PROTOCOL
Clinical Investigation Plan (CIP) - Clinical study of tooth enamel remineralization using an experimental remineralization product

Study Title	Clinical study of tooth enamel remineralization using an experimental remineralization product
Registration	NCT06166849 (www.clinicaltrials.gov)
Study-ID	IVAG-Study-ID: LL4003223 EC-Study-ID: "3DM" and "7TP" NCA-Study-ID: "DM 3908E"
Product	Experimental Fluoride Product
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Document Control
Name
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Sponsor: Ivoclar Vivadent AG, Bendererstrasse 2, 9494 Schaa, Liechtenstein

Revision History			
Version	**Date**	**Author**	**Remark on Amendments to the CIP**
1.0	17.09.2021	Dr. Ada Delean	Initial creation
2.0	24.10.2023	Dr. Ada Delean/Patrizia Elkuch-Hoch	Formal Adjustments

The Coordinating Investigator has approved the CIP version [2.0 (dated 24.10.2023), and confirm hereby to conduct the investigation according to the CIP, the current version of the World Medical Association Declaration of Helsinki, ISO14155 norm, ICH-GCP as far as applicable, and the local legally binding requirements. This includes in particular that the clinical investigation shall not begin until the required approval(s) have been obtained and that any additional requirements imposed by the EC or NCA shall be followed, if appropriate.

Content

1. Synopsis

Sponsor/ Manufacturer	Ivoclar Vivadent AG Bendererstrasse 2 9494 Schaan Fürstentum Liechtenstein
Study Title	Clinical study of tooth enamel remineralization using an experimental remineralization product
Short Title	Clinical Evaluation of an Experimental Remineralization Product
Version/ Date	2.0/ 24.10.23
Registration:	NCT06166849 (www.clinicaltrials.gov)
Clinical investigation category and Rationale	Medical Device Clinical Trial
Background and Rationale:	Dental caries develops when the homeostasis between phasic demineralization and remineralization of the tooth surface is out of balance. Topically applied fluoride delays demineralization and promotes remineralization. The Experimental Fluoride Product is a two-step fluoride-based remineralization system consisting of an aqueous fluoride solution (component A) and an ethanolic nanosolution of calcium fluoride (component B). After sequential application, the two components form a protective calcium-fluoride layer that is intended to promote remineralization of incipient enamel lesions and increase the acid resistance of dental tissue. The condition treated is incipient carious lesions or white spot lesions (WSL) on permanent teeth. Fluoride varnishes represent the current standard of care for non-invasive remineralization of early caries. Another more invasive treatment option is infiltration.
Objective(s):	Efficacy of an investigational medical device (Experimental Fluoride Product, Ivoclar-Vivadent AG, Schaan, Liechtenstein) compared to no treatment
Outcome(s):	The remineralizing effect of the product will be evaluated based on different outcome variables: • International Caries Detection and Assessment System (ICDAS) score • Lesion size • Surface texture (roughness) of the injured surface • Laser fluorescence • Visual assessment

Clinical investigation design:	Interventional split-mouth randomized -controlled clinical study
Inclusion / Exclusion criteria:	Female/male adult patients (age ≥ 18) consulting at the dental service department of UMF Iuliu Haţieganu, Cluj-Napoca, Romania. Inclusion criteria: At least two incipient carious lesions on the buccal or oral surface of permanent teeth; active carious lesions; patient at risk of caries; vital teeth. Exclusion criteria: Pregnancy; enamel removal at the investigation site; allergies against ingredients of the investigational device; chronic diseases.
Intervention: Measurements and procedures	At the initial session, the teeth will be professionally cleaned. Lesions will be isolated with cotton rolls and lingual suction and dried for ~5 seconds. Component A will be applied with a microbrush (60 s reaction time, removal of residual material). Component B will be applied with a new microbrush and will be allowed to dry for ≥ 30 s. Patients are instructed to not rinse, eat, or drink for 1 hour.
Control Intervention (if applicable):	No treatment will be done.
Number of Participants with Rationale:	It is aimed to include 40 subjects. Accordingly, the test and control group will involve ≥40 teeth. Exact numbers of teeth in both groups depend on the number of lesions presenting in subjects.
Duration of the investigation:	For each included patient, the study will run for one year.
Investigation Schedule:	Intervention, 1 day (optional), 4 weeks, 4 months, 12 months
Study Coordinator:	Dr. Radu Chisnoiu
Principal Investigator:	Dr. Ada Delean
Investigation Site(s):	Single-centre, Discipline of Odontology, Endodontics and Oral Pathology, University of Medicine and Pharmacy «Iuliu Haţieganu», Moţilor Street 33, Cluj-Napoca, Cluj, Romania
Statistical Considerations:	See Chapter 4.
Compliance Statement:	This clinical investigation will be conducted in compliance with the CIP (protocol), the current version of the Declaration of Helsinki, ISO EN 14155, ICH-GCP (as far as applicable) as well as all national legal and regulatory requirements.

2. Definitions, Terms, Abbreviations

ADE	Adverse Device Effect. Adverse events (see below) that are related to the MD under investigation or the comparator and to the procedures involved. *For users or other persons this is restricted to events related to the MD.*
AE	Adverse event (Art. 2 Abs 57 MDR): Any untoward medical occurrence, unintended disease or injury or any untoward clinical signs (including an abnormal laboratory finding) in subjects, users or other persons whether or not related to the MD.
Castor EDC	Electronic data capturing (EDC) platform from the company Castor
CE	Conformité Européenne (Label on products complaint to European Medical Device Legislation)
CER	Clinical Evaluation Report
CIP	Clinical Investigation Plan
CIR	Clinical Investigation Report
Clinical studies	Systematic investigation in one or more human subjects, undertaken to assess the clinical performance, effectiveness or safety of a medical device. Note: For the purpose of this document, “clinical investigation” or “clinical trial” are synonymous with “clinical study”
DD	Device Deficiency (Art. 2 Abs 59 MDR): Inadequacy of a medical device related to its identity, quality, durability, reliability, safety or performance, of an investigational device, including malfunction, user errors and inadequate information supplied by the manufacturer. *The definition includes deficiencies related to the investigational MD or the comparator MD.*
(e)CRF	(electronic) Case Report Form
ICH-GCP	International Conference on Harmonisation – Good Clinical Practice
IB	Investigator's Brochure
ICF	Informed Consent Form
ISO	International Organization for Standardization
MD	Medical Device
Directive)	
PI	Principal Investigator
SAE	Serious adverse event: (Art. 2 Abs 58 MDR) Any adverse event (see definition above) that led to any of the following: (a) death, (b) serious deterioration in the health of the subject that resulted in any of the following: (i) life-threatening illness or injury, (ii) permanent impairment of a body structure or a body function, (iii) hospitalization or prolongation of patient hospitalization*, (iv) medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function,

	(v) chronic disease, (c) foetal distress, foetal death or a congenital physical or mental impairment or birth defect. *Note: planned hospitalization for pre-existing condition, or a procedure required by the CIP, without a serious deterioration of the health status of the subject, is not considered an SAE
SADE	Suspected Serious Device Effect.
Subjects	SAE related to the MD and/or the comparator Participants (i.e. Patients) that are included in a clinical investigation.

3. Study Schedule

	Recruitment meeting	First visit	1 day	4 weeks	4 months	1 year
Inclusion/exclusion criteria	X					
Patient information	X					
Obtaining consent		X				
Clinical dates		X				
Case Report Form (CRF)		X	(X)	X	X	X
Measuring lesions		X		(X)	(X)	(X)
Photographic recording		X	(X)	X	X	X
Product application		X				

4. Statistical Considerations

Statistical methods are limited to descriptive statistics and to simple parametric or non-parametric tests (depending on data distribution).