Active Demineralization on Tooth Surfaces."

A. Study Design

Patients were treated between January 14, 2017, and May 04, 2017. The database for this PMA reflected data collected through 11 May 2017 and included 111 patients. There were four investigational sites.

The study was a prospective, multi-site, non-randomized clinical study to evaluate both the clinical safety and performance of the CALCIVIS Imaging System for identifying active demineralization on the surfaces of teeth on a patient population ≥ 6 years old. The study was carried out under Clinical Study Plan CAL-02-2014.

The study was conducted by five, General Dental Practitioners, in four United Kingdom Dental Practices. Investigators were selected according to qualification, experience, availability of suitable patients, adequate facilities, and dental personnel to conduct the study. Patients were recruited from routine practice lists over a four-month period, who had one unrestored, accessible, free smooth buccal surface on a canine or incisor, identified with no visible lesion (coded ICDAS 0 – SOUND), and/or one unrestored, accessible, erupting or erupted molar or pre-molar with an ACTIVE visible lesion identified (coded ICDAS 2 or 3). ICDAS 1 lesions (lesions with first visible enamel changes on the ICDAS scale) were not evaluated in the clinical study to investigate the use of the CALCIVIS Imaging System.

Patients who met the inclusion and exclusion criteria, who could adhere to the study schedule and give written informed consent, were invited to participate in the clinical study. Study patients were recruited between January and May 2017, with each Investigator contributing approximately equal numbers of teeth from each tooth population.

The study assessed the agreement between the CALCIVIS Imaging System and dentist rating from captured images of suitable teeth in two teeth populations: 'no visible lesions - sound', and 'active lesions' coded ICDAS 2 or 3. After all the images were taken and verified as acceptable by the originating Investigator, an independent review of the Calcivis images was undertaken to assess the presence or absence of elevated luminescence on the surface to the teeth imaged with the CALCIVIS

imaging system. This was carried out by one of the other Investigators and the data used for the primary analysis.

Subjects provided no more than one tooth of each tooth population. The study sample size was calculated in terms of the number of teeth of each tooth population required. The number of subjects required was 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 were 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: $p_{a,i}=0.5$
vs.
H1: $p_{a,i}>0.5$

for each tooth status population i, i.e., 'no visible lesions' and 'active lesions,' 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.

The statistical analysis was performed using SAS version 9.2 or higher. All statistical tests were conducted one-sided with a 2.5% level of significance and no adjustment made for multiple testing.

All patients on whom the CALCIVIS Imaging System was used were included in the Safety Population. The Agreement Population included all teeth on which there was a dentist ICDAS score.

The percentage agreement of the original dentist ICDAS score and the independent reviewer Calcivis finding ('no luminescence' or 'luminescence') was presented, along with an exact one-sided 97.5% confidence interval and p-value comparing the percentage agreement to 0.5 for the following:

- Teeth rated with 'no visible lesion' that are assessed as 'no luminescence' by the Calcivis imaging system;
- Teeth rated with an 'active lesion' that are assessed as 'luminescence' by the Calcivis imaging system.

The analysis of agreement was performed on the Agreement Population. Patient and User questionnaire data and adverse events were summarized descriptively for the Safety Population. There was no interim analysis for this study.

There was no core laboratory use, Data and Safety Monitoring Board (DSMB) or Independent Data Monitoring Committees (IDMC). However, after all the images were taken and verified as acceptable by the originating Investigator, an independent review of the Calcivis images was undertaken to assess the presence or absence of elevated luminescence on the surface of the tooth imaged with the CALCIVIS imaging system. This was carried out by one of the other Investigators and the data used for the primary analysis.

Sound tooth surfaces were considered the negative control.

1. Clinical Inclusion and Exclusion Criteria

   Enrollment in the CAL-02-2014 clinical study was limited to patients who met the following inclusion criteria.

   - Patient must be ≥ 6 years old
   - For tooth selection (see **Table 7** below), 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
     - 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
   - Patient and/or parent or guardian must be willing and able to give written informed consent
   - Patient and/or parent or guardian must be willing and able to adhere to study schedule

Table 7. Tooth Selection

Tooth status population	Exemplar tooth type and location	Additional criteria
Sound tooth	[a]Canine or incisor Away from gingival margin	Enamel should be shiny and feels hard and smooth when the tip of a probe is moved gently across the surface
Active Lesion	[b]Erupting or erupted Molars Fissure pits of occlusal surface	Surface of enamel should be whitish/yellowish opaque with loss of luster; feels rough when the tip of a probe is moved gently across the surface.[c] Lesion should be in a plaque stagnation area i.e. pits and fissures; approximally, near the gingival surface below the contact point

[a] Buccal surfaces of canines or incisors
[b] Occlusal surfaces of permanent molars and premolars
[c] Coded ICDAS 2 or 3

Patients were <u>not</u> permitted to enroll in the CAL-02-2014 clinical study if they met any of the following exclusion criteria:

- Any patient with recent tooth bleaching (within previous two weeks of imaging with the CALCIVIS imaging system)
- Any patient having on-going re-mineralization treatment including, but not limited to, high concentration prescription fluoride toothpaste
- Any patient with a fixed orthodontic appliance
- Any patient currently taking part in a clinical research study, or has taken part in a clinical research study in the previous three months
- Pregnant and/or nursing mothers

2. <u>Follow-up Schedule</u>
All patients were scheduled for examinations over two Study Visits. For the two Study Visits in the clinical study, refer to the Schedule of Events in **Table 8** below. Adverse events and complications were recorded at all visits.

STUDY VISIT 1:

Following written informed consent, patient demographics, date of birth, ethnicity, relevant medical history, and medications were collected. In addition, oral hygiene information was collected to include brushing regime, toothpaste, and any other dental products used.

The CALCIVIS Imaging System was prepared ready for imaging, while the Investigator prepared the teeth identified, by cleaning and air-drying. A reference

color photograph was taken with a standard intra-oral camera, and the ICDAS score and activity status of each selected tooth recorded.

Following further air-drying, the buccal or occlusal surfaces of the selected tooth or teeth were then imaged with the CALCIVIS Imaging System, and the patient's mouth rinsed out with tap water.

Any adverse events observed or volunteered by the patient were recorded.

At the end of the imaging procedures, the Investigator shared the images of the teeth with the patient. Patients were then asked to complete a Patient Questionnaire / Visual Analogue Scale. Visit 1 was then complete.

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

STUDY VISIT 2 – 7 TO 14 DAYS POST-IMAGING

At this visit, a final oral examination was performed by the Investigator, and any adverse events observed or volunteered by the patient were recorded.

All aspects of the clinical study were documented, including data from study procedures documented on Case Report Forms, details of screening/recruitment, device delivery/return, delegation of authority, and site visits recorded on logs. In addition, due to the use of the external light shields, a latex allergy log was generated and completed.

The key timepoints are shown below in **Table 8** for summarizing safety and effectiveness.

Table 8. Schedule of Events

	Screening	**Visit 1**			**Visit 2**
	Pre-Imaging	**Pre-Imaging**	**Imaging**	**Post-Imaging**	**Post-Imaging (7 to 14 days)**
Identification of patients / issue of Patient Information Sheet	**X**				
Written Informed Consent		**X**			

Inclusion / Exclusion criteria, demographics, oral hygiene		**X**			
Tooth ID (ICDAS score / activity status) and cleaning		**X**			
Intra-oral color photographs – tooth surface only		**X**			
CALCIVIS images			**X**		
Adverse Events		**X**	**X**	**X**	**X**
Image review – Dentist and Patient			**X**		
Patient Questionnaire / Visual Analogue Scale			**X**		
User Questionnaire			**X**		

3. Clinical Endpoints
   There were two primary objectives/endpoints for this clinical study:

   - SAFETY: To assess the safety of the CALCIVIS Imaging System - measured by the collection of all adverse events

   - EFFECTIVENESS: To assess the performance of the CALCIVIS Imaging System - measured by the presence or absence of elevated luminescence on the surface of the tooth determined from intra-oral image mapping of that surfaces of teeth (with or without a visible lesion).

   The secondary objective/endpoint was to assess the usefulness of the CALCIVIS Imaging System images as a communication tool between patient and dentist - measured by Questionnaires and/or Patient Visual Analogue Scales.

B. Accountability of PMA Cohort

A total of 111 patients were enrolled in the PMA study and available for analysis at the time of database lock (July 12, 2017) for the CAL-02-2014 clinical study. All patients attended Visit 1, while 109 patients attended Visit 2. For the missing patients under Visit 2, there was 1 patient withdrawn before CALCIVIS imaging and 1 patient did not return for Visit 2 after images were taken at Visit 1. Therefore, data from a

total of 110 (99.1%) patients were included for analysis at the completion of the study in both the safety and agreement populations.

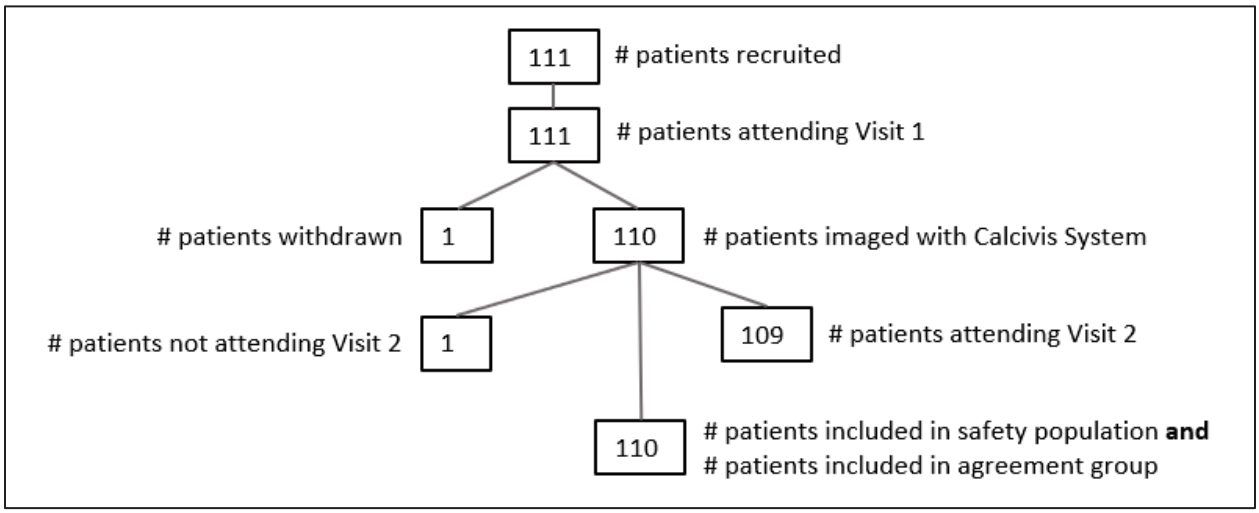

Figure 3. Patient Accountability Tree

C. Study Population Demographics and Baseline Parameters

The demographics of the study population are typical for a caries detection study and considered a reasonable representation for use of the CALCIVIS Imaging System in the US.

Data from a total of 110 patients were included in the safety and agreement populations of the clinical study. Patients were recruited between January 14, 2017, and May 04, 2017, with final patient follow-up on May 11, 2017. There were 61 males (55.5%) and 49 females (44.5%) recruited for the study, with an age range of 7 to 74 years – mean 24.3 years, standard deviation (S.D.) 12.22. For the clinical study, 107 patients (97.3%) were white and 2.7% were Asian or black.

D. Safety and Effectiveness Results

1. Safety Results

   The analysis of safety was based on all 110 patients included in the safety population for the CAL-02-2014 clinical study that had images taken with the CALCIVIS Imaging System at Visit 1.

   There were no patient related Adverse Events reported for the study.

   There were three Device Deficiencies (DD) reported:

   - Patient 01-62 – initially the Investigator documented that the device had 'self-fired' when trying to access the upper left seven for both the first and second images. The device was removed from the site and replaced with

another device. Internal investigations showed a fault in the dimension tolerance between the housing and the activator button causing premature triggering of the device by pressure on the housing near the actuation button.

- Patient 01-20 – the Investigator reported the device would not connect to the laptop and, therefore, images could not be taken. The device was removed from the site and replaced with another device. Internal investigations showed the device to have a faulty connection.

- Patient 01-78 – device failed to dispense fluid; therefore, no images could be taken. The device was removed from the site and replaced with another device. Internal investigations highlighted an intermittent live video feed error, caused by a drop in the Universal Serial Bus (USB) data feed to the software.

None of the above device deficiencies were considered serious. All three device deficiencies were also documented as part of Calcivis Quality Management System.

2. Effectiveness Results

The analysis of effectiveness was based on the 110 patients evaluated at the Visit 1, baseline time point. Key effectiveness outcomes are presented in **Table 9** and **Table 10**.

From the 110 patients imaged with the CALCIVIS Imaging system, there were overall totals of 96 sound teeth and 96 active teeth imaged. From these combined 192 images taken, 16 images could not be used for the primary analysis. (6 images were excluded as uninterpretable due to out of focus or unacceptable coverage of solution, 8 images were not saved, and 2 images were excluded due to premature or accidental firing of the device.). This resulted in 90 images of sound teeth and 86 images of active teeth for the primary analysis.

Table 9. Agreement between Original Dentist (ICDAS Score) and Independent Dentist Interpretation (CALCIVIS imaging system) - Primary Analysis Agreement Population

Original Dentist		Agreement – Independent Dentist – Calcivis imaging system		
ICDAS	N	**n(%)**	**p-value**	**1-sided 97.5% CI Lower Bound**
No visible lesion (ICDAS 0)	90	88 (97.8%)	<0.0001	0.9220
Active lesion (ICDAS 2 or 3)	86	78 (90.7%)	<0.0001	0.8249
All teeth	176	166		

Primary Analysis

Of the 192 teeth with an eligible ICDAS score, 16 did not provide data for the primary analysis of agreement, providing a total of 176 teeth.

A total of 90 teeth with no visible lesions (ICDAS 0 - sound) and 86 teeth with an active lesion (ICDAS 2 and 3) were included in the primary analysis. Of the teeth with an active lesion, 51 (59.3%) were ICDAS 2 and 35 (40.7%) were ICDAS 3. Of the 90 teeth with no visible lesion, 88 were deemed to show no luminescence, a negative percent agreement of 97.8%. This was statistically significantly greater than the performance goal of 50% agreement ($p<0.0001$) with a one-sided 97.5% confidence interval of 92.2%.

Of the 86 teeth with an active lesion, 78 were deemed to show luminescence, a positive percent agreement of 90.7%. This was statistically significantly greater than the performance goal of 50% agreement ($p<0.0001$) with a one-sided 97.5% confidence interval of 82.5%.

Since both of the agreement measures are significantly greater than chance agreement (50%), this study was deemed a success.

Table 10. Agreement between Original Dentist (ICDAS Score) and Independent Dentist Interpretation (CALCIVIS imaging system) - Secondary Analysis Agreement Population

Original Dentist		Agreement – Independent Dentist – Calcivis imaging system		
ICDAS	N	**n(%)**	**p-value**	**1-sided 97.5% CI Lower Bound**
No visible lesion (ICDAS 0)	92	88 (95.7%)	<0.0001	0.8924
Active lesion (ICDAS 2 or 3)	90	78 (86.7%)	<0.0001	0.7787
All teeth	182	166		

Secondary Analysis
Secondary analysis includes patients on whom the CALCIVIS Imaging System was used, but the images were missing for reasons unrelated to the assessment outcome (ambient light ingress, out of focus, etc.)

Therefore, the 6 teeth (2 with no visible lesion and 4 with an active lesion) with missing CALCIVIS Imaging System results due to problems with the CALCIVIS Photoprotein coverage or blurred images were included in the secondary analysis as non-agreements.

In this case the negative percent agreement was 95.7%. This was statistically significantly greater than the performance goal of 50% agreement ($p<0.0001$) with a one-sided 97.5% confidence interval of 89.2%. Furthermore, the positive percent agreement was 86.7%. This was statistically significantly greater than the performance goal of 50% agreement ($p<0.0001$) with a one-sided 97.5% confidence interval of 77.9%.

Secondary Objectives
Patient Questionnaires showed positive feedback based on the two questions asked - with over 84% of patients (93 out of 110 patients) rating their overall experience with CALCIVIS Imaging System as “Good,” and over 96% of patients (106 out of 110) rating seeing images of their teeth and having the dentist explain their situation as “Helpful.”

User Questionnaires were completed at the end of the Visit 1 imaging session, with relevant questions being answered on a three-point scale with the Investigators and dental nurses. In response to the four questions, over 80% rated preparing the CALCIVIS Imaging System “Easy,” and over 55% of responses rated using the CALCIVIS Imaging System as “Easy.” Additionally, 49.2 % of the user’s responses rated their overall experience with the CALCIVIS Imaging

System as "Easy," and when asked if the instruction provided were sufficient to understand how to use the CALCIVIS Imaging System, 85.2% of the user's responses stated "Easy."

3. Subgroup Analyses
   There was no sub-group analysis for the primary clinical study.

4. Pediatric Extrapolation
   In this premarket application, existing clinical data was found to support the reasonable assurance of safety and effectiveness of the proposed device in pediatric patients (≥ 6 yrs. old) primarily based on the Summary of Supplemental Clinical Information, see Section XI below.

E. Financial Disclosure

The Financial Disclosure by Clinical Investigators regulation (21 CFR 54) requires applicants who submit a marketing application to include certain information concerning the compensation to, and financial interests and arrangement of, any clinical investigator conducting clinical studies covered by the regulation. The pivotal clinical study included five investigators. None of the clinical investigators had disclosable financial interests/arrangements as defined in sections 54.2(a), (b), (c), and (f). The information provided does not raise any questions about the reliability of the data.

XI. SUMMARY OF SUPPLEMENTAL CLINICAL INFORMATION

Hands-of-User case series (CS01/2018) were conducted for supplemental clinical information in June 2018, under the study entitled "CS01-2018 In-mouth Hands of the User Study Case Series." The purpose of this clinical case series was to carry out a "hands-of the user" evaluation of the design of the CALCIVIS Applicator in a clinical setting, with five clinicians who all had previous experience (20+ patients each) with the CALCIVIS Imaging System. For each of the five clinicians, 3 children (≥ 6 yrs. old) with primary dentition and 3 adult patients with permanent dentition were selected from routine general dental practice lists. For each patient, the CALCIVIS Imaging System and the CALCIVIS Applicator were prepared according to the User Manual instructions to simulate clinical use, and the clinicians were provided an opportunity for feedback to improve the User Manual.

The evaluation covered the following five areas: CALCIVIS Imaging System preparation, imaging process, quality of images, tooth surface access, and CALCIVIS Imaging System dismantling and cleaning.

A maximum of four teeth per patient (occlusal surfaces) were imaged, following teeth cleaning, rinsing, and thorough air-drying by routine clinical procedures. Images of the occlusal surfaces of the teeth were taken to challenge the usability of the device to access and imaged teeth surfaces. The images from the patients were stored on the laptop provided

with the CALCIVIS Imaging System, and the quality of the images were assessed by the same clinician who took the images, for the following criteria:

- Adequate focus,
- Ambient light ingress,
- Saliva contamination, and
- Adequate photoprotein tooth coverage.

With the device still connected to enable live video-streaming for positioning, the clinician then evaluated the CALCIVIS Imaging System and design of the CALCIVIS Applicator for accessibility of all relevant surfaces (if present) for the both primary and permanent dentition. Finally, the CALCIVIS Imaging System was dismantled and cleaned according to the User Manual.

Results

A total of 15 children (≥ 6 yrs. old) with mainly primary dentition, and 15 adults with permanent dentition were selected for the study by the five clinicians.

The usability of the CALCIVIS Applicator was assessed both through the User Questionnaires and through the clinician's own assessment of the quality of the images they took for four criteria: adequate focus, no ambient light ingress seen, no saliva contamination seen, and adequate photoprotein coverage. The Users' Questionnaire responses averaged 79% positive for adequate focus, 89% positive for no ambient light ingress, 87% positive for no saliva contamination, and 87% positive for adequate photoprotein coverage. The results for children with primary teeth were found to be slightly lower than that for adults; however, the difference was minimal.

The following was concluded for the design of the CALCIVIS Applicator:

- Clinicians familiar with the device experienced adequate image focus and photoprotein coverage, with exclusion of ambient light and saliva.
- Some changes to the User Manual were required to highlight the need to prime without the light shield in place and to press firmly to achieve best focus, ambient light shielding, and photoprotein coverage.

Accessibility of the CALCIVIS Imaging System with the applicator was assessed on all tooth types and accessible tooth surfaces for both primary and permanent teeth. In addition, the permanent teeth from three children with mixed dentition were also assessed.

Assessments were carried out on accessible coronal surfaces of both primary and permanent teeth; however, for some of the primary incisors and canines, there were very few teeth available for assessment as these teeth are often not present in children (≥ 6 yrs.). This was similar in the case of the permanent teeth for the adults, where there were fewer teeth for assessment for UR8, UL8, LL8 and LR8 (alpha-numeric system of dental notation[3]).

For the primary teeth, access to all teeth types and accessible surfaces was found possible, but some were found more challenging, such as first and second molars. The situation for adults is similar with access to all teeth types and accessible surfaces possible; however, in this evaluation, there was only one tooth surface that could not be accessed – LL8 buccal surface (alpha-numeric system of dental notation).

Therefore, in conclusion, this Hand-of User evaluation has shown:

- Acceptable images of primary teeth can be taken with the CALCIVIS Imaging System.
- That occlusal, buccal, and lingual surfaces of both primary and permanent teeth can be accessed with the CALCIVIS Imaging System – with caution for some posterior teeth.
- Clinician feedback on their own usability of the CALCIVIS Applicator with regard to prevention of ambient light ingress, saliva contamination, adequate focus, and sufficient photoprotein coverage is positive.
- User Manual revisions added to highlight the need to prime without the light shield in place, to press firmly to achieve best focus, ambient light shielding and photoprotein coverage; and providing more details of clinical conditions that may preclude the use of the CALCIVIS Imaging System, along further guidance on accessibility to the posterior teeth.

XII. PANEL MEETING RECOMMENDATION AND FDA'S POST-PANEL ACTION

In accordance with the provisions of section 515(c)(3) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the Dental Products Panel, an FDA advisory committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

XIII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

The principal safety and effectiveness information for the CALCIVIS Imaging System is derived from preclinical studies and from the primary CAL-02-2014 clinical study detailed.

Preclinical Data

Preclinical testing performed during the design and development of the CALCIVIS Imaging System confirmed the product design characteristics, specifications, and intended use.

The *in vitro* design verification testing conducted on the system demonstrated that the performance characteristics met the product specifications.

Clinical Data

Clinical study endpoints from the primary CAL-02-2014 clinical study were met, confirming that the CALCIVIS Imaging System is effective for use to provide images of active demineralization on tooth surfaces, as an aid to the assessment, diagnosis and treatment planning of demineralization associated with caries lesions on patients (6 years and older) with, or at risk of developing, demineralization associated with caries lesions, on accessible coronal tooth surfaces.

Primary Analysis

Table 11. Agreement between Original Dentist (ICDAS Score) and Independent Dentist Interpretation (CALCIVIS imaging system) - Primary Analysis Agreement Population

Original Dentist		Agreement – Independent Dentist – Calcivis imaging system		
ICDAS	N	**n (%)**	**p-value**	**1-sided 97.5% CI Lower Bound**
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Active lesion (ICDAS 2 or 3)	86	78 (90.7%)	<0.0001	0.8249
All teeth	176	166		

Of the 192 teeth with an eligible ICDAS score, 16 did not provide data for the primary analysis of agreement, providing a total of 176 teeth.

A total of 90 teeth with no visible lesions (ICDAS 0 - sound) and 86 teeth with an active lesion (ICDAS 2 and 3) were included in the primary analysis. Of the teeth with an active lesion, 51 (59.3%) were ICDAS 2 and 35 (40.7%) were ICDAS 3.

Of the 90 teeth with no visible lesion, 88 were deemed to show no luminescence, a negative percent agreement of 97.8%. This was statistically significantly greater than the performance goal of 50% agreement ($p<0.0001$) with a one-sided 97.5% confidence interval of 92.2%.

Of the 86 teeth with an active lesion, 78 were deemed to show luminescence, a positive percent agreement of 90.7%. This was statistically significantly greater than the performance goal of 50% agreement ($p<0.0001$) with a one-sided 97.5% confidence interval of 82.5%.

Since both of the agreement measures are significantly greater than chance agreement (50%), this study can be deemed a success supporting the indication for use to provide images of active demineralization on tooth surfaces, as an aid to the assessment, diagnosis, and treatment planning of demineralization associated with caries lesions.

B. Safety Conclusions

The risks of the CALCIVIS Imaging System are based on nonclinical laboratory studies as well as data collected in the clinical studies conducted to support PMA approval as described above.

Preclinical Data

The biocompatibility evaluation demonstrated that the patient contact components provide reasonable assurance of safety and acceptability for clinical use.

Clinical data

From the primary CAL-02-2014 clinical study, all 110 patients were included in the safety population of having images taken with the CALCIVIS Imaging System at Visit 1.

There were no patient related Adverse Events reported for the clinical study.

C. Benefit-Risk Determination

The probable benefits of the device are also based on data collected in the clinical studies conducted to support PMA approval as described above.

The study was intended to show the safety and effectiveness of the CALCIVIS Imaging System to provide images of active demineralization on tooth surfaces in a clinical setting. When used to characterize demineralization in teeth, it is anticipated that the CALCIVIS Imaging System will provide the following potential benefits:

- Aid in treatment planning of dental carious lesions.
- Aid in clinical decision making.
- Aid in communication between dentist and patients.

The probable risks of the device are also based on data collected in the clinical study conducted to support PMA approval as described above and on data derived from nonclinical laboratory and toxicology studies.

All 110 patients that are included in the safety population had images taken with the CALCIVIS Imaging System at Visit 1. There were no patient related Adverse Events reported for the study.

ISO 10993 compliant preclinical toxicological studies on the CALCIVIS Photoprotein showed no signs of toxicity. The biocompatibility evaluations provide reasonable assurance of safety and acceptability of the patient contact components for clinical use.

1. Patient Perspectives

Patient perspectives considered during the review included:

The CALCIVIS Imaging System has been designed and developed to support the practice of preventive dentistry. In the primary CAL-02-2014 clinical study, Patient Questionnaires showed positive feedback based on two questions - with over 84% of patients rating their overall experience with CALCIVIS Imaging System as "Good," and over 96% of patients rating seeing images of their teeth and having the dentist explain their situation as "Helpful".

In conclusion, given the available information above, the data support that for capturing images of active demineralization on accessible coronal tooth surfaces, as an aid to the assessment, diagnosis and treatment planning of demineralization associated with caries lesions, the probable benefits outweigh the probable risks.

D. Overall Conclusions

The data in this application support the reasonable assurance of safety and effectiveness of the CALCIVIS Imaging System when used in accordance with the indications for use.

The clinical study results demonstrate effectiveness in adult and pediatric patients with both primary and secondary effectiveness end points being met. Safety of the CALCIVIS Imaging System was established based on the absence of patient related Adverse Events in the clinical studies, and the demonstration of biocompatibility and the absence of toxicity seen in preclinical studies.

XIV. CDRH DECISION

CDRH issued an approval order on 3/07/2023. The final conditions of approval cited in the approval order are described below.

1. Please address the following as non-clinical post-approval requirements for assessment of the microbial control and microbiology product quality:

    a. Provide in-process data from three batches for the end of fermentation culture purity IPC 8 samples.

    b. Provide data to demonstrate the effect of kanamycin removal from the production culture media. Provide the report, summary of the study and the results, and the methods used to analyze the data. If the data support removal of kanamycin, submit a plan for the removal of kanamycin from the photoprotein manufacturing process.

c. Provide in-process and release data for the bioburden test and release data for the absence of specified organisms test obtained from two additional drug substance and drug product lots.

d. Provide qualification data from in-process and release samples for the bioburden method and from release samples for the specified microorganism detection method using samples from two additional lots.

e. Provide summary data and the study report for the antimicrobial effectiveness study conducted according to USP <51> using photoprotein DP reconstituted in a commercial batch of diluent, which is at the end of the shelf life.

2. Please address the following as non-clinical post-approval requirements for assessment of the Chemistry Manufacturing Control (CMC) product quality:

a. Revise the release and stability specification acceptance criteria for protein content by UV absorbance at 280 nm based on the protein content determination using experimental instead of theoretical extinction coefficient. Protein content testing performed at different steps of drug substance (DS) and drug product (DP) manufacturing process was determined using the theoretical extinction coefficient. In order to meaningfully correlate the results from different steps and specification acceptance criteria (in-process control, DS and DP), revise the protein content values and acceptance criteria throughout the PMA documentation based on the experimental extinction coefficient. This information may be provided as part of the PMA annual report, instead of a non-clinical post-approval study report.

b. Develop and validate an assay that is suitable for accurately and reliably monitoring impurities in photoprotein Formulated Bulk Drug Product (FBDP) and Final Container Drug Product (FCDP) at release and on stability. Establish appropriate specification acceptance criteria for levels of impurities and implement the analytical method for testing impurities in FBDP and FCDP at release and on stability. The final study report for method validation will be submitted in accordance with 21 CFR 601.12.

c. Develop and validate an assay that is suitable for accurately and reliably monitoring host cell protein (HCP) in the photoprotein drug substance (DS). Establish appropriate specification acceptance criteria for HCP level and implement HCP testing by revising the current DS release specification. The final study report for method validation will be submitted in accordance with 21 CFR 601.12.

i. For additional considerations of this request, you indicated that you plan to use commercial ELISA kit for detection of *E.coli* host cell proteins (HCP). The anti- *E.coli* HCP antibodies need to be qualified for their ability to detect potential HCP impurities. Provide data demonstrating that the anti- *E.coli* HCP antibodies employed can detect the majority of proteins present in an *E.coli* cell extract. These data should include 2D SDS-PAGE gels of the

range of HCPs detected by a sensitive protein stain, such as silver stain, compared to the range detected by Western Blot analysis using the antibody employed in the ELISA. It is possible to use a similarly sensitive and discriminating assay instead of the 2D SDS-PAGE assay. If an alternative pathway is pursued, consultation with the Agency is recommended. These data should be used to determine the approximate percent of potential HCP impurities that are recognized by the HCP antiserum. It is the Agency's experience that analysis of HCP coverage by a 1-dimensional SDS-PAGE gel method is not sufficiently informative for this purpose.

The applicant's manufacturing facilities have been inspected and found to be in compliance with the device Quality System (QS) regulation (21 CFR 820).

XV. APPROVAL SPECIFICATIONS

Directions for use: See device labeling.

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions, and Adverse Events in the device labeling.

Post-approval Requirements and Restrictions: See approval order.

XVI. REFERENCES

1. Neuhaus K, W, Schlafer S, Lussi A, Nyvad B. Infiltration of Natural Caries Lesions in Relation to Their Activity Status and Acid Pretreatment in vitro. Caries Research 2013;47:203-210.

2. Stauffacher S, Carvalho TS, Eick S, Lussi A, Neuhaus KW. 63rd ORCA Congress. July 6-9, 2016, Athens, Greece: Abstracts. Caries Research 2016;50:180-270.

3. Grace M. Dental Notation. British Dental Journal 2000;188(5):229.