3M Deutschland GmbH
3M Oral Care
ESPE Platz
82229 Seefeld
Germany

Clinical Investigation Plan

Clinical performance of a new esthetic, self-ligating orthodontic bracket

3M Oral Care study number CR 16/14

Confidential

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1. CLINICAL STUDY SYNOPSIS

Study Synopsis	
Study Title:	Clinical performance of a new esthetic, self-ligating orthodontic bracket
Sponsor	3M Deutschland GmbH 3M Oral Care ESPE Platz 82229 Seefeld, Germany
Investigators	Principal Investigator: Thorsten Grünheid, DDS, Dr med dent, PhD Division of Orthodontics University of Minnesota 6-324 Moos Health Sciences Tower 515 Delaware Street SE Minneapolis, MN 55455 + 1 612-625-3903 tgruenhe@umn.edu Co-Principal Investigator: Brent E. Larson, DDS, MS Director, Division of Orthodontics University of Minnesota 6-320 Moos Health Sciences Tower 515 Delaware Street SE Minneapolis, MN 55455 +1 612-626-9202 Larso121@umn.edu
Investigation site	Division of Orthodontics, University of Minnesota, 515 Delaware Street SE, Minneapolis, MN 55455
Statistical support	Provided by the Biostatistical Design and Analysis Center (BDAC) at the University of Minnesota on consultation basis

Monitor	Cindy Zehrer 3M Health Care Oral Care Solutions 3M Center Building St. Paul, MN 55144 +1 651-733-8985 clzehrer1@mmm.com
Outcome measure(s)	Bracket door stability Ability of door to hold the archwire in the bracket slot Bracket's ability to rotate teeth Clinicians' satisfaction with the bracket Patient comfort in comparison with other brackets
Study Design:	Prospective, Pilot, Clinical evaluation of a prototype
Estimated # of Subjects:	30 subjects in 2 cohorts of 15 (no statistical justification, sample size chosen based on number of available brackets)
Patient Population:	Subjects will be recruited from the pool of individuals undergoing orthodontic treatment at the University of Minnesota.
Test material:	Lower Anterior EXD-952 Self-ligating Brackets (MBT, 0.022" slot)
Other materials:	EXD-952 Open/Close Instrument EXD-952 Debonding Instrument Clarity Advanced (MBT, 0.022" slot) maxillary brackets Victory Series low profile (MBT, 0.022" slot) mandibular brackets 0.014" and 0.016" Nickel-Titanium archwires 0.019x0.025" Stainless Steel archwires

Subjects:	Inclusion Criteria: • Permanent mandibular dentition including incisors, canines, premolars, and first molars (includes subjects treated with the extraction of premolars) • Mandibular incisors with sound, non-carious buccal enamel and no pretreatment with chemical agents such as hydrogen peroxide Exclusion Criteria: • Mental/emotional/developmental disability • Inability to give informed consent • Cleft lip and/or palate, craniofacial anomaly, or syndrome • Obvious oral hygiene issues such as excessive plaque accumulation, gingivitis, and/or pre-existing white spot lesions • Prosthodontic or restored substrate extending on the labial surface of mandibular incisors • Deep bite • Known allergies to any study materials
Data Analysis Planned:	Calculation of bracket failure rate Analysis of responses to specifically-designed surveys aimed at determining clinicians' satisfaction with clinical performance of the bracket and patient comfort.
Study Duration:	Estimated at 2-3 years (until all study subjects have completed orthodontic treatment)

Description of Study Procedure:	A cohort of 15 patients starting orthodontic treatment with fixed appliances will receive EXD-952 Ceramic Self-ligating bracket on all mandibular incisors and a different type of brackets on the remaining mandibular teeth. Tooth movement will be initiated using 0.014" or 0.016" Nickel-Titanium archwires. A second cohort of 15 patients will receive EXD-952 Ceramic Self-ligating bracket on all mandibular incisors in a later phase of their ongoing orthodontic treatment. The mandibular incisor brackets will be removed and EXD-952 Ceramic Self-ligating brackets placed instead. Other mandibular brackets will remain in place. Tooth movement will be performed using 0.019x0.025" Stainless Steel archwires. In both cohorts bracket door stability, the ability of the door to hold the archwire in the bracket slot, the bracket's ability to rotate teeth, clinicians' satisfaction with the bracket, and patient comfort in comparison with other brackets will be assessed. The evaluation for each patient will last for at least until one archwire change (cohort 1) or one appointment interval (6-8 weeks, cohort 2). After the evaluation period, EXD-952 Ceramic Self-ligating brackets will remain in place until the orthodontic treatment is completed.
Reports:	Reports will be prepared after the initial evaluation period (Initial Report), at the end of each year over the course of the study (Annual Reports), and after all patients have completed treatment (Final Report).

2. Background Information

2.1 Background

Conventional brackets require elastomeric or wire ligatures to hold the archwire in the bracket slot. In contrast, self-ligating brackets use some form of door or clip to secure the wire eliminating the need for elastomeric or wire ligatures. Self-ligating brackets were first conceived in 1935 and there are many designs on the market today. The most popular and well known is the Damon bracket, developed by Dr. Dwight Damon. Self-ligating brackets have been suggested to offer a number of advantages, including lower levels of friction resulting in more biological forces, decreased treatment times, fewer visits to the office, faster space closure, and fewer periodontal complications.

2.2 Name and Description of the Investigational Product

EXD-952 Ceramic Self-ligating Brackets are a new type of esthetic brackets developed by 3M Oral Care Solutions. The brackets have a sliding door and are composed of alumina (aluminum oxide) with small amounts of related oxide compounds (glass powder), which gives them a clear appearance. A nickel-titanium wire serves as part of the door mechanism and is attached to the bracket using 3M ESPE™ Scotchbond™ Universal Adhesive. FDA 510(k) submission of EXD-952 is planned for the end of 2016.

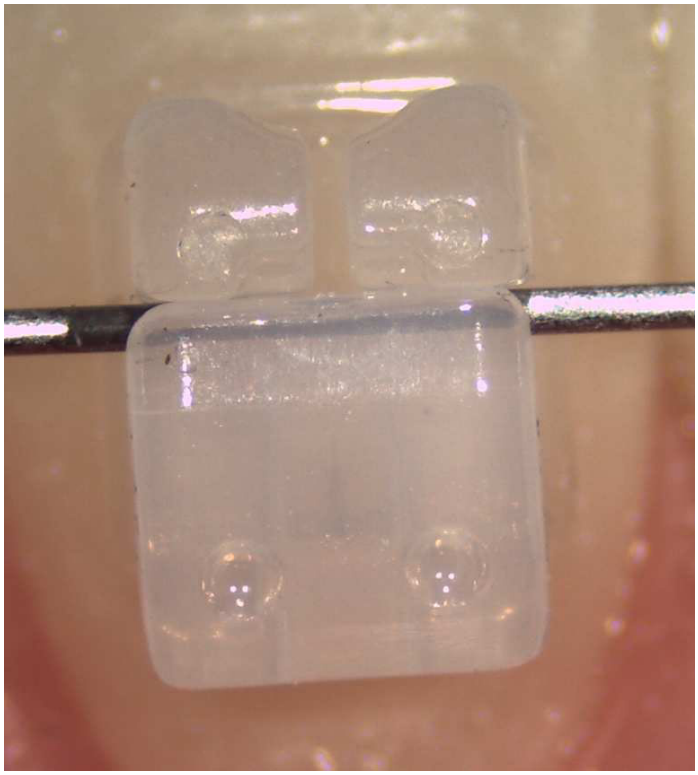


Figure 1: EXD-952 bonded to a typodont tooth.

Figure 2: EXD-952 components on a black background show the high translucency of the brackets.

2.3 GCP and Regulatory Requirements

This study will be conducted in compliance with this protocol and GCP including 45 CFR 160 & 164 (Authorization for Use/Disclosure of PHI), 21 CFR 50 (Informed Consent), and 56 (IRBs).

2.4 Risk/Benefit Summary

The investigational product is expected to qualify as a non-significant risk IDE exempt device. Final risk determination will be made by the Institutional Review Board (IRB) at the University of Minnesota.

2.4.1 Risks of Study Participation

The risks associated with the new bracket include wear of enamel surfaces of teeth in contact with the bracket, increased risk of tooth damage when bonded to teeth with large restorations, porcelain crowns, or facings, and losing fractured portions of the bracket in the patient's mouth. However, these risks are not specific to the study and are associated with the use of other ceramic orthodontic brackets as well. Similar to most orthodontic brackets on the market, the new bracket contains nickel and chromium. A small percentage of the population is known to be allergic to nickel and/or chromium.

A risk associated with record keeping is breach of confidentiality. All efforts will be made to keep patient information private. Moreover, patient names will be made anonymous and replaced with a unique identification number. All data will be reported using this number and only the investigators will know which identification number corresponds to which individual.

2.4.2 Benefits of Study Participation

Study patients seeking orthodontic treatment will be treated with tooth-colored ceramic brackets without additional charge ($239 value). They will receive no other direct benefit for participating in this study. However, future orthodontic patients could benefit from the knowledge acquired as the results of this study may help develop better orthodontic materials.

2.4.3 Study Compensation

Study patients already undergoing orthodontic treatment will each receive a $150 gift card upon completion of orthodontic treatment.

3. Study Objectives and Purpose

The objective of the study is to evaluate the clinical performance of EXD-952 in orthodontic treatments. Specifically, this study aims at assessing bracket door stability, strength of door to hold the arch wire, the bracket's ability to rotate teeth, clinicians' satisfaction with the bracket, and patient comfort in comparison with other brackets.

4. Study Design

4.1 Study Type

Prospective, Pilot, Pre-market feasibility study/Clinical evaluation of a prototype.

4.2 STUDY MATERIALS

EXD-952 Ceramic Self-ligating Brackets
Open/Close Instrument for EXD-952 Self-Ligating Ceramic Brackets
Debonding Instrument for EXD-952 Self-Ligating Ceramic Brackets

4.3 OTHER MATERIALS

Victory Series Low Profile brackets for remaining mandibular teeth
Clarity Advanced brackets for maxillary teeth
Transbond XT light-cure adhesive and primer

4.4 ESTIMATED STUDY TIMELINE

Start of Study:	2016-12-01
End of Initial Evaluation:	2017-03-01
End of Study:	2020-03-01

The estimated study timeline above is based on previous experiences with clinical studies carried out at the Division of Orthodontics at the University of Minnesota. The actual timeline will depend on factors such as IRB review time, subject recruitment, and duration of orthodontic treatment of the study participants.

4.5 REPORTING PERIODS

The PI will provide the Sponsor with the following written reports:
Initial report: This report will be provided within 60 days after all study subjects in cohort 1 have completed one archwire change and all subjects in cohort 2 had at least one adjustment visit after placement of the investigational brackets. This report will include data related to the primary outcome measures.
Annual progress reports: Progress reports will be provided annually and will include data on bracket failure and adverse events until all study subjects have completed orthodontic treatment.
Final report: A final report will be provided after all study subjects have completed orthodontic treatment.

4.6 STUDY PROCEDURES

The study will involve two patient cohorts – (1) a cohort of patients seeking orthodontic treatment and (2) a cohort of patients already receiving orthodontic treatment with fixed applicances.

This way, the robustness and performance of EXD-952 can be evaluated in different treatment phases. The information acquired in the different treatment phases is important for business decisisions.

Cohort 1:
Fifteen consecutive patients presenting for comprehensive orthodontic treatment with fixed appliances at the University of Minnesota, who are willing to participate, will have their maxillary incisors, canines, and premolars bonded with conventional ceramic orthodontic brackets (Clarity Advanced, 3M), mandibular incisors bonded with self-ligating ceramic orthodontic brackets (EXD-952, 3M), and mandibular canines and premolars bonded with conventional metal brackets (Victory Series Low Profile, 3M). A Nickel-Titanium archwire (0.014" or 0.016") will be used as an initial mandibular archwire. The perceived ability of the bracket to hold the archwire, ease of handling, and ease of opening/closing the door will be assessed using a custom-designed survey. After the first archwire change (expected 6-8 weeks after initial bonding) the bracket's ability to rotate teeth, clinicians' satisfaction with the bracket, and patient comfort in comparison with other brackets will be assessed using custom-designed surveys. There will be photodocumentation at the initial appointment and at the first archwire change to assess the bracket's ability to rotate teeth. Any bracket failures (e.g. decementation, failure of door etc.) and adverse events will be documented. The initial evaluation for each patient will last for at least until one archwire change.

After the evaluation period, EXD-952 Ceramic Self-ligating brackets will remain in place until the orthodontic treatment is completed.

Cohort 2:
Fifteen patients undergoing comprehensive orthodontic treatment with fixed appliances at the University of Minnesota, who are willing to participate, will have their mandibular incisor brackets removed and EXD-952 brackets placed instead. Other mandibular brackets will remain in place. A rectangular Stainless Steel archwire (0.017x0.025" or 0.019x0.025") will be used as a working mandibular archwire. The perceived ability of the bracket to hold the archwire, ease of handling, and ease of opening/closing the door will be assessed using a custom-designed survey. After the first adjustment visit after placement of EXD-952 brackets (expected 6-8 weeks later) the bracket's ability to control inclination of teeth, clinicians' satisfaction with the bracket, and patient comfort in comparison with other brackets will be assessed using custom-designed surveys. There will be photodocumentation at the bonding appointment and at the adjustment visit. Any bracket failures (e.g. decementation, failure of door etc.) and adverse events will be documented. The initial evaluation for each patient will last for at least one appointment interval (6-8 weeks).

After the evaluation period, EXD-952 Ceramic Self-ligating brackets will remain in place until the orthodontic treatment is completed.

If EXD-952 brackets fail in the course of the study they will be initially replaced with EXD-952 brackets. Should the same EXD-952 brackets fail for a second time in the same patient, all EXD-952 brackets will be removed and replaced with conventional brackets. 3M will cover the cost for replacing failed brackets.

4.7 Study Termination/Subject Discontinuation or Withdrawal

Conditions that may warrant termination of the study include but are not limited to the following:

- The discovery of an unexpected, serious, or unreasonable risk to study subjects;
- Insufficient adherence to protocol requirements;
- Submission of knowingly false information from the Investigator to 3M Oral Care;
- Termination/withdrawal of IRB approval;

- A decision on the part of 3M Oral Care to suspend or discontinue evaluation of the investigational product. In this case, patients will finish their treatments with the study brackets in place but brackets will no longer be evaluated.

4.7.1 Subject Discontinuation

- Subjects may withdraw from the study at any time. EXD-952 brackets will remain in place unless the patients requests the brackets to be removed.
- The Investigators may exclude individual subjects from the study at any time in the event of illness, adverse events,lack of compliance, treatment failure, protocol deviations, administrative reasons, or other reasons that would render the subject unsuitable for the purposes of this study.
- A subject will be removed from the study if two or more (≥50%) study brackets have been classified as failed. In that case, all EXD-952 brackets placed in the subject will be removed and replaced with conventional brackets
- The trial will be terminated for safety reasons if the cumulative failure rate of study brackets reaches or exceeds 50%.

In case of study withdrawal and subsequent drop-out, there will be no subject replacement. Date and reason for withdrawal will be recorded. The data collected on the subject to the point of withdrawal remains part of the study database unless the subject expresses that the data be erased. There will be no additional follow-up data collected after subject withdrawal.

In case of an adverse event, the specific event will be recorded on the Adverse Event Report Form and communicated to the IRB. The subject will be followed until the event is resolved.

4.8 DROP-OUT ESTIMATION

Considering the short study duration,the estimated drop-out rate is expected to be low. Therefore, there will be no over-recruitment of subjects.

4.9 PROTOCOL MODIFICATIONS

4.9.1 Protocol Amendments

The party initiating an amendment must confirm it clearly in writing using the Amendment/Administrative Revision form. It must be signed and dated by 3M Oral Care and, in the case of a significant amendment, the Principal Investigators (PIs). A significant amendment means one that affects the safety, rights or welfare of subjects, the scope of the investigation, or the scientific quality of the study.

3M Oral Care will submit significant protocol amendments to the PIs for submission to the IRB. 3M Oral Care will also notify the PIs when a protocol amendment may be implemented.

4.9.2 Protocol Deviations

A deviation is a departure from the protocol that will likely affect the safety, rights or welfare of subjects, the scope of the investigation or the scientific quality of the study.

A protocol deviation is only for an individual subject. Protocol deviations are documented on the appropriate CRF and on the Protocol Deviation Form.

Deviations that potentially affect (1) subject safety, rights or welfare, (2) data integrity or (3) compromise the statistical analysis of the study require immediate communication to 3M Oral Care. The PI will contact and submit a completed Protocol Deviation Form to the 3M Oral Care study monitor within 24 hours of identifying the occurrence.

5. Inclusion / Exclusion criteria

Inclusion Criteria:

- Mandibular permanent dentition including incisors, canines, premolars, and first molars (includes subjects treated with the extraction of premolars)
- Mandibular incisors with sound, non-carious buccal enamel and no pretreatment with chemical agents such as hydrogen peroxide

Exclusion Criteria:

- Mental/emotional/developmental disability
- Inability to give informed consent
- Cleft lip and/or palate, craniofacial anomaly, or syndrome
- Obvious oral hygiene issues such as excessive plaque accumulation, gingivitis, and/or pre-existing white spot lesions
- Prosthodontic or restored substrate extending on the labial surface of mandibular incisors
- Deep bite
- Known allergies to any study materials

5.1 Subject Consent

The PI must ensure that written informed consent to participate in the investigation is obtained before including any individual as a subject in the investigation. The PI must provide the prospective subject or their legal representative sufficient opportunity to consider whether or not to participate, and minimize the possibility of coercion or undue influence. The process is designed to 1) give the subject all the information that they need, 2) ensure that the subject understands the information and 3) give the subject a chance to consider study participation. The process should permit the subject to ask questions and exchange information freely.

6. Primary outcome measures

- Bracket door stability
- Ability of door to hold the archwire in the bracket slot
- Bracket's ability to rotate teeth
- Clinicians' satisfaction with the bracket
- Patient comfort in comparison with other brackets

7. Adverse Events

Adverse events will be recorded immediately with attention to the onset, severity, and duration of the event as well as its relationship to the study product using the Adverse Event Reporting Form. In the event that the described research activity results in an injury, treatment will be available, including first

aid, emergency treatment, and follow-up care as needed. Care for such injuries will be billed in the ordinary manner to the patient's insurance company. In the event that the described research activity results in tooth damage such as wear of enamel surfaces of teeth in contact with the bracket, tooth damage upon debonding and/or losing fractured portions of the bracket in the patient's mouth, treatment will be available at the study sponsor's expense. Any treatment in response to the adverse event will be noted and the subject must be followed until resolution.

All adverse reactions will be reported to the local IRB and to 3M Oral Care (in this order) as soon as possible and without unduly delay. All serious adverse events will be reported to the local IRB and to 3M Oral Care within 24 hours or sooner if possible after becoming aware of the situation. Subjects removed from study participation at the request of the sponsor or clinical team receive full compensation for their participation.

Any clinically significant abnormal laboratory finding, serious or unanticipated Serious Adverse Event or other medical event which results in the withdrawal of a subject from the study must be followed until resolution with appropriate medical management or as deemed necessary (with the Sponsor's agreement).

7.1 ADVERSE EVENTS AND ADVERSE DEVICE EFFECTS

Adverse Event (AE) – Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the tested medical device.

Note 1: this definition includes events related to the investigational medical device or the comparator.

Note 2: this definition includes events related to the procedures involved.

Note 3: for users or other parties, this definition is restricted to events related to investigational medical devices.

Adverse Device Effect (ADE) – Adverse event related to the use of a tested medical device.

Note 1: this definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device.

Note 2: this definition includes any event resulting from an error use or from intentional misuse of the investigational medical device.

7.2 DEVICE DEFICIENCIES

Device Deficiency – Inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance
Note: device deficiencies include malfunctions, misuse or use errors, and inadequate labelling.

7.3 SERIOUS ADVERSE EVENTS, SERIOUS ADVERSE DEVICE EFFECT AND UNANTICIPATED SERIOUS ADVERSE DEVICE EFFECTS

Serious Adverse Event (SAE) – Adverse event that:

a) led to death

b) led to a serious deterioration in the health of the subject that

1) resulted in a life-threatening illness or injury,
2) resulted in a permanent impairment of a body structure or a body function
3) required in-patient hospitalization or prolongation of existing hospitalization
4) resulted in medical or surgical intervention to prevent permanent impairment to body structure or a body function

Serious Adverse Device Effect (SADE) – Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.

Unanticipated Serious Adverse Device Effect (USADE) – Serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report.

Note: anticipated serious adverse device effect (ASADE) is an effect which by its nature, incidence, severity or outcome has been identified in the risk analysis report.

7.4 TIME PERIOD FOR PRINCIPAL INVESTIGATOR TO REPORT ADVERSE EVENTS

The PI shall:

a) record every adverse event and observed device deficiency, together with an assessment of the event and report it to the local IRB and to 3M Oral Care as soon as possible and without unduly delay;

b) report all serious adverse events and all adverse events and device deficiencies that could have led to a serious adverse device effect to the local IRB and to 3M Oral Care within 24 hours or sooner if possible after becoming aware of the situation; this information shall be promptly followed by detailed written reports as necessary so that 3M Oral Care can evaluate the event and report to the proper regulatory authority and/or IRB;

c) supply the local IRB and 3M Oral Care with any additional requested information related to the safety reporting of a particular event.

7.5 PROCESS FOR REPORTING ADVERSE EVENTS/DEVICE DEFICIENCIES

Local events: The PI is responsible for the classification of local adverse events and reports to the local IRB and to 3M Oral Care.

3M Oral Care is responsible for the ongoing safety evaluation of the clinical study and shall:

a) review the PI's assessment of all adverse events and determine and document in writing their seriousness and relationship to the tested device; in case of disagreement between 3M Oral Care and the PI(s), 3M Oral Care shall communicate both opinions to concerned parties, as defined in c) and d) below

b) review all device deficiencies and determine and document in writing whether they could have led to a serious adverse device effect; in case of disagreement between 3M Oral Care and the principal investigator(s), 3M Oral Care shall communicate both opinions to concerned parties, as defined in c) and d) below

c) report to the IRB all serious adverse events and device deficiencies that could have led to a serious adverse device effect, if required by national regulations or by the IRB

d) report to regulatory authorities, within 10 working days of notification of the event, all serious adverse events and device deficiencies that could have led to a serious adverse device effect, if required by national regulations

e) ensure that the IRB and the regulatory authorities are informed of significant new information about the clinical study, and

f) in case of serious adverse device effects and device deficiencies that could have led to serious adverse device effects, determine whether the risk analysis needs to be updated and assess whether corrective or preventive action is required.

Descriptions of reactions or complaints must include:

- duration
- severity (mild, moderate, severe)
- PI's opinion as to the relationship to the test product (unknown, probably related, or probably not related). If determined "probably not related" was the event: present before the study, due to the primary disease, due to concomitant medications, due to an undercurrent illness, or another reason.
- Photo documentation for internal use will be performed if possible.

7.6 EMERGENCY CONTACT DETAILS FOR REPORTING SERIOUS ADVERSE EVENTS

All serious adverse events must be reported to the local IRB and to 3M Oral Care within 24 hours, or sooner if possible, of becoming aware of the situation. The serious adverse event must be assessed for the following: date of onset, date ceased, frequency, intensity, action taken, treatment required and relationship to test product.

This information should be transmitted to the 3M Oral Care Monitor immediately:

Cindy Zehrer
3M Health Care, Oral Care Solutions
3M Center Building
St. Paul, MN 55144-1000
Telephone: 1 651 733 8985
FAX:1 651 737 8114
Email: clzehrer1@mmm.com

8. STATISTICS

Descriptive statistics will be applied to the data to provide summaries about the sample and about the observations that have been made.

9. MONITORING

3M Oral Care as sponsor of this study will monitor the proper conduct of the study with regard to protocol adherence and validity of the data recorded on the CRFs. 3M Oral Care has therefore assigned a study monitor to this study. The progress of the study will be monitored by:

- Periodic on-site review
- Telephone communications
- Review of CRFs

The Investigator will give the 3M Oral Care study monitor access to source documents that support data on the CRFs and make available such records to authorized 3M Oral Care, quality assurance, IRB, and regulatory personnel for inspection and/or copying if required (study-related records only) upon request and with the patient's written permission.

10. ETHICS /IRB

Approval to conduct this study will be obtained from the IRB at the University of Minnesota. Informed consent will be obtained from all participating patients and clinicians. In case of minors, consent will be obtained from a parent or guardian; assent will be obtained from the minor.

This study will be conducted in accordance with the principles that have their origin in the Declaration of Helsinki. The study will start only after approval of the protocol and consent form by the IRB. The approval letter or notice must contain the IRB name, study title and IRB Code Number. 3M Oral Care, prior to study initiation, must receive a copy of the IRB approval letter.

11. DATA HANDLING AND RECORD KEEPING

11.1 PRE-STUDY DOCUMENTATION REQUIREMENTS

Prior to study initiation, the PI must provide 3M Oral Care with the following documents:

- Study protocol including any amendments in place prior to study initiation
- IRB approved consent and assent forms form
- IRB approval letter

Prior to study initiation, both parties will ensure that a signed study contract is in place.

11.2 Completion and Return of Case Report Forms

The Investigator will review all CRF entries for completeness and accuracy. If a correction is required, a single line must be drawn through the error. The person making the correction will initial, date, and provide a reason for the error (if not self-evident).
The Investigator must review and sign each CRF in a timely fashion following completion and make them available to the 3M Oral Care study monitor for inspection. Before acceptance, the monitor will review the CRFs to assure accuracy and completeness. In addition, any data queries prepared after the original CRFs have been completed must be answered promptly.

11.3 Records and Retention Requirements

Members of the research team will record data on paper forms. All paper forms will be stored in a secured room. Paper forms may be scanned to obtain electronic data. All electronic data will be stored on a secure network drive with restricted access. All personnel handling study data are required to have current IRB and HIPAA training certification. Data analysis will be performed by the principal investigator or one member of the statistical consulting unit and subsequently verified by another, using a statistical software system.

In order to comply with regulatory requirements, the PI must maintain the required study records during the investigation and for 5 years after the date on which the study is terminated.

Records that must be maintained by the PI include:

- Signed study protocol, amendments, deviations
- IRB approval of protocol, consent form, assent form and amendments to either
- Applications to the IRB
- Signed consent and assent forms
- Case report forms
- Adverse event reports
- Final Report

12. SIGNATURES

Agreed to by the Principal investigator and the representative for the Sponsor (3M), subject to final approval by all relevant parties.

Principal Investigator: Thorsten Grünheid, DDS, Dr. med. dent, PhD Division of Orthodontics University of Minnesota 6-324 Moos Health Sciences Tower 515 Delaware Street SE Minneapolis, MN 55455 USA	Sponsor Representative: Julia Farr, Dr. rer. nat. Clinical Research Manager 3M Oral Care 3M Deutschland GmbH Espe Platz 82229 Seefeld Germany
Date: 11/03/2016	Date: 11/07/2016

13. APPENDIX

13.1 INSTRUCTIONS FOR USE EXD-952 – DRAFT VERSION

EXD-952 Ceramic Self-ligating Brackets
Instructions For Use

Indications for use
This product is intended for use in orthodontic treatment.

Warnings
• Brackets are for single use only. Use of recycled brackets may compromise material integrity, bond strength, patient safety and overall product performance.
• Due to the hardness of ceramic brackets, bonding brackets in occlusion should be avoided to prevent wearing of enamel surfaces during all phases of treatment.
• Deep bite cases should be opened prior to bonding with EXD-952 Ceramic Self-ligating Brackets to prevent wearing of enamel surfaces. Unitek™ Elastomeric Ligatures with Guard are designed to help protect opposing tooth surfaces from occlusal interference and from potential enamel wear. Bite plates and other intrusion mechanics may also be necessary to prevent bracket to tooth contact. Indications for using Unitek Elastomeric Ligature with Guard modules include deep bite cases, protection of cusp tips during retraction and situations in which tooth to bracket contact is possible during finishing.
• Instruct patients not to chew or bite on hard substances such as hard candy, ice, carrots, etc. Careful and thorough patient instruction is a key to avoiding appliance or enamel damage.
• Bonding of ceramic brackets to compromised teeth (i.e., with large restorations, peg laterals or preexisting conditions) can increase the risk of tooth damage.
• Bonding to porcelain crowns or facings may cause chipping or breakage of the crown or facing during treatment or debonding.
• It is recommended to debond EXD-952 brackets using the provided EXD-952 Bracket Debonding Instrument. No other debonding instrument is recommended to debond EXD-952 brackets. Doing so may result in fractured tie-wings, losing fractured portions of bracket in patient's mouth, or tooth damage.
• It is recommended to debond EXD-952 brackets without ligation or archwire and with the doors open. Extra precautions need to be taken to assure that bracket parts are held securely.
• If a bracket fractures during treatment or debonding, use a diamond bur to carefully remove the ceramic parts. Failure to follow the correct debonding procedure may lead to tooth damage.
• The EXD-952 brackets contain nickel and/or chromium. A small percentage of the population is known to be allergic to nickel and/or chromium. If an allergic reaction occurs, direct patient to consult a physician.

Bracket Identification and Bracket Positioning
•EXD-952 brackets are identifiable by a color coded recessed distal gingival dot.
• Colored reference markers provide vertical and horizontal visual guidance for bracket positioning. These reference markers are water soluble.
• It is recommended that the patient brush after bonding, but before the placement of the archwire to remove the reference markers.

Bracket Bonding
Remove adhesive flash at bonding to minimize staining of the adhesive and reduce the risk of bracket breakage during the debonding procedure. EXD-952 brackets feature mechanical retention on the bonding base. No special primers or pretreatments are necessary.
EXD-952 brackets can be bonded using traditional direct methods. No change in bonding technique is necessary. EXD-952 brackets can be bonded with the doors open or closed. For bonding procedures, please follow the adhesive manufacturer's recommendations. When placing EXD-952 brackets, it is suggested that the bracket be placed in a sliding motion, occlusal to gingival, forcing excess adhesive to the incisal edge of the bracket for easier clean-up. Care must be taken when cleaning up adhesive flash so as not to disturb the final positioning before adhesive curing. Before placing the archwire, patient should brush to remove the reference markers.

Bracket Opening/Closing
To open the self-ligating door of EXD-952 brackets, insert the tip of the provided EXD-952 Open/Close Instrument into the horizontal groove (as referenced as A in **Figure 1: Opening the door)** just occlusal to the door and twist the tool 90 degrees (1/4 turn) in either direction. This opens the door.
NOTE: If not using the provided EXD-952 Open/Close Instrument to open the doors, extra caution should be taken to not pull down on the door too hard or too far.
To close the self-ligating door of EXD-952 brackets:
Option A: Ensure the wire is fully seated. Then push the door closed with your finger. **(Figure 2a: Closing the door with your finger).**
Option B: Use EXD-952 Open/Close Instrument to close the door.

1. Rest the tool's notches (as referenced as B in **Figure 2b: Open/Close instrument alignment)** in onto the bracket's archwire with the separate pointer aligned above (or below) the EXD-952 bracket's open door.
2. Pressing and/or torqueing the wire lightly with the tool, ensure the wire is fully seated.
3. Squeeze the tool, pushing the pointer (as shown in **Figure 2b: Open/Close instrument alignment)** against the open door. Continue squeezing until the door is closed.

Debonding Instrument
Use the provided EXD-952 Bracket Debonding Instrument, to debond the EXD-952 brackets.
Important: Clean the jaws of the provided EXD-952 Bracket Debonding Instrument after debonding each bracket to ensure even contact and force distribution.

Debonding Procedure
Note: It is recommended to debond EXD-952 brackets with the archwire and ligation removed and door open **(Figure 3: debond procedure without archwire (3a) position of tool and (3b and 3c) rocking motion**).
1) Remove adhesive flash around base of bracket to be debonded. Note: Failure to remove flash around bracket base, especially on the mesial-distal sides, may result in incomplete debonding.
2) Place the centering guide of the provided EXD-952 Bracket Debonding Instrument vertically into the center of the bracket perpendicular to the archwire slot (**Figure 3a: position of tool)**. Be sure that the inner ledges of the instrument are symmetrically positioned against the tie-wings of the bracket.
3) Gently squeeze instrument handles until the EXD-952 bracket collapses. Gently rock the bracket in the mesial or distal direction to completely separate the bracket from the enamel, if necessary (**Figure 3b and 3c: rock)**.
Note: Extra caution should be taken to maintain the hold on the bracket to keep the debonded bracket parts in the instrument tips.

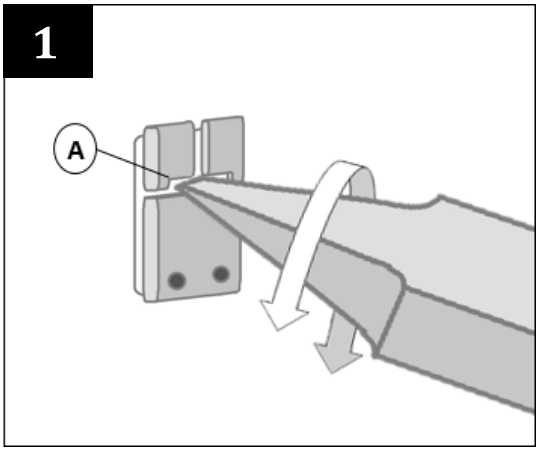
Bracket Rebonding Procedure

In the case of a spontaneous bond failure, it may be necessary to rebond a bracket. The following steps are recommended:

1. Carefully inspect the bracket for any damage. Brackets that have fractured through the vertical debonding slot cannot be rebonded and must be replaced. If the bracket is cracked or damaged in any way, replace the bracket.
2. Remove any excess adhesive. Extra care must be taken to prevent chipping or breaking of the bracket. Use a hand scaler to remove any excess flash from around the edges of the bracket. **Do not use a bur. Do not attempt to scrape adhesive from the base of the bracket or attempt to micro-etch the adhesive as this may damage the bracket's bonding surface.**
3. If the bracket has been contaminated (e.g., moisture), rinse the bracket in isopropyl alcohol and allow to dry.
4. Prepare the tooth surface and bond the bracket using the procedure as described by the adhesive manufacturer.

Torqueing Precautions

EXD-952 brackets are capable of withstanding all normal torque requirements. However, care should be taken when making large torqueing activations since large corrections with full size stainless steel wires may result in bracket failure and should be avoided.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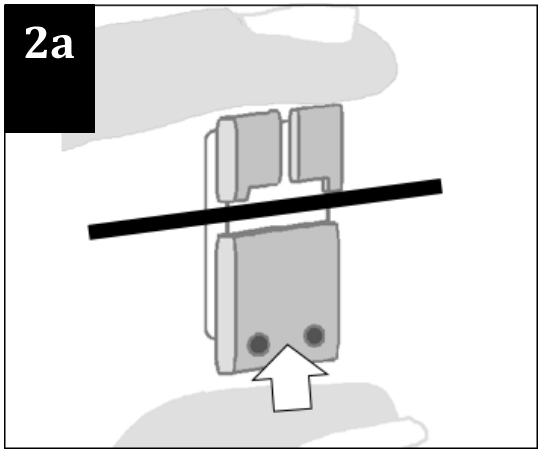
A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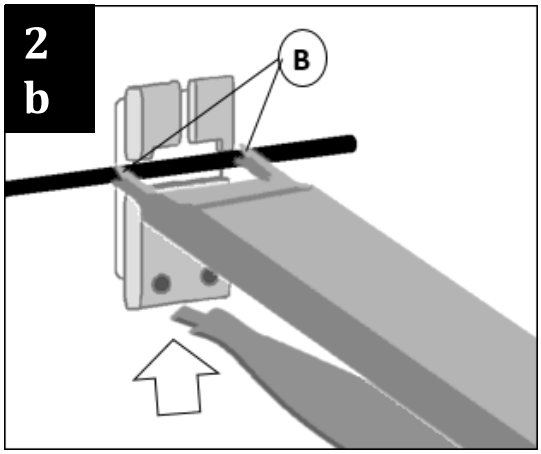
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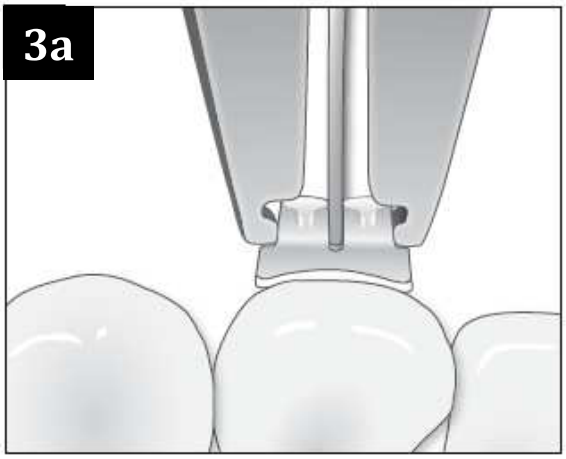
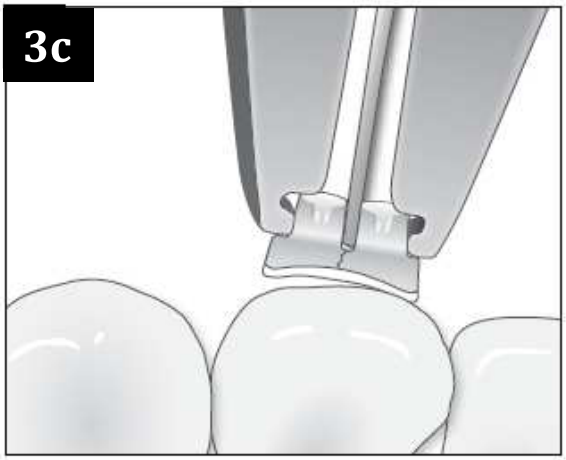
b
B


3a


3
b


3c