Clinical Study Protocol - Evaluation of Effectiveness of a Novel Remineralizing Agent: A Randomized Controlled Clinical Trial

Study Title	Evaluation of Effectiveness of a Novel Remineralizing Agent: A Randomized Controlled Clinical Trial
Registration	https://clinicaltrials.gov
Study-ID	IVAG-Study-ID: LL4406332 Institution-Study-ID: N/A
Product	Experimental Fluoride Application
Project Number	62 13 06
Document-ID	LL4470462
Document Version	1.0
Document Date	21.03.2022

Document Control		
Name	**Date**	**Signature**
Study Coordinator Mutlu Özcan Prof. Dr. Dr. h.c., Ph.D, University of Zurich Division of Dental Biomaterials Center of Dental Medicine Clinic of Reconstructive Dentistry Plattenstrasse 11, CH-8032, Zurich, Switzerland Mobile: [redacted] E-mail: [redacted]	06.05.2022	[redacted]

Revision History			
Version	**Date**	**Author**	**Remark on Amendments to the CIP**
1.0	21.03.2022	Burcu Gözetici Çil Mutlu Özcan	Initial creation

The Coordinating Investigator has approved the CIP version [1.0 (dated 21.03.22), 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.

SPONSOR SIGNATURE PAGE

We, the undersigned, have read this protocol and agree that it contains all necessary information required to conduct the study.

Ivoclar Vivadent AG
Bendererstrasse 2, 9494 Schaan
Liechtenstein

[redacted]

Patrik Oehri
Senior Director CQM & Regulatory Affairs, PRRC

[redacted]

Dr. Thomas Völkel
Head of Department Scientific Services / Deputy PRRC
Study Management

INVESTIGATOR STATEMENT

I have read protocol and agree that it contains all necessary details for carrying out the study described and in conformance with Good Clinical Practices (GCPs), the current version of the World Medical Association Declaration of Helsinki, ISO14155 norm and applicable regulatory requirements. I agree to maintain the confidentiality of all information received or developed in connection with the protocol.

Burcu Gözetici Çil

Printed Name of Investigator

[redacted]

Signature of Investigator

12.05.2022

Date

1. Synopsis

Sponsor/ Manufacturer	Ivoclar Vivadent AG Bendererstrasse 2 9494 Schaan Fürstentum Liechtenstein
Study Title	Evaluation of Effectiveness of a Novel Remineralizing Agent: A Randomized Controlled Clinical Trial
Short Title	n.a.
Version/ Date	1.0/ 21.03.22
Registration:	https://clinicaltrials.gov
Clinical investigation category and Rationale	Medical Device Clinical Trial
Background and Rationale:	Active non-cavitated caries lesions on buccal surfaces teeth scored with ICDAS code 1 or 2 are characterized by white chalky appearance as a result of loss of minerals from the tooth structure. The progression of these lesions can be reversed or arrested by application of some therapeutic agents, enhancing remineralization. Fluoride varnishes are considered to be the first choice of treatment for this purpose. Fluoride varnishes with high concentration of fluoride provides calcium fluoride formation which acts as a reservoir for both calcium and fluoride. The release of these ions during acidic challenges inhibits further dissolution of hydroxyapatite crystals of the dental hard tissues. In the present pilot clinical study, the test material containing - calcium fluoride nanosol in addition to high level of ammonium fluoride content will be evaluated. Ammonium fluoride solution and calcium fluoride solutions are designed to be applied separately to form a protective layer. Application of calcium fluoride in combination with high concentration of fluoride is anticipated to have beneficial effects on the repair of incipient caries lesions with ICDAS code 1 and 2.
Objective(s):	Comparison between investigational medical device (Exp. Fluoride Appl. Ivoclar-Vivadent AG, Schaan, LI) and control product (Fluor Protector S, Ivoclar-Vivadent AG, Schaan, LIE)
Outcome(s):	Primary outcome:

	• Evaluation of the change in lesion size and mineral content based on Qraycam measurements at baseline, after 1, 6 and 12 months. Secondary outcome: • Clinical evaluation of the lesion progression according to ICDAS and Nyvad criteria at baseline, 1, 6 and 12 months. • Digital pictures for secondary evaluation by the observers to calculate inter-examiner reliability.
Clinical investigation design:	Randomized controlled blinded evaluation in split-mouth design
Inclusion / Exclusion criteria:	At least two early caries lesions (arrested or progressive) on buccal sides of two teeth in two different quadrants. Inclusion criteria: • Subjects are required to have at least two active non-cavitated white spot lesions (WSLs) on buccal surfaces of anterior teeth or premolars (ICDAS code 1 and 2; Nyvad score 1) • Age between 13 and 50 years • No untreated caries lesions or periodontal disease • No systematic disease or medication (such as antidepressants, antibiotics etc.) that affects salivary flow rate • Subjects claimed regular brushing at least twice a day • Subjects had to agree to keep the scheduled recall appointments for 1 year. Exclusion criteria: • Inactive non-cavitated lesions (Nyvad Score 4) • Lesions with microcavity, cavitation, chipping or discoloration • Lesions at buccal side of the molars • Lesions adjacent to restoration • Developmental white spot lesions such as enamel hypoplasia

	• Pregnant and breastfeeding women
Intervention: Measurements and procedures	The investigational medical device Experimental Fluoride Application, consists of an aqueous fluoride solution and an ethanol-based solution of calcium fluoride nanosol, which is supplied in two separate bottles which will be applied directly on enamel.
Control Intervention (if applicable):	Fluor Protector S (Ivoclar Vivadent AG, Schaan, Liechtenstein) is a protective varnish containing ammonium fluoride. It will be applied on enamel of teeth in the control group. The application is according the instruction for use within the indication.
Number of Participants with Rationale:	23, rationale see statistical considerations
Duration of the investigation:	6 months estimated duration for the main investigational plan (e.g. from start of screening of first participant to last participant processed and finishing the clinical investigation) 1 year 6 months of First-Participant-In until Last-Participant-Out
Investigation Schedule:	Intervention, 4 weeks, 6 months, 12 months recall
Study Coordinator:	Mutlu Özcan Prof. Dr. Dr. h.c., Ph.D, University of Zurich Division of Dental Biomaterials Center of Dental Medicine Clinic of Reconstructive Dentistry Plattenstrasse 11, CH-8032, Zurich, Switzerland Mobile: [redacted] E-mail: [redacted]
Principal Investigator:	Dr. Burcu Gözetici Istanbul Medipol University School of Dentistry Department of Restorative Dentistry Birlik Mah., Bahçeler Cd. No:5, 34230 Esenler Istanbul, TURKEY E-mail: [redacted]
Investigation Site(s):	Single-centre
Statistical Considerations:	t-test allows a sample size of 23 patient with power of 80% at a significance level of 5%.

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

Study Periods	**Screening, Patient information**	**Treatment, Intervention (Enrolment)**	**Follow-Up (Recall)**		
Visit	**1**	**2 x**	**3**	**4**	**5**
Time (hour [h], day [d], week [wk], month [mt])	12 mt	1 h	4 w	6 mt	12 mt
Patient Information	x				
Informed Consent	x				
Medical History	x				
In- /Exclusion Criteria	x	x			
Tooth Examination	x				
Vitality test	x				
VAS for tooth sensitivity	x				
Intraoral pictures		x	x	x	x
Recording ICDAS and Nyvad scores		x	x	x	x
Professional cleaning of tooth suface		x			
QrayCam Pro measurement		x	x	x	x
Adverse events (incl. SAE)	x	x	x	x	x
Concomitant medications	x	x	x	x	x