Clinical Trial Protocol of Medical Device

Protocol Number: MDI 0102

A prospective, multi-center, randomized, and controlled clinical trial protocol for the evaluation of the safety and efficacy of Filtek™ Bulk Fill Posterior Restorative in the direct restoration of Class I and II cavities of posterior teeth

Name of Investigational Medical Device: Filtek™ Bulk Fill Posterior Restorative

Models: 4863TK, 4864TK, 4863A1, 4863A2, 4863A3, 4863B1, 4863C2, 4864A1, 4864A2, 4864A3, 4864B1, 4864C2

Clinical Trial Institution: Peking University Hospital of Stomatology

Category of Investigational Medical Device: Category III Medical Device

Category III Medical Device Requiring Review and Approval of Clinical Trials

Yes ☐ No ☑

Similar Products in China Yes ☑ No ☐

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Investigator: Prof. Wang Xiaoyan

Sponsor: 3M ESPE Dental Products

Agent: Minnesota Mining Manufacturing (Shanghai) International Trade Co., Ltd.

Instruction Page

1. For multi-center clinical trials, only the lead unit should be filled out for the Clinical Trial Institution field on the cover with other institutions listed in the protocol content.

2. For multi-center clinical trials, only the Coordinating Investigator should be filled out for the Investigator field on the cover.

Table of Contents

Protocol Abstract **1**

1. Sponsor **7**

1.1 Name of the Sponsor 7
1.2 Address of the Sponsor 7
1.3 Contact information of the Sponsor 7
1.4 Qualifications of the Sponsor 7
1.5 Name, address, and contact information of the agent and the relevant qualifications 7

2. List of all the clinical trial institutions and investigators in the multicenter clinical trial and protocol signatures **7**

3. Objective and content of the clinical trial **8**

3.1 Purpose 8
3.2 Content 8

4. Background data of the clinical trial **8**

5. Characteristics, structural composition, working principles, and mechanism of action of the product and scope of the trial **9**

5.1 Characteristics, structural composition, working principles, and mechanism of action of the investigational device and scope of trial 9
5.1.1 Characteristics of the product 9
5.1.2 Structural composition, working principles and mechanism of action of the product 10
5.1.3 Specifications and model 10
5.1.4 Scope of application 10

5.2 Characteristics, structural composition, working principles, and mechanism of action of the control product (Filtek™ Z350XT Restorative) and scope of trial 10
5.2.1 Characteristics of the product 10
5.2.2 Structural composition, working principles and mechanism of action of the product 10
5.2.3 Models and specifications 11
5.2.4 Scope of application 11

6. Indications, contraindications, and precautions of the product **11**

6.1 Indications, contraindications, and precautions of the investigational device 11
6.1.1 Indications 11
6.1.2 Contraindications 11
6.1.3 Precautions 11

6.2 Indications, contraindications, and precautions of the control device 12
6.2.1 Indications 12
6.2.2 Contraindications 12
6.2.3 Precautions 12
7. Overall design 12
7.1 Trial design 12
7.1.1 Trial objective 12
7.1.2 Selection and justification of methodology 12
7.1.3 Measures to reduce and prevent bias 12
7.1.4 Investigational and control devices 13
7.1.5 Subject selection 14
7.1.6 Evaluation methodology of efficacy 17
7.1.7 Evaluation methodology of safety 18
7.2 Trial procedures 18
7.2.1 Screening and baseline visit: 18
7.2.2 Cavity filling 20
7.2.3 Follow-up visit 1 week after the filling procedure 21
7.2.4 Follow-up visit 1 year after the filling procedure 21
7.3 Standard operation procedures relevant to the trial/control device 23
7.4 Storage and management of the investigational and control products 26
7.5 Auditing schedule 26
8. Statistical considerations 26
8.1 Statistical design, methodology, and analysis procedures 26
8.1.1 Statistical design (test of hypothesis) 26
8.1.2 Statistical analysis methodology 27
8.1.3 Statistical analysis procedures 27
8.2 Determination of sample size 27
8.2.1 Total sample size 27
8.2.2 Number of cases in the clinical trial of each disease and justifications, significance level, and statistical power 28
8.2.3 Number of cases enrolled by each clinical trial institution 28
8.3 Estimated dropout rate 28

8.4 Passed/failed criteria of clinical trial results....29
8.5 Criteria to terminate the trial based on statistical justifications....29
8.6 Statistical procedures for all data as well as handling procedures for missing, unused, or incorrect data (including early removal and withdrawal) and unreasonable data....29
8.7 Extent of deviations in the report to original Statistical Analysis Plan....29
8.8 Subject selection criteria for inclusion in the analysis....30
8.9 Exclusion of special information when testing the hypothesis and its justifications....30
9. Data management....30
9.1 Completion and transfer of Case Report Forms....30
9.2 Data entry and modification....30
9.3 Locking of database....30
9.4 Data processing and record keeping....31
10. Feasibility analysis....31
11. Quality control of the clinical trial....32
11.1 Training....32
11.2 Monitoring of centers....32
12. Ethics and informed consent of the clinical trial....33
12.1 Ethics considerations....33
12.2 Approval of the protocol....33
12.3 Informed consent....33
13. Report of adverse events and device defects....33
13.1 Adverse events....33
13.2 Serious adverse events....34
13.3 Determination of severity of an adverse event....34
13.4 Evaluation of the causal relationship between AEs and investigational devices....34
13.5 Device defect and its report....36
13.6 Report procedures and contact information....36
14. Deviations and amendments to the clinical protocol....37
14.1 Deviations to the protocol....37
14.2 Amendments to the protocol....37
15. Direct access to original data and files....37
15.1 Case Report Forms....37
15.2 Source files....37
15.3 Direct access to original data and files....38
15.4 Archive of original records....38
16. Finance and insurance....38
17. Clinical trial report....39
18. Confidentiality....39
19. Agreements on the publication of trial results....39

20. Responsibilities of all the parties.....39

References.....43

Statement of Investigator.....44

A prospective, multi-center, randomized, and controlled clinical trial protocol for the evaluation of the safety and efficacy of Filtek™ Bulk Fill Posterior Restorative in the direct restoration of Class I and II cavities of posterior teeth

Protocol Abstract

Protocol No.:	MDI 0102
Trial Title:	A prospective, controlled, randomized, and multi-center clinical trial for the evaluation of the safety and efficacy of Filtek™ Bulk Fill Posterior Restorative in the direct restoration of Class I and II cavities of posterior teeth
Trial Objective:	Evaluation of the safety and efficacy of Filtek™ Bulk Fill Posterior Restorative 1 week and 1 year after its application in the direct restoration of Class I and II cavities of posterior teeth;
Clinical Trial Institution:	Peking University Hospital of Stomatology Hospital of Stomatology Wuhan University Beijing Stomatological Hospital Capital Medical University
Target Population:	Healthy population with Class I and II cavities of posterior teeth to be restored
Trial design:	This clinical trial adopts a two-arm, randomized, controlled, and noninferiority design to evaluate the safety and efficacy of Filtek™ Bulk Fill Posterior Restorative in direct restoration of Class I and II cavities of posterior teeth. Another resin product of 3M, i.e. Filtek™ Z350XT Universal Restorative, which has already been marketed in China, is used as the control device in this trial. It is estimated that a total of 240 subjects meeting the inclusion/exclusion criteria will participate in this trial. All of the subjects will be randomly assigned into the treatment or control group using a centralized randomization system for the filling and restoration of Class I or II cavities of posterior teeth. All of the selected subjects will be evaluated immediately and followed up in the outpatient department 1 week and 1 year after the filling procedure. The clinical acceptance rate of the filling after 1 year will be used as the primary efficacy measure. In the follow-up visits, the fillings will be evaluated by two evaluators from the clinical evaluation committee, which is independent of this trial and appointed by each clinical trial institution respectively (if the conclusions of two evaluators are inconsistent, the evaluation of a third evaluator with higher seniority shall be adopted). The evaluator will conduct independent clinical evaluations according to the relevant requirements of CFDA's Technical Review Guidelines for the Registration of Dental Resin Filling Materials (see Appendix 1 for details). All of the relevant clinical data generated in this trial will be collected, compiled, statistically analyzed, and determined by independent data management and statistics centers and clinical audit departments. Observe the measures listed in the Technical Review Guidelines for the Registration of Dental Resin Filling Materials (Appendix 1) and the occurrences of adverse events, and accurately evaluate the immediate, short-term and long-term efficacy, and safety of Filtek™ Bulk Fill Posterior Restorative.

Inclusion criteria	1. Male or female, 18-70 years old (including 18 and 70 years) 2. Healthy, with no major systemic disease 3. Normal mouth openness 4. Molar (preferred) or premolar 5. Cavities satisfying any of the following 4 conditions: ① Class I cavities, including those that need to be restored again after a previously failed filling; ② Class II cavities, with lesion on tooth locations other than second molars (including a failed previous filling which needs to be restored again now), and the gingival margin after cavity preparation on the proximal surface located at the gingival crown margin; ③ Class II cavities, with a lesion on second molars, no missing third molars, and the gingival margin after cavity preparation on the proximal surface located at the gingival crown margin; ④ Class II cavities, with a lesion on second molars, missing third molars, lesion on the Mesial Occlusal (MO) or Mesial Occlusal Distal (MOD) surface of second molars (including a failed previous filling, which needs to be filled again now), and the gingival margin after cavity preparation on the proximal surface located at the gingival crown margin; 6. Cavity size: minimum buccolingual distance on the occlusal surface (approx.) not less than 1/3 of buccolingual distance between the cusps; 7. The opposing tooth is natural; 8. Depth of the lesion reaching at least the middle layer of dentin with normal pulp vitality; 9. The subjects agree to participate in the trial and sign the Informed Consent; 10. The subject is compliant and committed to follow-up visits.
Exclusion criteria	1. Allergic constitution or allergic to multiple drugs; allergy history of polymer based materials, such as dental resin; 2. Aggressive caries; severe periodontitis; abnormal salivary gland function; temporomandibular joint disorder; 3. Poor oral health. DMFT: > 4 for 18~34 years old, >5 for 35~70 years old; 4. Teeth with special staining; 5. Non-carious tooth, such as pathological wear (nocturnal molars, clenching habits), acid erosion, or subfissure; 6. Abnormal occlusion; 7. Severe systemic diseases; mental illness; 8. Breastfeeding, pregnant and at childbearing age with intention to conceive (positive pregnancy test result); 9. The subject is determined to be poor compliance and could not complete the trial as required as determined by the investigator; 10. The cavity is determined to be unsuitable for resin filling by the investigator; 11. Pulp already exposed or close to be exposed at the bottom; 12. The subject plans to go overseas within 1 year or cannot complete the 1 year follow-up visit after the procedure due to other reasons; 13. The subject also participates in a clinical trial of the other drug or medical device, which has not reached its clinical endpoint; 14. The subject is not tolerant of or willing to use the rubber dam.
Interventions and group assignment:	All the subjects will be randomly assigned into the treatment or control group using centralized randomization system. The investigational product (Filtek™ Bulk Fill Posterior Restorative) will be used in the filling of Class I and II cavities of the posterior teeth of subjects from the treatment group. The control product (Filtek™ Z350XT) will be used for filling and restoration in the subjects from the control group. The control product was approved for marketing by the CFDA (National Medical Products Administration) for 5 years (since 2011) with

	clinically validated safety and efficacy. Clinical evaluation will be performed immediately after the filling and restoration. The measures include the retention and fracture of the filling, marginal fracture of the filling, contour and marginal adaptation, proximal contact, color match, surface roughness, surface staining, marginal discoloration, secondary caries and pulp status. All of the subjects will return to the clinical trial institution for outpatient follow-up 1 week and 1 year after filling and restoration according the protocol, and the clinical evaluation will be conducted in accordance with Appendix 1.
Randomization and blinding:	The subjects will be randomly assigned into the treatment group (Filtek™ Bulk Fill Posterior Restorative) or control group (Filtek™ Z350XT) for the filling and restoration of Class I and II cavities of posterior teeth with corresponding investigational or control product. Since all the investigators need to follow the product instructions, the investigators will not be blinded to whether the subject is using the investigational product or control product. However, neither the subjects nor the clinical evaluators will know whether the subjects are restored with the investigational device (Filtek™ Bulk Fill Posterior Restorative) or the control device (Universal Restorative-Filtek™ Z350XT).
Efficacy measures:	**1. Primary efficacy measures** ● Clinical acceptance rate of the filling at the 1 year follow-up visit after the filling procedure According to the Clinical Trial Guideline for Polymer-based Dental Restorative Materials (YY/T 0990-2015), the definition of clinically acceptable filling at the 1 year follow-up visit is: grade A for retention and fracture of the filling 1 year after the filling procedure; grade A or B for marginal fracture, contour, and marginal adaptation of the filling. **2. Secondary efficacy measures:** ● Clinical acceptance rate of the filling at the 1 week follow-up visit after the filling procedure: According to the Clinical Trial Guideline for Polymer-based Dental Restorative Materials (YY/T 0990-2015), the definition of clinically acceptable filling at the 1 week follow-up visit is: grade A or B 1 week after the filling procedure for all of the measures listed in Appendix 1, including the retention and fracture of the filling, marginal fracture, contour and marginal adaptation, proximal contact, color match, surface roughness, surface staining, marginal discoloration, secondary caries and pulp status; ● Proximal contact, color match, surface roughness, surface staining, marginal discoloration, secondary caries and pulp status 1 year after the filling procedure
Safety measures:	After the subject signs the Informed Consent, all adverse events (AE) and serious adverse events (SAE) will be recorded until the subject completes the trial or prematurely withdraws from the trial for various reasons. All adverse events, whether they are observed by the investigator or voluntarily reported by a subject, should be recorded in the original medical record and the AE page of CRF (Case Report Form).
Consistency evaluation:	The evaluation criteria in Appendix 1 will be used to evaluate the clinical effect of the filling. Before the formal start of this trial, all clinical evaluators (3 evaluators in each center) will be instructed on the evaluation criteria by systematic training and perform the evaluation of 20 clinical digital photos of the filling according to the criteria in Appendix 1. Shooting angle and aperture size will be consistent for all photos. All the evaluators will score and record the score of each photo according to the criteria in Appendix 1, and will be finally evaluated for consistency. A Kappa ≥ 65% is considered as good consistency.

	Operators (at least 2 operators in each center) will also unify each step of the operation procedures. Three clinical evaluators from a same clinical trial institution will comprise the clinical evaluation committee of their own clinical trial institution. The clinical evaluation after filling will be completed by 2 evaluators from the evaluation committee. If the clinical evaluations of these 2 evaluators are inconsistent, the evaluation of a third evaluator with higher seniority shall be adopted.
Sample size:	It is estimated that 240 patients will be enrolled in this trial, and randomly assigned to the treatment or control group at 1:1 ratio. The number of cases in each group is 120. The calculation of the sample size is based on the primary endpoint measure, i.e. clinical acceptance rate of the filling at the 1 year follow-up visit. Based on the existing clinical evidence and estimation by the clinical experience of experts, and assuming the clinical acceptance rate in the control group 1 year after restoration is 97% and it is estimated that the treatment group can reach the same effective level after using the investigational product, with a clinically recognized noninferiority margin of 7% after discussion, a significance level of 5% at two tails, a statistical power of 80%, and a maximum possible dropout rate of 20%, about 120 patients should be included in each group with a total of 240 patients to be included in both groups.
Statistical design:	This trial will adopt a prospective, multicenter, randomized, and controlled design, using the Filtek™ Z350XT as the control, which is also a resin filling material and has similar and comparable characteristics, uses, and indications to the investigational device. The noninferiority design will be adopted to prove that the safety and efficacy of the investigational device are not inferior to the control device, which was already approved for marketing with clinically validated safety and efficacy.
Trial duration:	The enrollment period is estimated to be 6 months. The follow-up period is 1 year. Therefore, it will take about 18 months from the enrollment of first subject to the completion of the trial by the last subject.

Flow diagram of the trial

Time points	Screening - baseline visit		Cavity filling	Immediately after filling	1 week (±3 d) after the filling procedure	1 year (±1 mo) after the filling procedure
	Preoperative screening	Screening after cavity preparation				
Informed Consent	X					
Inclusion/Exclusion Criteria	X	X				
Medical history/ demographic data	X					
Pregnancy test	X					
Basic physical examination	X[1)]					
Oral examination	X[2)a]	X[3)]		X[4)a]	X[a]	X[a]
X-ray examination[b]	X			X[5)]	X[5)]	X
Digital photos	X	X		X	X	X
Record of operation procedures		X	X			
Randomization		X[6)]				
Clinical evaluation/Scoring				X[7)]	X[7)]	X[7)]
Record of AEs	X	X	X	X	X	X

1) Basic physical examination including blood pressure, heart rate, and respiration.

2) During preoperative screening, an oral examination is required to determine whether the mouth openness, tooth location, cavity type, antagonist (whether natural), cavity size, tooth staining, and lesion depth meet the inclusion/exclusion criteria. For subjects who satisfy the inclusion criteria initially, record the tooth location and basic characteristics of all the diseased teeth in the oral cavity as well as the cavity type, tooth location, lesion depth, pulp vitality, tooth staining, and periodontal lesion of the selected teeth in detail.

Normal pulp vitality is defined as no symptoms of abnormal pulp vitality, whether determined by clinical symptoms or an X-ray. The response is normal as determined by the pulp vitality test.

3) After cavity preparation, conduct an oral examination again to confirm the lesion depth, cavity size, and gingival margin after cavity preparation on the proximal surface (Class II cavities), and to determine whether the cavity after preparation is suitable for resin filling (to confirm that the thickness of remaining teeth after cavity preparation is appropriate, so as to avoid tooth fracture caused by thin residual teeth). Confirm whether the inclusion/exclusion criteria are met after cavity preparation.

4) Oral examination shall be conducted again after the filling procedure to confirm whether the filling is in occlusal contact and the occlusal relationship is normal. For Class II cavities, it is necessary to confirm whether the filling is in contact with adjacent tooth and proximal contact is restored. Check whether there is any abnormal oral soft tissue around the restored teeth.

5) Conduct an X-ray examination immediately after the procedure. If the examination is not carried out right afterwards, it can also be conducted within 1 week after the procedure.

6) Randomization can be applied in the central randomization system after the results of both the initial screening and screening after cavity preparation meet the inclusion/exclusion criteria, while failed cases should not be included in the randomization.

7) Measures to be evaluated immediately after the filling procedure include: retention and fracture, marginal fracture, contour and marginal adaptation, proximal contact, color match, surface roughness, surface staining, marginal discoloration, secondary caries and pulp status.

Measures of the tooth at the 1 week follow-up visit after the filling procedure include: retention and fracture, marginal fracture, contour and marginal adaptation, proximal contact, color match, surface roughness, surface staining, marginal discoloration, secondary caries and pulp status, which are the secondary measures of the trial.

Measures of the tooth at the 1 year follow-up visit after the filling procedure include: retention and fracture, marginal fracture, contour, and marginal adaptation, which are the primary endpoints of the trial. Meanwhile, following measures (secondary measures) will be evaluated and scored: proximal contact, color match, surface roughness, surface staining, marginal discoloration, secondary caries and pulp status.

a. Examination of oral soft tissues will be conducted before cavity preparation, immediately after filling, 1 week after filling, and 1 year after filling, as measures to evaluate the safety of resin products.

b. Periapical radiograph is required for the X-ray examination.

1. Sponsor

1.1 Name of the Sponsor

3M ESPE Dental Products

1.2 Address of the Sponsor

2510 Conway Street, St. Paul MN, US 55144-1000

1.3 Contact information of the Sponsor:

1-651-7369883

1.4 Qualifications of the Sponsor

The relevant qualification documents of the Sponsor include ISO approval documents, which were already submitted in the ethics submission

1.5 Name, address, and contact information of the agent and the relevant qualifications

Name of Agent: Minnesota Mining Manufacturing (Shanghai) International Trade Co., Ltd.
Address of Agent: Part A, Building 1, No. 858, Yinglun Road, China (Shanghai) Pilot Free Trade Zone
Contact Information of Agent: 86-21-62753535
The relevant qualification documents of the Agent were already submitted in the ethics submission, including business license, organization code certificate, license for operation, business permit and tax registration certificate as well as the Sponsor's quality certification system documents and the power of attorney to entrust the agent.

2. List of all the clinical trial institutions and investigators in the multicenter clinical trial and protocol signatures

Leading Unit: Peking University Hospital of Stomatology

List of Principal Investigators:

Codes of Clinical Trial Institutions	Names of Clinical Trial Institutions	Investigator	Professional Title	Contact Information	Signature of Investigator	Date of Signature
01	Peking University Hospital of Stomatology	Wang Xiaoyan	Chief Physician	010-82195525		
02	Wuhan University Hospital of Stomatology	Chen Zhi	Chief Physician	027-87686209		
04	Beijing Stomatological Hospital Capital Medical	Zhang Chen	Chief Physician	010-57099230		

	University					

3. Objective and content of the clinical trial

3.1 Purpose

Evaluation of the safety and efficacy of Filtek™ Bulk Fill Posterior Restorative 1 week and 1 year after its application in the filling of Class I and II cavities of posterior teeth.

3.2 Content

Referencing to the requirements of the Technical Review Guidelines for the Registration of Dental Resin Filling Materials and the Clinical Trial Guideline for Polymer-based Dental Restorative Materials, the primary efficacy measure of this trial is the clinical acceptance rate of the filling at the 1 year follow-up visit after the filling procedure. This trial adopts a two-arm, randomized, and controlled design. All the relevant clinical data generated in this trial will be collected, compiled, statistically analyzed, and determined by independent data management and statistics centers and clinical audit departments. All the selected subjects will be evaluated at the 1 week and 1 year follow-up visits after the procedure in the outpatient department to observe the measures listed in the Technical Review Guidelines for the Registration of Dental Resin Filling Materials (Appendix 1) and the occurrences of adverse events, and accurately evaluate the immediate, short-term and long-term efficacy, and safety of Filtek™ Bulk Fill Posterior Restorative.

After signing the Informed Consent, the subjects will be included in the screening stage, while those who meet all the inclusion criteria and do not meet any of exclusion criteria will formally be included in the trial. Since the evaluation that are based on inclusion and exclusion criteria will be conducted at both the initial screening and screening after cavity preparation, the screening stage of this trial includes the initial screening and screening after cavity preparation. Then, the filling procedure will be performed. After the completion of cavity filling, the subjects will be evaluated immediately (visual examination, probing, dental floss examination, temperature test), and the immediate postoperative evaluation of the filling will be conducted using the scoring criteria as stipulated in Appendix 1 as follows: retention and fracture, marginal fracture, contour and marginal adaptation, proximal contact, color match, surface roughness, surface staining, marginal discoloration, secondary caries and pulp status, and recorded in the original medical record and electronic Case Report Form. The immediate postoperative restoration results need to meet the clinical expectations. If the immediate postoperative restoration results do not meet the clinical expectations and the filling cannot be repaired and needs a filling of another brand, all the details should be recorded. All fillings without a grade A postoperative restoration result will also be included in the final statistical analysis to evaluate its possible influence on the outcome.

4. Background data of the clinical trial

Composite resins for posterior restoration have been applied rapidly since the 1990s. At present, the composite resin is widely used in many countries to restore the tooth defect, contour, and function of the posterior tooth in a nearly complete replacement of silver amalgam.[1] This is mainly due to the fact that the resin has the following characteristics that

the silver amalgam does not have: ① esthetic ② environmentally friendly ③ its adhesion to dental tissues is through chemical and micro-mechanical adhesion rather than simple mechanical adhesion ④ maximized preservation of healthy dental tissues. In comparison, the composite resins for posterior restoration have been greatly improved in terms of distribution, particle size, and content of filler and also mechanical and physical properties, resulting reduced polymerization shrinkage, enhanced wear resistance performance, and greatly improved clinical operational performance.

The bulk-fill composites for posterior restoration (a translucent composite resin material with higher curing depth) was first applied in the clinical restoration and treatment of posterior defect at the start of 2000.[3] In vitro experiments showed that the success rate of less but thicker material is the same as that of incremental filling at a smaller thickness[4–7], while the risk of voids or failure due to thinner increment could be avoided.[2] It is also reported in the literature that the bulk-fill materials have acceptable creep deformation, which is within the range of other composite resin materials.[2]

3M™ Filtek™ Bulk Fill Posterior Restorative is a bulk-fill material. It is a filling and restoration composite material that can be activated by visible light and is optimized to restore posterior tooth more simply and quickly. When Filtek™ Bulk Fill Posterior Restorative is applied in a tooth with the methacrylate-based dental adhesive (such as the dental adhesive manufactured by 3M ESPE), the restoration can be permanently adhered to the tooth tissue. This bulk-fill resin material is more convenient and quicker to apply in comparison to the traditional composite resin materials and can save the operation time for the filling procedure.

3M™ Filtek™ Bulk Fill Posterior Restorative was marketed and sold in the United States, Canada, and Western Europe in September 2014 and has been widely used clinically without any AE report or complaint up to now. This trial is a pre-marketing clinical validation trial in China, and will comply the Helsinki Declaration and CFDA's Good Clinical Practice of Medical Device Clinical Trial (March 23, 2016), and will be designed and implemented in references to the requirements of CFDA's Technical Review Guidelines for the Registration of Dental Resin Filling Materials[9] and the Clinical Trial Guideline for Polymer-based Dental Restorative Materials[10] in order to evaluate the clinical safety and efficacy of Filtek™ Bulk Fill Posterior Restorative 1 week and 1 year after the restoration of Class Ⅰ and II cavities of posterior teeth using a randomized controlled trial design method.

5. Characteristics, structural composition, working principles, and mechanism of action of the product and scope of the trial

5.1 Characteristics, structural composition, working principles, and mechanism of action of the investigational device and scope of trial

5.1.1 Characteristics of the product

3M™ Filtek™ Bulk Fill Posterior Restorative is a filling and restoring composite material activated by visible light and optimized to restore posterior tooth more simply and quickly. When Filtek™ Bulk Fill Posterior Restorative is applied in a tooth with the methacrylate-based dental adhesive (such as the dental adhesive manufactured by 3M ESPE), the restoration can be permanently adhered to the tooth tissue.

5.1.2 Structural composition, working principles and mechanism of action of the product

The filler used in Filtek™ Bulk Fill Posterior Restorative is the same as that used in the traditional light cured composite resin - Filtek™ Z350XT Universal Restorative (control device), and is a passive medical device with high strength, high wear resistance, X-ray opaque, reduced shrinkage, and good operability. Filtek™ Bulk Fill Posterior Restorative uses a high molecular weight monomer to effectively reduce shrinkage and form a highly interlinked network with high strength. [redacted] At the same time, Filtek™ Bulk Fill Posterior Restorative is also used to restore anterior teeth that need translucent shades, due to the good retention of polishing luster. All shades are X-ray opaque. Their applying method is also the same to that of conventional incremental resin. When the cavity depth is greater than 5 mm, it can be layered again. However, since the maximum curing depth allowed for one layer is greater, the number of layering times and the time required for filling are both reduced to a certain extent. Therefore, it is simpler and more convenient to use in clinical applications.

5.1.3 Specifications and model

Kits: 4863TK, 4864TK

In syringes: 4863A1, 4863A2, 4863A3, 4863B1, 4863C2

In capsules: 4864A1, 4864A2, 4864A3, 4864B1, 4864C2

5.1.4 Scope of application

This product is used for the direct or indirect restoration of anterior and posterior teeth.

5.2 Characteristics, structural composition, working principles, and mechanism of action of the control product (Filtek™ Z350XT Restorative) and scope of trial

5.2.1 Characteristics of the product

3M™ Filtek™ Z350XT is a universal resin used for anterior and posterior teeth and can be activated by visible light. It is easy to manipulate, with high strength and good attrition resistance performance, natural and almost real color after curing, a variety of colors available (including dentin, enamel, and body colors), good polishability and retention of polishing luster.

5.2.2 Structural composition, working principles and mechanism of action of the product

Universal Restorative is a kind of composite resin filling material that can be cured by visible light for the filling and restoration of anterior and posterior teeth. All colors are radio opaque. Its filler consists of: non-agglomerated/non-aggregated silica filler, non-agglomerated/non-aggregated zirconia filler, and aggregated zirconia/silica filler (comprising silica and zirconia particles). The resins of dentin, enamel and body colors all

have agglomerated particles with an average size of 0.6~20 microns. The average size of agglomerated particles in transparent tooth color resin is: 0.6~20 microns. For example, the dental adhesive from 3M ESPE can permanently bond resin restorations to tooth tissues. The product is available in many colors, such as dentin, body, enamel, and transparent colors. Syringes will be provided for this trial.

5.2.3 Models and specifications

In syringes: 7018A1B, 7018A2B, 7018A3B, 7018A3.5B, 7018B1B, 7018C2B

5.2.4 Scope of application

Direct or indirect restoration of anterior and posterior teeth.

6. Indications, contraindications, and precautions of the product

6.1 Indications, contraindications, and precautions of the investigational device

6.1.1 Indications

- Direct restoration of anterior and posterior teeth (including occlusal surface)
- Base/liner under direct restorations
- Core build-ups
- Splinting
- Indirect restorations, including inlays, onlays, and veneers
- Restorations of deciduous teeth
- Extended fissure sealing in molars and premolars
- Repair of defects in porcelain restorations, enamel, and temporaries

6.1.2 Contraindications

No known contraindications, but it should be used with caution in patients known to be allergic to acrylic acid.

6.1.3 Precautions

Wash with ample water if it comes into contact with oral soft tissues for a long time. In case of allergic reaction, seek medical attention and remove the product when necessary and avoid using the product in the future.

To mitigate the allergic reaction risk, doctors should try to avoid coming into contact with these materials when using the device, especially the uncured product. In case of skin contact, wash the skin with soap and water. It is suggested to wear protective gloves and adopt a non-contact technique. Acrylate may penetrate the gloves that are normally used. If the product comes into contact with the gloves, remove and discard the gloves, wash your hands immediately with soap and water, and then wear new gloves again. In case of an allergic reaction, seek medical advice immediately.

6.2 Indications, contraindications, and precautions of the control device

6.2.1 Indications

- Direct restoration of anterior and posterior teeth (including occlusal surface);
- Post-core technique;
- Splinting;
- Indirect restorations, including inlays, onlays, and veneers.

6.2.2 Contraindications

No known contraindications, but it should be used with caution in patients known to be allergic to acrylic acid

6.2.3 Precautions

Wash with ample water if it comes into contact with oral soft tissues for a long time. In case of allergic reaction, seek medical attention and remove the product when necessary and avoid using the product in the future.

To mitigate the allergic reaction risk, doctors should try to avoid coming into contact with these materials when using the device. especially the uncured product. In case of skin contact, wash the skin with soap and water. It is suggested to wear protective gloves and adopt a non-contact technique. Acrylate may penetrate the gloves that are normally used. If the product comes into contact with the gloves, remove and discard the gloves, wash your hands immediately with soap and water, and then wear new gloves again. In case of an allergic reaction, seek medical advice immediately.

7. Overall design

7.1 Trial design

7.1.1 Trial objective

Evaluation of the safety and efficacy of Filtek^{TM} Bulk Fill Posterior Restorative 1 week and 1 year after its application in the filling of Class I and II cavities of posterior teeth.

7.1.2 Selection and justification of methodology

The investigational product is a bulk-fill resin. As required in CFDA's Technical Review Guidelines for the Registration of Dental Resin Filling Materials, its clinical trial should be conducted in reference to the Clinical Trial Guideline for Polymer-based Dental Restorative Materials, which is applicable to the polymer-based dental restorative materials used in the direct restoration of posterior tooth defects, to restore Class I and II cavities of posterior teeth, in order to evaluate the safety and efficacy of 3M's Filtek^{TM} Bulk Fill Posterior Restorative in clinical application (not including the evaluation of other new functions).

7.1.3 Measures to reduce and prevent bias

The evaluation of all the observation measures will be conducted by independent

evaluators from each clinical trial institution immediately after the procedure and at the 1 week and 1 year follow-up visits. Each center will appoint three senior dentists to set up a clinical evaluation committee to complete an evaluation consistency test on all the evaluators from all the clinical trial institutions before the start of the trial.

The evaluation criteria in Appendix 1 will be used to evaluate the clinical effect of the filling. Before the formal start of this trial, all the clinical evaluators will be instructed on the evaluation criteria by way of systematic training, and they will undergo an evaluation on the 20 clinical digital photos of the fillings according to the criteria in Appendix 1. Shooting angle and aperture size will be consistent for all photos. All the evaluators will score and record the score of each photo according to the criteria in Appendix 1, and will be finally evaluated for consistency. A Kappa ≥ 65% is considered as good consistency.

The fillings from each center will be directly evaluated by 2 evaluators from the evaluation committee. If the clinical evaluations of these 2 evaluators are inconsistent, the evaluation of a third evaluator with higher seniority shall be adopted.

7.1.4 Investigational and control devices

The following devices used in this trial are provided by 3M

Investigational device: Filtek™ Bulk Fill Posterior Restorative

Model and specifications: In syringes: 4863A1, 4863A2, 4863A3, 4863B1, 4863C2

Control device: 3M™ ESPE™ Filtek™ Z350XT

Model and specifications: In syringes: 7018A1B, 7018A2B, 7018A3B, 7018A3.5B, 7018B1B, 7018C2B

In this trial, shades A1, A2, A3, B1, C2 of Filtek™ Bulk Fill Posterior Restorative and shades A1B, A2B, A3B, A3.5B, B1B, C2B of 3M™ ESPE™ Filtek™ Z350XT will be provided. The shades to be provided will be used in the clinical trial as much as possible, but the actual specifications and models will depend on the actual conditions of subjects and actual requirements in clinical application.

In addition to investigational and control devices, the following devices will be used in the trial:

Adhesive system: 3M™ ESPE™ Single Bond Universal Adhesive

Curing light: 3M™ Elipar S10 LED Light

Polishing system: 3M™ Sof-lex Finishing and Polishing System

Matrix bands: provided by the Sponsor (agent)

Probe (for evaluation): provided by the Sponsor (agent)

Bur: provided by the Sponsor (agent)

Rubber dam: provided by the Sponsor (agent)

7.1.5 Subject selection

A total of 240 male and female subjects at 18~70 years old, who need the filling of Class I and II cavities of the posterior teeth (including substitute filling), will be enrolled.

For subjects who fail to pass the screening, only their information recorded in the corresponding screening period will be collected and recorded in their original medical records and screening inclusion forms, while their data will be entered into the trial database. The subjects who withdraw after enrollment will not be recruited again, and their withdrawal reasons shall be recorded in the original medical records and case report forms. Their data must be included in the trial database and reported.

All the subjects who are enrolled in the trial and have given their informed consents will be recorded, regardless of whether they will receive the filling procedure.

7.1.5.1 Inclusion criteria

1) Male or female, 18-70 years old (including 18 and 70 years)
2) Healthy, with no major systemic disease
3) Normal mouth openness
4) Molar (preferred) or premolar
5) Cavities satisfying any of the following 4 conditions:
   ① Class I cavities, including those that need to be restored again after a previously failed filling;
   ② Class II cavities, with a lesion on tooth locations other than second molars (including a failed previous filling, which needs to be filled again now), and the gingival margin after cavity preparation on the proximal surface located at the gingival crown margin;
   ③ Class II cavities, with a lesion on second molars, no missing third molars (including a failed previous filling, which needs to be filled again now), and the gingival margin after cavity preparation on the proximal surface located at the gingival crown margin;
   ④ Class II cavities, with a lesion on second molars, missing third molars, lesion on the Mesial Occlusal (MO) or Mesial Occlusal Distal (MOD) surface of second molars (including a failed previous filling, which needs to be filled again now), and the gingival margin after cavity preparation on the proximal surface located at the gingival crown margin;
6) Cavity size: minimum buccolingual distance on the occlusal surface (approx.) not less than 1/3 of buccolingual distance between the cusps;
7) The opposing tooth is natural;
8) Depth of the lesion reaching at least the middle layer of dentin with normal pulp vitality;
9) The subjects agree to participate in the trial and sign the Informed Consent;

10) The subject is compliant and committed to follow-up visits.

7.1.5.2 Exclusion criteria

1) Allergic constitution or allergic to multiple drugs; allergy history of polymer based materials, such as dental resin;
2) Aggressive caries; severe periodontitis; abnormal salivary gland function; temporomandibular joint disorder;
3) Poor oral health, DMFT: > 4 for 18~34 years old; >5 for 35~70 years old;
4) Teeth with special staining;
5) Non-carious tooth diseases, such as pathological wear (nocturnal molars, clenching habits), acid erosion, or subfissure;
6) Abnormal occlusion;
7) Severe systemic diseases; mental illness;
8) Breastfeeding, pregnant (positive pregnancy test result) and at childbearing age with intention to conceive;
9) The subject is determined to be poor compliance and could not complete the trial as required as determined by the investigator;
10) The cavity is determined to be unsuitable for resin filling by the investigator;
11) Pulp already exposed or close to be exposed at the bottom;
12) The subject plans to go overseas within 1 year or cannot complete the 1 year follow-up visit after the procedure due to other reasons;
13) The subject also participates in a clinical trial of the other drug or medical device, which has not reached its clinical endpoint;
14) The subject is not tolerant of or willing to use the rubber dam.

If multiple caries of a subject meet the inclusion/exclusion criteria, the investigator will select the enrolled tooth by giving priority to molars; If all teeth that meet the inclusion/exclusion criteria are molars, the investigator can enroll any tooth and indicate the enrolled tooth number in the original medical record and case report form. If other teeth that are not included need to be treated at the same time, the name of filling resin (when other marketed products than Filtek^{TM} Z350XT are required) and the tooth location number for such filling should be recorded.

7.1.5.3 Termination of the trial

1) In case of any SAE related to the materials, the Principal Investigator, Ethics Committee and/or Head of Clinical Pharmacology Center, Persons in charge of national or local drug administration may terminate the entire trial from the perspective of ethics;

2) During the trial, if more than 10% of the subjects have mild AEs related to the investigational materials, such as allergic reaction of oral mucosa, an application can be submitted to the Ethics Committee to terminate the entire trial after

communicating with the Principal Investigator;

3) If a center or investigator is in breach of the approved protocol, the Good Clinical Practice of Medical Device Clinical Trial (GCP) or the contract, the Sponsor may point out such breach and takes necessary measures (such as retraining) for correction. If the situation is serious or has not improved, affecting the normal performance of the trial, the Sponsor has the right to require the trial to be terminated at the center.

If the trial is terminated, the investigator/center will be compensated for their reasonable incurred expenses (except for the reasons stipulated in Article 3).

7.1.5.4 Withdrawal from the trial

All the subjects who have given their informed consents, passed the screening and been enrolled in the trial can withdraw from the trial at any time for any reason, without affecting their interests or subject to any punishment in any form. Withdrawal reasons must be recorded in the original medical records and case report forms. Withdrawal reasons include:

1) The subject withdraws their informed consent and requests to be removed from the trial at any time and for any reason;

2) Serious deviation to the protocol;

3) Cannot participate in the trial further due to health reasons;

4) Cannot attend follow-up visits due to moving to another address or other reasons;

5) The Investigator removes the subject from the trial for their health;

6) Withdrawal from the trial due to AE;

7) Loss to follow-up due to various reasons;

As long as all the trial contents are not completed as required by the protocol, these cases shall be treated as withdrawal/dropout cases

In case of loss to follow-up and dropout, the investigator should try their best to contact a subject and record the reason, such as by door-to-door visit, appointment for follow-up, telephone, mail and etc. For a subject who withdraws from the trial due to adverse events, the adverse event must be recorded in the original case and case report form, and the Sponsor shall be notified. All source data and source files of all the enrolled and participated subjects shall be kept regardless of whether they are removed or not.

7.1.5.5 Expected involvement time of subjects

The trial will be conducted as required in CFDA's Technical Review Guidelines for the Registration of Dental Resin Filling Materials with its design in reference to the Clinical Trial Guideline for Polymer-based Dental Restorative Materials, to set the clinical evaluation measures of subjects 1 year after filling as the primary clinical endpoint, so that the involvement time of each subject is about 1 year from the beginning of screening to the completion of the trial. During this period, the subject can withdraw from the trial at any time for any reason, and the investigator can also remove the subject to protect the interests of the

subject. Withdrawal reasons of subjects will be recorded in the original medical records and case report forms and also analyzed in statistical analysis.

7.1.5.6 Expected duration of the clinical trial and justifications

This trial consists of a screening period (the initial screening period, screening after cavity preparation period), a 1-week follow-up period and a 1-year follow-up period. During the screening period, various examinations required in the protocol will be carried out to enroll the subjects who meet the inclusion and exclusion criteria. The examinations and evaluations in the initial screening period will be completed within 0.5 days. The subjects passing the initial screening will make an appointment with the investigator for cavity preparation and filling, which duration to be required is related to the complexity of diseased teeth and will be completed within 0.5 days. The subjects passing the screening after cavity preparation will be immediately scored on evaluation measures after the procedure, and the subjects with passing grades will be included for 1 week and 1 year follow-up visits.

Schedule of screening enrollment: a total of 240 subjects will be enrolled within 6 months after the start of the trial.

Schedule of follow-up visits: 1 week and 1 year outpatient follow-up visits after the filling procedure.

It is estimated that the trial will take about 18 months from the enrollment of first subject to the completion of the trial by the last subject.

7.1.5.7 Number of subjects required for the clinical trial and their enrollment time

This trial will adopt a two-arm, randomized, controlled, and noninferiority design. In reference to the Clinical Trial Guideline for Polymer-based Dental Restorative Materials and in consideration of the characteristics and post marketing clinical study data in other countries of the control device, the primary measure is the clinical acceptance rate of the filling at the 1 year follow-up visit after the filling procedure, and assuming the clinical acceptance rates are 97% for both treatment and control groups, a noninferiority margin of 7% and a dropout rate of 20%, a total of 240 subjects will be enrolled in and complete the trial. The 240 subjects will be recruited by 3 clinical trial institutions, and the enrollment period is estimated as 6 months in consideration of the number of patients of each center, possible screening failure rate, and the number of investigators.

7.1.6 Evaluation methodology of efficacy

1) The primary efficacy measure is the clinical acceptance rate of the filling at the 1 year follow-up visit after the filling procedure

According to the Clinical Trial Guideline for Polymer-based Dental Restorative Materials (YY/T 0990-2015), the definition of clinically acceptable filling at the 1 year follow-up visit is: grade A for retention and fracture of the filling 1 year after the filling procedure; grade A or B for marginal fracture, contour, and marginal adaptation of the filling.

2. Secondary efficacy measures:

- Clinical acceptance rate of the filling at the 1 week follow-up visit after the filling

procedure:

According to the Clinical Trial Guideline for Polymer-based Dental Restorative Materials (YY/T 0990-2015), the definition of clinically acceptable filling at the 1 week follow-up is: grade A or B 1 week after the filling procedure for all the evaluation measures, including retention and fracture of the filling, marginal fracture, contour and marginal adaptation, proximal contact, color match, surface roughness, surface staining, marginal discoloration, secondary caries and pulp status;

- Proximal contact, color match, surface roughness, surface staining, marginal discoloration, secondary caries and pulp status 1 year after the filling procedure

Scoring criteria for each item are listed in Appendix 1. The score of each item shall be recorded in the original medical record and case report form of the trial as required.

7.1.7 Evaluation methodology of safety

All AEs and SAEs will be collected and recorded from the time when the subject signs the Informed Consent to the time when the subject completes the trial or withdraws from the trial early. Primary measures include the examination of oral soft tissues and secondary caries and pulp stimulation. Because the investigational device is filling resin for posterior tooth, which will be used by local application, its safety evaluation is mainly concentrated in the oral cavity. The evaluation will be conducted before filling, immediately after filling, 1 week after filling, and 1 year after filling, in which the oral soft tissues to be examined include but not limited to buccal mucosa, lip, upper jaw, floor of mouth and tongue, and record all abnormalities and conduct statistical analysis.

The subjects can also report any local and systemic abnormalities to the investigator at any time. If necessary, they can make an appointment with the investigator for examination as soon as possible.

Evaluation methodology of secondary caries and pulp status are as stipulated in Appendix 1, and should be conducted before filling, immediately after filling, 1 week after filling, and 1 year after filling. If there is any abnormality and the investigator determines that it is clinically significant, it should be determined as an AE.

7.2 Trial procedures

7.2.1 Screening and baseline visit

The subjects should be informed in detail before any of examinations. After signing the Informed Consent, the subjects will be included in the following screening stage, while those who meet all inclusion criteria and do not meet any of the exclusion criteria will be formally included in the trial.

(1) Pre-operative initial screening (First screening) - before cavity preparation:

Conduct a formal informed consent process for all the subjects and let them sign the informed consent form. Record basic information of the subjects who have already sign the Informed Consent and conduct preoperative screening examinations based on the

inclusion/exclusion criteria. The subjects who satisfy the inclusion/exclusion criteria of the initial screening will be included in the cavity preparation phase, or they will be determined as failed cases and will not be included in the whole data set analysis. Failed cases can make appointments with their doctors to have their cavities restored with other marketed materials.

Procedures before cavity preparation:

1） Sign the Informed Consent and assign Screening No.
2） Screen and select eligible subjects based on inclusion/exclusion criteria
3） Systematic and oral medical histories
4） Medication history
5） Demographic data
6） Basic physical examination
7） Pregnancy check
8） Oral examination
9） X-ray examination (Periapical radiograph)
10） Examination of digital photos

(2) Cavity preparation (Second screening) - after cavity preparation

Procedures after cavity preparation and before filling

1） Confirm a subject still satisfies the inclusion/exclusion criteria;
2） Oral examination;
3） Examination of digital photos;
4） AEs

Conduct an oral examination after cavity preparation based on the inclusion/exclusion criteria. The subjects who satisfy the inclusion/exclusion criteria of screening after cavity preparation will be included in cavity filling phase, or they are determined as screening failures and will not be included in the whole data set analysis. The subjects who fail the screening after cavity preparation will receive the Filtek^{TM} Z350XT resin (Control device) manufactured by 3M and marketed in 2011 domestically for free filling after failing the screening.

Record the specific information of cavity preparation in detail, including removed material during the cavity preparation, whether local anesthesia is applied, cavity type, cavity margin conditions, cavity size, maximum depth of cavity, cavity bottom conditions, gingival margin after cavity preparation, etc.

7.2.2 Cavity filling

Perform cavity filling by the following the intraoperative requirements (see 7.3 for details). Record the cavity filling procedure in detail, including whether to cover pulp or base, use of rubber dam and matrix band, acid etching, rinsing, bonding, curing time, and layers of resin filling.

Procedures of cavity filling

1） Cavity filling;
2） Immediately evaluation after filling;
3） X-ray examination (Periapical radiograph);
4） Examination of digital photos;
5） AEs;

After the filling of a posterior defect (including the treatment and control groups), immediately conduct the clinical evaluation according to the standards in Appendix 1. The following items will be evaluated by visual inspection, probing, dental floss inspection, and temperature test: retention and fracture of the filling, marginal fracture of the filling, contour and marginal adaptation, proximal contact, color match, surface roughness, surface staining, marginal discoloration, secondary caries and pulp status.

The immediate postoperative restoration results should meet the clinical expectations. For fillings with immediate postoperative evaluation results failing the clinical expectations, the investigator shall repair the filling or use the original material for another filling to ensure all the measures of the filling meet the clinical requirements. If another material is required to be used instead for a subject, the subject should be removed from the trial. All evaluation results and operations must be recorded in the original medical records and case report forms. All fillings without a grade A postoperative restoration result will also be included in the final statistical analysis to evaluate its possible influence on the outcome.

7.2.3 Follow-up visit 1 week after the filling procedure

At the 1 week outpatient follow-up visit after the filling procedure, record the use of teeth in the past week by routine inquiry, conduct oral examination, test pulp vitality, and take digital photos, while confirming whether the postoperative X-ray examination has been completed, and if not, conduct an X-ray examination at the 1 week follow-up visit. Evaluate and record the scores on the following measures: retention and fracture of the filling, marginal fracture of the filling, contour and marginal adaptation, proximal contact, color match, surface roughness, surface staining, marginal discoloration, secondary caries and pulp status.

If there is any AE from the procedure to this follow-up visit, record the data in detail.

1） Conduct clinical evaluation as stipulated in Appendix 1 and record the results
2） Oral examination
3） Examination of digital photos
4） Record of AEs
5） Complete the follow-up visit

7.2.4 Follow-up visit 1 year after the filling procedure

At the 1 year outpatient follow-up visit after the filling procedure, record the use of teeth in the past year by routine inquiry, conduct oral examination, test pulp vitality, and take digital photos and X-ray radiography. Focus on the evaluation of the following measures: retention and fracture, marginal fracture, contour, and marginal adaptation.

Evaluate and record the scores on the following measures: proximal contact, color match, surface roughness, surface staining, marginal discoloration, secondary caries and pulp status.

If there is any AE from last to this follow-up visit, record the data in detail.

1) Conduct clinical evaluation as stipulated in Appendix 1 and record the results
2) Oral examination
3) X-ray examination (Periapical radiograph)

4) Examination of digital photos
5) Record of AEs
6) Complete the trial

Flow diagram of the trial

Time points	Screening - baseline visit		Cavity filling	Immediately after filling	1 week (±3 d) after the filling procedure	1 year (±1 mo) after the filling procedure
	Preoperative screening	Screening after cavity preparation				
Informed Consent	X					
Inclusion/Exclusion Criteria	X	X				
Medical history/ demographic data	X					
Pregnancy test	X					
Basic physical examination	X[1)]					
Oral examination	X[2)a]	X[3)]		X[4)a]	X[a]	X[a]
X-ray examination[b]	X			X[5)]	X[5)]	X
Digital photos	X	X		X	X	X
Record of operation procedures		X	X			
Randomization		X[6)]				
Clinical evaluation/Scoring				X[7)]	X[7)]	X[7)]
Record of AEs	X	X	X	X	X	X

1) Basic physical examination including blood pressure, heart rate, and respiration.
2) During preoperative screening, an oral examination is required to determine whether the mouth openness, tooth location, cavity type, antagonist (whether natural), cavity size, tooth staining, and lesion depth meet the inclusion/exclusion criteria. For subjects who satisfy the inclusion criteria initially, record the tooth location and basic characteristics of all the diseased teeth in the oral cavity as well as the cavity type, tooth location, lesion depth, pulp vitality, tooth staining, and periodontal lesion of the selected teeth in detail.
Normal pulp vitality is defined as no symptoms of abnormal pulp vitality, whether determined by clinical symptoms or an X-ray. The response is normal as determined by the pulp vitality test.
3) After cavity preparation, conduct an oral examination again to confirm the lesion depth, cavity size, and gingival margin after cavity preparation on the proximal surface (Class II cavities), and to determine whether the cavity after preparation is suitable for resin filling (to confirm that the thickness of remaining teeth after cavity preparation is appropriate, so as to avoid tooth fracture caused by thin residual teeth). Confirm whether the inclusion/exclusion criteria are met after cavity preparation.

4) Oral examination shall be conducted again after the filling procedure to confirm whether the filling is in occlusal contact and the occlusal relationship is normal. For Class II cavities, it is necessary to confirm whether the filling is in contact with adjacent tooth and proximal contact is restored. Check whether there is any abnormal oral soft tissue around the restored teeth.
5) Conduct an X-ray examination immediately after the procedure. If the examination is not carried out right afterwards, it can also be conducted within 1 week after the procedure.
6) Randomization can be applied in the central randomization system after the results of both the initial screening and screening after cavity preparation meet the inclusion/exclusion criteria, while failed cases should not be included in the randomization.
7) Measures to be evaluated immediately after the filling procedure include: retention and fracture, marginal fracture, contour and marginal adaptation, proximal contact, color match, surface roughness, surface staining, marginal discoloration, secondary caries and pulp status.
Measures of the tooth at the 1 week follow-up visit after the filling procedure include: retention and fracture, marginal fracture, contour and marginal adaptation, proximal contact, color match, surface roughness, surface staining, marginal discoloration, secondary caries and pulp status, which are the secondary measures of the trial.
Measures of the tooth at the 1 year follow-up visit after the filling procedure include: retention and fracture, marginal fracture, contour, and marginal adaptation, which are the primary endpoints of the trial. Meanwhile, following measures (secondary measures) will be evaluated and scored: proximal contact, color match, surface roughness, surface staining, marginal discoloration, secondary caries and pulp status.
a. Examination of oral soft tissues will be conducted before cavity preparation, immediately after filling, 1 week after filling, and 1 year after filling, as measures to evaluate the safety of resin products.
b. Periapical radiograph is required for X-ray examination.

7.3 Standard operation procedures relevant to the investigational/control device

All intraoperative procedures should follow the product instructions.

1) Pre-treatment

Clean tooth surface to remove pigment and calculus.

2) Selection of shade

Before isolating the tooth, use a standard VITAPAN® classical shade selection guide to choose an appropriate color for the restorative material.

Note: Since the bulk-fill composites for posterior restoration is translucent, the location of the restoration, color of residual tooth, or the adjacent restoration will influence the final appearance of the restoration.

3) Isolation of moisture: use a rubber dam to isolate moisture.

4) Cavity preparation:

Posterior filling and restoration: prepare the cavity, the line angle and point angle should be more rounded. It is recommended to use the hardness method for debridement. After cavity preparation, carefully check the cavity shape and confirm that the cavity size is suitable for resin filling. It is required to confirm that the cavity bottom is located in the dentin without being close to or exposing pulp.

5) Placement of matrix band

Posterior filling and restoration: place a metal matrix band dedicated for resin and firmly retain it with a wedge. Select an appropriate matrix band to form proximal contour and contact area. Adjust the matrix band to seal the gingival area to avoid the formation of overhang.

Note: Acid-etch enamel and apply an adhesive when necessary and then place the matrix band.

6) Adhesive system

Use the 3M™ ESPE™ Dental Adhesive System (3M™ ESPE™ Single Bond Universal Adhesive) to bond the bulk-fill composite for posterior restoration to tooth tissues. It is recommended to use the selective acid-etching adhesive technique to etch enamel for 15 s but not dentin, apply the adhesive on enamel and dentin for 20 s, air dry for 5 s and light cure for 10 s. (Please strictly follow the product instructions of the adhesive system to understand the complete product instructions and precautions). After the adhesive is cured, continue to isolate blood, saliva, and other liquids, and immediately apply the bulk-fill composite for posterior restoration. In order to exclude the influence of other materials to this trial as far as possible, it is recommended to avoid using of cavity base.

7) Delivery

Follow the corresponding instructions of the selected delivery system.

8) Filling

(8.1) Avoid intense lighting in the work area. Exposure of the composite resin to intense light may lead to premature polymerization.

(8.2) Overfill the cavity slightly to allow the composite resin to cover the cavity margin. Use an appropriate resin finishing tool to shape the contour. For cavities with an appropriate depth, it is suggested to restore with one filling. If the cavity depth exceeds the maximum curing depth, two fillings should be delivered.

9) Curing

The product will be cured with a 3M ESPE Curing Light to cure each incremental layer by irradiating the entire surface with a high intensity visible light source, while the guide tip should be positioned as close to the filling material as possible. The output power of curing light shall be measured before each curing.

When using the investigational device - Filtek™ Bulk Fill Posterior Restorative, the suggested curing time and power are:

Cavity classification	Thickness of each incremental layer	3M™ ESPE™ LED Curing Light (output power 1,000-2,000 mW/cm^2)
Class I cavities	4 mm	20 s
Class II cavities	5 mm	10 s occlusal, 10 s buccal, 10 s lingual

Note: For filling and restoration of Class II cavities, remove the matrix band before curing at buccal and tongue sides.

When using the control device - Filtek™ Z350XT Universal Resin, the suggested curing time and power are:

Tooth shade	**Increase thickness**	**Curing time**
Dentin shade, enamel shade, translucent shade	2.0 mm	20 s
Dentin shade, A6B and B5B	1.5 mm	40 s

10) Profiling

Use fine-grained diamonds, burs or grinding stones to profile the surface of the restoration.

11) Adjustment of the occlusal surface

Use a piece of thin articulating paper to check occlusion. Check the centric and lateral occlusal contacts. Use a fine-grained polishing diamond bur or grinding stone to remove excess material and fine tune the occlusal relationship.

12) Polishing

Use the Sof-Lex™ Finishing and Polishing System to polish.

During the filling procedure, record the clinical operation procedures in detail, such as whether the soft scale on tooth surface, dental calculus, detritus or original filling are removed, whether local anesthesia is applied, cavity location, depth and type, cavity preparation conditions, whether cavity clean up is performed and the materials used in the clean up, whether the pulp is already exposed or close to be exposed at the bottom, whether to cover pulp or base and the materials used in the treatment, filling method of resin, supporting adhesive system, curing conditions of resin, and finishing and polishing system used for the filling, etc.

7.4 Storage and management of the investigational and control products

The transportation, usage, and recovery of Filtek™ Bulk Fill Posterior Restorative (investigational device) and Filtek™ Z350XT (control device) will be recorded in detail in corresponding transportation, usage and recovery forms, which will be saved in the investigator's folder. Meanwhile, all the centers are required to have independent and qualified storage site satisfying the storage conditions of Filtek™ Bulk Fill Posterior Restorative, which will be used for their storage and safeguarded by designated staff. The investigational and control products should be stored at room temperature away from intense light. When being stored at room temperature, the shelf life of the product is 3 years. The expiration date is printed on its outer package. After the end of the trial, all used and unused investigational and control products will be returned to the address of the Sponsor, unless there is relevant existing product destruction SOP in a center.

7.5 Auditing schedule

Monitors of or appointed by the Sponsor (or its agent) will regularly audit all clinical trial institutions, including whether the data recorded in the case report forms are consistent with the original data, whether there are any missing data, signatures on the Informed Consent and the informed consent process, whether there is any deviation from the protocol and whether the documents required to be saved by the clinical trial institution are complete, so as to ensure that the trial is conducted according to the protocol and the trial data is complete and accurate. The detailed auditing schedule will be determined by the Sponsor before enrolling and strictly followed by the monitors. An Audit Report must be submitted to the Sponsor for review within 1 week after each audit visit.

8. Statistical considerations

8.1 Statistical design, methodology, and analysis procedures

8.1.1 Statistical design (test of hypothesis)

This trial will adopt a prospective, multicenter, randomized, and controlled design, using the Filtek™ Z350XT as the control, which is also a resin filling material and has similar and comparable characteristics, uses, and indications to the investigational device. The noninferiority design will be adopted to prove that the safety and efficacy of the investigational device are not inferior to the control device, which was already approved for marketing with clinically validated safety and efficacy. Corresponding statistical design and test of hypothesis are:

$$H_0 : p_T - p_C \leq -\Delta$$
$$H_1 : p_T - p_C > -\Delta$$

Where p_T is the expected success rate of the filling in corresponding treatment group, p_C is the expected success rate of the control group and Δ is the noninferiority margin (absolute value).

8.1.2 Statistical analysis methodology

Descriptive analyses: count data will be described by frequency and constituent ratio; measurement data will be described by mean value, standard deviation, maximum, minimum, median, 25th and 75th quantiles.

Statistical analysis of baseline demographic data: in addition to descriptive analysis, continuous correction χ^2 test will be used for group comparison of the count data, while Fisher's exact test will be used when the theoretical frequency is lower than 5 in more than 25% cells. For group comparison of measurement data, group t-test will be used for those that are normally distributed, while Wilcoxon Rank Sum test will be used for those that are not normally distributed.

Efficacy analysis: for the primary efficacy measure - 1 year success rate of the filling, CMH Chi square test adjusted for center effect will be used for group comparison. In addition to the estimation of success rates of the treatment and control groups, the difference between groups on efficacy and its 95% confidence interval will also be estimated. For within-group comparisons of measurement data of other efficacy measures, pairwise t-test will be used for those that are normally distributed, while Wilcoxon Sign Rank test will be used for those that are not normally distributed. Between group comparisons will be the same as those in baseline analysis.

Safety evaluation: describe the number and proportion of cases who are normal before restoration and abnormal after restoration by treatment and control groups, respectively. AEs are described by the number and incidence of adverse events, and the proportions will be tested by continuous correction χ^2 test or Fisher exact probability test. At the same time, the specific symptoms and severity of all AEs occurred in each group as well as their relationships to the investigational product will be described in detail.

A significance level of 0.05 at two tails will be set for all statistical analyses. All statistical analyses will be performed using the statistical software SAS® 9.4.

8.1.3 Statistical analysis procedures

All the procedures involved in the statistical analysis will comply with the stipulations in ICH E9 and the relevant requirements in the Guidelines of Biometrics in Clinical Trials of Drugs as issued by the China Food and Drug Administration (CFDA). Meanwhile, all statistical analysis procedures will strictly follow the Standard Operation Procedures (SOP) of the Medical Statistics Department of National Cardiovascular Center.

8.2 Determination of sample size

8.2.1 Total sample size

It is estimated that 240 patients will be enrolled in this trial, and randomly assigned to the treatment or control group at 1:1 ratio. The number of cases in each group is 120. The calculation of the sample size is based on the primary endpoint measure, i.e. clinical acceptance rate of the filling at the 1 year follow-up visit.

8.2.2 Number of cases in the clinical trial of each disease and justifications, significance level, and statistical power

Since the scope of application of the investigational device is direct or indirect restoration of both anterior and posterior teeth, and based on existing clinical evidence and estimation by the clinical experience of experts, and assuming the clinical acceptance rate in the control group 1 year after treatment is 97% and it is estimated that the treatment group can reach the same effective level after using the investigational product, with a clinically recognized noninferiority margin of 7% after discussion, a significance level of 5% at two tails, a statistical power of 80%, and a maximum possible dropout rate of 20%, about 120 patients should be included in each group with a total of 240 patients to be included in both groups.

Corresponding sample size calculation is:

$$n = \frac{\left[\mu_{1-\alpha}\sqrt{2\bar{p}(1-\bar{p})} + \mu_{1-\beta}\sqrt{p_T(1-p_T)+p_C(1-p_C)}\right]^2}{(\Delta-(p_T-p_C))^2}$$

Where p_T is the expected fusion effectiveness of the treatment group, p_C is the expected effectiveness of the control group, $\bar{p}$ is the mean effectiveness of both groups, Δ is the noninferiority margin, μ is the quantile of standard normal distribution, α is the level of Type I Error, which is set at 0.025, and β is the level of Type II Error, which is set at 0.2.

8.2.3 Number of cases enrolled by each clinical trial institution

This trial will be conducted in multiple clinical trial institutions at the same time. In principle, the number of enrolled cases will be evenly distributed among centers as much as possible to ensure adequate representation of each center. However, considering the feasibility and progress of enrollment, the number of enrolled cases will be adjusted based on actual situation to keep sample size balanced among centers as far as possible, and the final sample size of a specific center should not exceed 50% of total sample size.

8.3 Estimated dropout rate

Since the subjects defined in the inclusion/exclusion criteria of this trial are Class I or II cavities of the posterior teeth, and only the vital teeth with cavities extending into middle and deep dentin are selected, it is unreasonable to require the subjects, who have no obvious cold and hot soreness before and after the procedure and only a simple “tooth filling”, to return to the hospital for reexamination 1 year later. Based on the experience of the investigators, the 1-year follow-up rate in such situations will be about 10-20%, In this trial, the investigators and supervisors will try their best to follow up the subjects 1 year later to reduce the loss rate of follow-up. A dropout rate of 20% will be used to estimate the sample size.

8.4 Passed/failed criteria of clinical trial results

Determining whether the trial results are passed or failed from a statistical perspective is equivalent to verifying by testing initial hypothesis. For this study, the primary endpoint measure is the clinical acceptance rate of the filling at the 1 year follow-up visits. The comparisons in the trial will be checked with a noninferiority test. The trial results will be used to prove that the restorative material of the treatment group has the same therapeutic effect comparing with the control group.

In conclusion, determination of the trial results will be based on the difference on success rate between the treatment and control groups. When subtracting the effectiveness value of control group from that of treatment group, if the lower limit of the 95% CI of the difference is greater than -7%, then the non-inferiority conclusion is accepted. Otherwise, the non-inferiority conclusion is rejected.

8.5 Criteria to terminate the trial based on statistical justifications

There is no scheduled interim analysis and corresponding early termination criteria in this trial, so this is not applicable. All statistical analyses shall be conducted after data collection, cleaning, and final locking.

8.6 Statistical procedures for all data as well as handling procedures for missing, unused, or incorrect data (including early removal and withdrawal) and unreasonable data

All statistical analysis procedures will strictly follow the Standard Operation Procedures (SOP) of the Medical Statistics Department of National Cardiovascular Center. Please refer to the relevant documents for details.

For the analysis of possible missing data in the process, Carry Forward methods will be used for missing data of primary endpoint measures, and the specific Carry Forward methods will be described in the Statistical Analysis Plan. Generally, single value Carry Forward method will be used, such as LOCF (Last Observation Carry Forward) or WCCF (Worst Case Carry Forward) strategy, to carry forward the missing data of primary endpoints. Carry Forward method will not be applied for other missing data.

Wrong and unreasonable data will be handled in the data cleaning process before statistical analysis. The information of patients, who withdraw or are removed from the trial, will be included in the final statistical analysis. In the Statistical Report, specific reasons for all withdrawals or removals will be described in detail, while for those missing primary measures due to early withdrawal, Carry Forward method will be applied according to the aforesaid missing value handling strategy.

8.7 Extent of deviations in the report to original Statistical Analysis Plan

The Statistical Analysis Plan will be confirmed by the Sponsor and Principal Investigator and finalized before locking the database. Before finalization, the initial Statistical Analysis Plan can be modified depending on actual situations of the trial process. In principle, main analysis principles, methods, and analysis sets will not be modified, and all the modifications will be recorded.

8.8 Subject selection criteria for inclusion in the analysis

Safety Set: include all the subjects who are formally enrolled, receive the filling and complete at least 1 follow-up visit. Statistical analysis will be carried out for the following analysis population. The analysis population needs to be clearly defined before starting the statistical analysis, which includes:

Full analysis set (FAS): the set of subjects determined according to the Intention-To-Treat principle, which refers to the data set composed of all the subjects who are included in randomization and receive the investigational product. For the subjects with no observation on primary efficacy measures, WCCF (Worst Case Carry Forward) strategy will be used to carry forward the missing data.

Per Protocol Set (PPS): refers to the subgroup of treatment population who complete the trial, while excluding those who seriously violate the protocol (referring to the violation of the inclusion criteria or exclusion criteria by the subjects, etc.).

The analysis of primary efficacy measures will be based on the FAS and PPS at the same time. In addition, all baseline demographic data and analysis of secondary efficacy measures will be based on the FAS, so as to the safety evaluation (therefore, SS is not defined separately).

8.9 Exclusion of special information when testing the hypothesis and its justifications

In this clinical trial, all the subjects who have received the investigational device will be included in the analysis and used for testing hypothesis, so no information will be excluded.

9. Data management

9.1 Completion and transfer of Case Report Forms

In this trial, electronic Case Report Forms will be used while hard copy original medical records will be provided. The original medical records and the electronic Case Report Forms must be completed by the investigators. Each formally enrolled subject must have their original medical record completed and entered into the EDC system. The entered electronic Case Report Forms will be reviewed by the monitors and go through data management process, and the contents of the electronic Case Report Forms cannot be modified.

9.2 Data entry and modification

If there is any question about the electronic Case Report Forms, the data manager will inquire the study personnel using the Query Form (QF) and contact the study personnel via the monitors to provide answers and reply as soon as possible. The data manager shall modify, confirm, and enter any data according to the answers of study personnel, and can send QF again, if necessary.

9.3 Locking of database

After the data is reviewed and confirmed to be correct, the data manager, Principal Investigator, statistical analysts, Sponsor and monitors shall jointly review the data, complete the final definition and determination of analysis population, and then the data manager will lock the database.

Generally, the locked database or files will not be changed again.

9.4 Data processing and record keeping

In the clinical trial, it is required to ensure all observations and discoveries are accurately and completely recorded, and also carefully filled in the original medical records and electronic Case Report Forms. The records of the clinical trial shall be treated as original data and shall not be changed at will. If it is necessary to make a modification, its justifications shall be provided and the modification should be signed and dated. The clinical trial institution shall properly keep the clinical trial data at least for 10 years after the completion of the clinical trial, and the Sponsor shall retain the clinical trial data until the medical device is not in use anymore.

10. Feasibility analysis

The investigational device (Filtek^{TM} Bulk Fill Posterior Restorative) was approved to market in September 2014 in the US, Western Europe, and Canada. So far, there is no report of any adverse event and also no recall record, so its safety and efficacy are proved in clinical applications. The trial is designed as required in CFDA's Technical Review Guidelines for the Registration of Dental Resin Filling Materials and the Clinical Trial Guideline for Polymer-based Dental Restorative Materials. The clinical acceptance rate of the filling and noninferiority margin are determined by the relevant clinical data and literature. Although the follow-up visits may be challenging, the Sponsor (or its agent) and the investigators will take appropriate measures to ensure the compliance of the subjects. In conclusion, all factors are in favor of the success of this trial. However, the following factors may negatively influence the results.

Factors relevant to the operations of investigators

1) Factors that may affect bonding and, therefore, the evaluation results on retention and fractures of the filling at the 1 year follow-up visit:

- insufficient debridement;

- internal line angles of cavity are not rounded enough after cavity preparation;

- overhang enamel at cavity margin after preparation;

- insufficient acid-etching, bonding and curing time;

- thickness of remaining teeth after cavity preparation is too thin (less than 1 mm)

2) Factors that may affect marginal fracture at the 1 year follow-up visit after the procedure

- cusps of antagonist tooth pressing on the margin of the filling

- too small bevel angle and too big width at cavity margin after preparation

3) Factors that may affect the evaluation on color match

- incorrect shade selection at the initial filling

4) Factors that may affect pulp vitality immediately after the procedure, 1 week after the procedure, and 1 year after the procedure

- included cases with an excessively deep bottom after cavity preparation

Factors relevant to tooth use

1) Frequently eating food easy to leave stains after the procedure, excessive smoking, and other factors may affect the scores on tooth staining and color match at the 1 week and 1 year follow-up visits

2) Chewing hard objects by mistake after the filling procedure may affect the scores on the retention and fractures of the filling and marginal fracture at the 1 week and 1 year follow-up visits

11. Quality control of the clinical trial

The Sponsor/its agent is responsible for taking all measures to ensure that the investigators participating in the trial fully understand and perform the trial according to the protocol or can assign monitors to monitor the trial to ensure the integrity and accuracy of trial data.

11.1 Training

The Sponsor (or its agent)/Contract Research Organization (CRO) is responsible for providing training and guidance to the investigators and appropriate study personnel. Before enrolling any subject, all investigators shall be trained for the protocol and clinical study procedures. The investigators are responsible for ensuring that their designated study personnel will be fully trained for the protocol and study process.

The monitors or their delegates shall also be trained appropriately for the protocol, electronic Case Report Forms, or other relevant study procedures and processes.

11.2 Monitoring of centers

The Sponsor or IRB or competent authority may conduct quality assurance audit/inspection for this trial. The Quality Assurance auditor will review all medical records, the investigator's documents and communications related to the trial and the informed consent forms.

During the clinical trial, the monitors authorized and assigned by the Sponsor will visit each center regularly to check the original data to ensure that the contents of the electronic Case Report Forms are true, complete, and correct, so as to ensure that all of the contents of the protocol are strictly observed.

12. Ethics and informed consent of the clinical trial

This trial will be implemented by complying the Helsinki Declaration, ICH-GCP, CFDA's Good Clinical Practice of Medical Device Clinical Trial (No. 25, March 2016) and other applicable national laws and regulations.

12.1 Ethics considerations

The Medical Device Ethics Committee shall comply with the ethical guidelines of the Helsinki Declaration of the World Medical Congress and the provisions of the food and drug regulatory authorities, and review and approve the materials submitted by the Sponsor in consideration of protecting the rights and interests of the subjects, and also review, discuss, and issue written opinions to the applied clinical trial considering the risks that all participants may suffer and the compensation given in case of injury or death related to the clinical trial. The Ethics Committee shall track and supervise the clinical trial conducted by the clinical trial institution, and it may request in writing to suspend or terminate the clinical trial at any time when the rights and interests of the subjects cannot be guaranteed.

12.2 Approval of the protocol

Before starting the clinical trial, the protocol, Informed Consent, and other relevant documents shall be submitted to the Medical Device Ethics Committee for review. The clinical trial may only be started after being approved by the Ethics Committee. Any modification of the protocol and Informed Consent must be approved by the Ethics Committee before being implemented. All serious adverse events occurred during the clinical trial shall be reported in writing to the Ethics Committee and the (food) drug administration of the province, autonomous region, or municipality directly under the Central Government that accepts the registration application of the medical device.

12.3 Informed consent

Before being enrolled in this clinical trial, the subject must be provided the details by the investigator, including the trial objective, trial process, possible benefits and risks, possible adverse events, and countermeasures. Written informed consent of the subject must be obtained prior to the enrollment. Meanwhile, the version of informed consent form in use shall be the latest version approved by the Ethics Committee.

The Informed Consent shall be signed by both the investigator and the subject in duplicate, and each party shall keep one copy.

The investigator will report the latest subject safety information obtained from the Sponsor to the Ethics Committee and update the Informed Consent, when necessary.

13. Report of adverse events and device defects

13.1 Adverse events

Adverse events (AEs) refer to adverse medical events occurred in clinical trials, regardless of whether they are related to an investigational medical device.

For a condition exists before the use of the investigational product, or if a subject's health conditions are the same after the use (displayed intensity and frequency), such event will not be recorded as an adverse event. Similarly, the symptoms or signs of a subject, which are related to an existing disease, will not be recorded as an adverse event, unless their intensity, frequency, and duration increase. These existing diseases, symptoms, and signs will be recorded in the original medical records and electronic Case Report Forms.

13.2 Serious adverse events

Serious adverse events refer to the events causing death or serious deterioration of the health conditions of a subject during the clinical trial, including fatal diseases or injuries, permanent defects of body structure or function, hospitalization, or extension of hospitalization, medical or surgical interventions to avoid permanent defect of body structure or function, and also the events leading to fetal distress, fetal death or congenital abnormalities, congenital defects, and other events.

13.3 Determination of severity of an adverse event

The severity of an adverse event is described by the extent to treat the subject and/or required scope of treatment.

Clinical symptoms are classified as mild, moderate, and severe according to the scoring criteria shown in Fig. 1.

Fig. 1: Descriptions of severity of an adverse event

Grade	Descriptions
Mild (1)	no aggravation in general; temporary or slight discomfort; daily activities are not affected; no need for medical intervention/treatment.
Moderate (2)	Mild to moderate influences on daily activities; some auxiliary equipment may be required; no or only minimal medical intervention/treatment is required; subjects can actively recount and tolerate.
Severe (3)	Significant influences on daily activities; some auxiliary equipment is required in general; medical intervention/treatment is required; hard to tolerate

The difference between a severe AE and a SAE should be noted. A severe AE may not be a SAE. For example, a headache may be a severe AE, but it is not SAE unless it meets the definitions of SAE.

13.4 Evaluation of the causal relationship between AEs and investigational devices

Whether an adverse event is caused or affected by an investigational product is determined by reasonable evaluation of causal relationship by an investigator. The investigator must evaluate the causal relationships between all adverse events (including serious or non-serious adverse events) and the investigational device.

When evaluating the relationship between an adverse event and an investigational product, the following factors should be considered:

- Alternative etiology - is the adverse event caused by a potential disease under study or other known diseases?
- Existing relationship - is the adverse event observed before the subject receives the investigational drug (product) or similar drugs (products)?
- Temporal relation – is there a reasonable temporal relationship between the occurrence time of the adverse event and dosing time?
- Concomitant drugs (products) – is the adverse event a known side effect of concomitant drugs (products)?

The investigator will record their opinions on the relationship between an adverse event and the investigational drug (product) by the criteria in Table 2.

Table 2: Descriptions of the relationships of adverse events

Relationship	Descriptions
Unrelated	The event may be more easily explained by the existing health conditions of a subject, concomitant medication, or other reasons. The investigator believes that there is no relationship between the adverse event and the investigational product. In this case, the investigator should record the symptoms, concurrent/existing diseases, drug (product) treatment, trial process, or other reasons that they think may cause the adverse event.
Possibly unrelated	There is no reasonable time sequence between the utilization time of the product and the occurring time of the event. At the same time, the event does not comply with any known or expected responses of the investigational product and there may be other reasons. In this case, the investigator should record the symptoms, concurrent/existing diseases, drug treatment, trial process, or other reasons that they think may cause the adverse event.
Possibly related	The symptoms, concurrent/existing diseases or drug treatment of the subject or the trial process could not explain the event, and the event had a reasonable time relationship with the use of the investigational product. The causal relationship between the event and the investigational product cannot be excluded.
Quite possibly related	There is a reasonable time relationship between the use of the investigational product and the adverse event, and/or the adverse event was unlikely to be reasonably explained by other symptoms, concurrent/existing diseases, drug treatment, trial process or other reasons, or the severity of the adverse event can be alleviated by discontinuation of its use, but will recur when being used again.

Definitely related	The type of the adverse event has been confirmed as a definite adverse response and cannot be explained by other reasons. The occurring time of the event strongly indicates the causal relationship.

All adverse events determined as "Possibly related", "Quite possibly related", and "Definitely related" are categorized as "related" to the investigational product. All adverse events determined as "Unrelated" and "Possibly unrelated" are categorized as "unrelated".

13.5 Device defect and its report

Device defects refer to unreasonable risks that may endanger human health and life when a medical device is normally used during a clinical trial, such as labeling errors, quality problems, failures, etc.

The investigator shall record any device defect discovered in the clinical trial, analyze its reasons together with the Sponsor, compile a written analysis report, and propose to continue, suspend or terminate the trial, which shall be submitted to the Ethics Committee for review by the medical device clinical trial management department of the clinical trial institution.

13.6 Report procedures and contact information

All adverse events occurred during the clinical trial (that is, from the signing of the Informed Consent, throughout the entire observation period and until 1-year follow-up visit after restoration), whether serious and non-serious, shall be collected and recorded by the investigator on corresponding original medical record/SAE report form. Information to be recorded will include the descriptions of the event, severity, occurrence time, end time, relationship to the investigational device, measures taken, and outcomes. All adverse events, including those that continue after termination of the trial, must be followed up until all symptoms disappear or stabilize.

In case of any serious adverse event, the investigator shall immediately treat the subject appropriately, report in writing to the clinical trial management department of the clinical trial institution, and notify the Sponsor in writing. The medical device clinical trial management department shall submit a written report to corresponding Ethics Committee, food and drug administration department and health and family planning department of the province, autonomous region, or municipality directly under the Central Government where the clinical trial institution is located within 24 hours. In case of any death, the clinical trial institution and investigator shall provide all necessary information to the Ethics Committee and Sponsor.

For SAEs and device defects that may lead to SAEs, the Sponsor shall notify the food and drug administration department and the health and family planning department at the same administrative level within 5 workdays after being informed, and also other clinical trial institutions and investigators involved in the trial, who shall notify the Ethics Committee of the clinical trial institution via the medical device clinical trial management department in a timely manner.

The investigators can notify the Sponsor by using the Sponsor's contact information: Pan Shuang, Email: span7@mmm.com Office telephone: 021-22105287, mobile phone: 18621903981.

14. Deviations and amendments to the clinical protocol

14.1 Deviations to the protocol

The investigator shall record all deviations to the protocol and report these deviations periodically to the medical device clinical trial management department and Ethics Committee of the clinical trial institution and the Sponsor. To protect the rights and interests and safety and health of the subjects, if any deviation cannot be reported in time in an emergency, it shall be reported in writing as soon as possible after the event.

In case of any deviation to the protocol, the investigator shall be informed the non-compliance of their center. Corrective measures shall be taken when necessary. If protocol deviations still repeatedly occur after secondary training, the center may be removed from the trial.

14.2 Amendments to the protocol

During the clinical trial, if the clinical protocol and Informed Consent are modified, the implementation of such amendments will only continue after obtaining the written approval of the Ethics Committee. The investigator shall also report these amendments to the medical device clinical trial management department of the clinical trial institution in time.

15. Direct access to original data and files

15.1 Case Report Forms

This trial will use electronic Case Report Forms to record data, and the Sponsor will provide paper original medical records for each participant. On the original medical records and electronic Case Report Forms, all the data to be observed during the trial will be recorded (including the initial screening period, screening period after cavity preparation, 1 week and 1 year follow-up visits after the procedure, unscheduled follow-up visits, withdrawal of a subject, record of AEs/SAEs, and Statement of the Investigator page). The Investigator must sign the original medical records and electronic Case Report Forms, to confirm that all recorded data are checked, true and accurate.

15.2 Source files

Source files can prove the existence of subjects and the authenticity of collected data. Source files will be archived in the center of the Investigator, including:

- Outpatient records (printed, signed, and dated);
- Records of the investigator in the files of subjects;
- Original medical records
- Signed Informed Consent
- Randomization table (printed, signed, and dated)

- SAE report forms
- Records of device defects
- Digital photos (printed, signed, and dated);
- X-ray results (electronic version printed, signed, and dated);
- Pregnancy test results (originals or photocopies printed, signed, and dated)

Data in the electronic Case Report Forms must be consistent with those in the original files/original medical records, while any difference must be explained. Depending on the trial, the investigator may need past medical records or transfer records; or current medical records.

15.3 Direct access to original data and files

The investigator/clinical trial institution will agree to all monitoring, audits, IRB audits, and inspection of management relevant to the trial as well as provide direct access to all the relevant original data/source files and electronic medical records, including the copies of pathography and laboratory and medical examination results. All files must be available for inspection by the Sponsor's clinical associates, auditors, and health authorities (such as CFDA). Clinical Research Associates (CRA) and auditors may review all source files, electronic Case Report Forms, and Informed Consent. The authenticity and accuracy of data will be checked by reviewing the source files described in 15.2.

15.4 Archive of original records

A clinical trial center must keep all source files and necessary documents of this trial, including the signed Informed Consent, distribution records of investigational and control devices (products), case reports and other relevant records, in the National Drug Clinical Trial Institution of the hospital where the center is located at least for 10 years after the termination of the trial.

16. Finance and insurance

The Sponsor (or its agent) shall sign a clinical trial cooperation agreement with all clinical trial institutions, respectively, stipulating the rights and obligations of both parties and specifying the labor service fees, organization fees and other fees payable to investigators, which should be calculated by the number of subjects, including the cost for each successfully enrolled subject, each subject who fail to pass screening, and each follow-up visit. Reasonable compensation to each subject for participating in this trial shall also be included in the financial agreements between the Sponsor (or its agent) and investigators.

The Sponsor will bear all the treatment expenses and the corresponding economic compensation for the subjects who have suffered injury or death related to the clinical trial, except for the damage due to the misdemeanor of the medical institution and its medical personnel during the diagnosis and treatment activities.

17. Clinical trial report

The report for the clinical trial shall include its objectives, contents, analysis of the baseline data of enrolled subjects, statistical analysis results of the efficacy measures such as primary measures, secondary measures and etc., summary analysis of AEs and SAEs (if any), analysis of the compliance of the subjects and deviations to the protocol. Conclusions on the safety and efficacy of the investigational device based on the standards defined in the protocol shall also be included.

18. Confidentiality

To ensure the compliance with the stipulations issued by the State Food and Drug Administration and any applicable regulations on protection of personal information, all the parties shall maintain the confidentiality of protected medical information throughout the study process. Unauthorized access to all data will be denied. On the Case Report Forms and other trial records, a unique identification code will be assigned to each subject, and the subject names and all the relevant information that may expose their names shall not be disclosed to unauthorized personnel.

The investigator must keep confidential all the relevant information disclosed by the Sponsor or its agent, including but not limited to the protocol, characteristics of the investigational product, Case Report Form, and Investigator's Manual, and shall not disclose it to any third party without prior consent of the Sponsor. The investigator shall take the necessary measures to prevent the staff of the clinical trial institution from disclosing the relevant information.

19. Agreements on the publication of trial results

As the Sponsor, 3M ESPE Dental Product has all rights in the trial results. The Sponsor's agent will submit the final study report to the State Food and Drug Administration for registration. If the investigator will give a summary presentation or other oral presentations in an academic conference or in public, they must submit the draft summary, manuscript, and materials to be used for presentation in an academic conference to the Sponsor (or its agent) at least 30 workdays before the date of completion or other corresponding submission date. Without the written consent of the Sponsor or its agent, no one is allowed to publish or publicly describe the data and results related to the investigational device or trial.

20. Responsibilities of all the parties

20.1 Responsibilities of the Sponsor:

(1) provide the Investigator's Manual/Instructions for Clinical Trial of Medical Devices to each clinical trial institution;

(2) jointly design and develop the clinical trial protocol of medical devices with all clinical trial institutions, and sign the protocol agreed by both parties;

(3) provide QC passed Filtek™ Bulk Fill Posterior Restorative and related instruments to all the clinical trial institutions free of charge;

(4) provide a brief introduction of Filtek™ Bulk Fill Posterior Restorative and its Instruction for Use to clinical trial institutions and clinical facilities;

(5) provide the relevant training to clinical trial institutions/monitors before the trial;

(6) cooperate with a Contract Research Organization (CRO) to monitor the clinical trial;

(7) notify the (food) drug regulatory department of the province, autonomous region, municipality directly under the Central Government that accepts the registration application of the medical device and the State Food and Drug Administration in case of any serious side effect truthfully and timely, and also to other clinical institutions conducting clinical trials of the medical device;

(8) consider the termination of any clinical trial together with the clinical trial institutions. Before terminating any clinical trial of the medical device, the Sponsor shall notify the Ethics Committees of clinical institutions, the (food) drug regulatory department of the province, autonomous region, municipality directly under the Central Government accepting the registration application of the medical device and the State Food and Drug Administration, and provide justifications;

(9) compensate a subject according to the clinical trial contract of medical device, if the investigational product causes any injury of and damage to the subject;

(10) keep the clinical trial data at least for 10 years after the final product is put into use.

20.2 Responsibilities of clinical institutions and personnel:

(1) be familiar with all materials provided by the Sponsor and the use of the investigational product;

(2) jointly design and develop the clinical trial protocol of medical devices with the Sponsor;

(3) complete the clinical trial of Filtek™ Bulk Fill Posterior Restorative according to established “clinical trial protocol” within the specified period, including outpatient follow-up visits immediately, 1 week and 1 year after the procedure;

(4) explain the details of the investigational product to all the subjects truthfully. Before implementation of the clinical trial, the subjects must be given sufficient time to consider whether to participate in the clinical trial;

(5) truthfully record the side effects and AEs of the investigational product, analyze its causes and take appropriate treatment measures immediately. In case of any AE and serious side effects, the Sponsor should be notified truthfully and timely, so as to the Ethics Committee of the leading clinical trial institution, the Safety Supervision Department of the State Food and Drug Administration, local drug administrations and clinical trial associates. All serious side effects should be reported within 24 hours;

(6) In case of any side effect, the clinical trial personnel shall make clinical judgments in time and take corresponding measures to protect the interests of the subjects (necessary violations to the protocol should not be deemed as in violation of the contract, but they should be explained in the final report). When necessary, the Ethics Committee has the right to terminate the clinical trial immediately;

(7) If the clinical trial is terminated, the subjects, the Sponsor, the Ethics Committees, the (food) drug regulatory department of the province, autonomous region, municipality directly under the Central Government accepting the registration application of the medical device and the State Food and Drug Administration shall be notified, and the justifications shall be provided;

(8) take main responsibilities for the correctness, clarity, and reliability of all documents relevant to the clinical trial;

(9) Any modification of original data must be signed and dated by the authorized personnel and the original records should be kept for further inspection;

(10) The clinical facilities shall safely keep and manage all clinical trial data of the medical device at least for 10 years after the termination of the trial;

(11) submit the clinical trial report of Filtek™ Bulk Fill Posterior Restorative to the Sponsor in time after the termination of the trial, and take legal responsibilities for the correctness, clarity, and reliability of the report;

(12) must keep confidential of the product and the whole clinical process and relevant clinical documents.

20.3 Contract Research Organization (CRO):

(1) monitor the whole clinical trial process;

(2) inform the Sponsor and clinical trial institutions of various abnormalities in the use of Filtek™ Bulk Fill Posterior Restorative timely;

(3) perform the clinical trial protocol to report any deviation to the protocol to the Sponsor and reach an agreement with the Sponsor;

(4) ensure the investigators to use the device according to the clinical trial protocol and report any modification to the device or protocol to the Sponsor;

(5) ensure the trial is conducted as required by the Good Clinical Practice of Medical Device Clinical Trial (GCP) and Regulations on the Clinical Trials of Medical Devices (No. 25 Decree);

(6) ensure the subjects comply with the stipulated procedures and give informed consent;

(7) ensure the Case Reports are completed in time and all the data on the Case Reports are consistent with source data;

(8) record all AEs and side effects of the device by stipulated procedures and report them to the Sponsor;

(9) keep records of all withdrawals and removals, noncompliance of the subjects regarding medical advice, and termination of the clinical trial;

(10) ensure the files generated in the clinical trial process are true and complete.

(11) submit the clinical trial report of Filtek™ Bulk Fill Posterior Restorative to the Sponsor together with the clinical trial institutions in time after the termination of the trial, and take legal responsibilities for the correctness, clarity, and reliability of the report;

(12) keep confidential of the product and the whole clinical process and relevant clinical documents.

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Statement of Investigator

I agree to:

1. Conduct the clinical trial in strict compliance with the Declaration of Helsinki, current Chinese laws and regulations, and the requirements of its protocol.

2. Accurately record all the required data in the Case Report Forms (CRFs) and complete the clinical trial report on time.

3. Only use the investigational medical device for this clinical trial and record the reception and use of the investigational medical device in the clinical trial in detail and accurately, while keep all records.

4. Allow monitors and auditors authorized or designated by the Sponsor and the regulatory authorities to monitor, audit, and inspect the clinical trial.

5. Strictly follow the terms and conditions of the Clinical Trial Contract/Agreement signed by all parties.

I have read the entire clinical trial protocol, including the above statements, and I agree with all of the above statements.

Opinions of the Sponsor:
Signature (Stamp) Year Month Day

Opinions of the Investigator:
Signature Year Month Day

Opinions of the Clinical Trial Institution of Medical Device:
Signature (Stamp) Year Month Day

Appendix 1: Clinical evaluation criteria for Filtek™ Bulk Fill Posterior Restorative

Retention and fractures of the filling	Marginal fractures of the filling	Contour and marginal adaptation	Proximal contact	Color match	Surface roughness	Surface staining	Marginal discoloration and secondary caries	Pulp status
(visual examination)	(visual examination)	(visual examination, probing)	(visual examination, dental floss examination)	(visual examination)	(visual examination)	(visual examination)	(visual examination, probing, and X-ray examination)	(Vitality tests)
A. The filling is intact	A. No marginal fracture on the filling	A. Intact contour and continuous probing between the filling and tooth	A. Firm proximal contact	A. Matching color and transparency between the filling and adjacent tooth tissues	A. After air drying, the surface of the filling is smooth with luster and matching with surrounding tooth tissues	A. No staining on the surface of the filling	A. No discoloration at the interface between the filling and tooth	A. Normal (temperature test)
	B. Minor marginal fractures of the filling without exposed dentin, clinically acceptable	B. Pits on the surface of the filling and discontinuous probing between the filling and tooth without exposed dentin	B. Proximal contact is clinically acceptable	B. Slightly differences in color and transparency between the filling and adjacent tooth tissues	B. After air drying, the surface of the filling is smooth without luster		B. Partial discoloration at the interface between the filling and tooth, but not extending to pulp and removable by polishing	B. Temporarily sensitive (temperature test)
C. Fractured or partial/total loss of the filling	C. Marginal fractures of the filling with exposed dentin, clinically unacceptable	C. Severe attrition and dents on the surface of the filling with exposed dentin, or probes hooked at the margins of the filling	C. No proximal contact	C. Significant differences in color and transparency between the filling and adjacent tooth tissues	C. After air drying, the surface of the filling is rough with defects	C. Abnormal staining on the surface of the filling	C. Partial discoloration at the interface between the filling and tooth extending to pulp and not removable by polishing, or secondary caries	C. Sensitive and continuous pain, or delayed pain (temperature test)
								D. No response (electric pulp testing)