Clinical Investigation Plan

CIP number: 2000-CIP-0001

Version: 1.0

Date: 15-May-2024

Title: A prospective, two-armed, multicenter clinical study to evaluate efficacy, performance, and safety of Nighttime Aligners (worn 10-12 hours day or night) compared to Daytime Aligners (worn 20-22 hours day/night)

NCT number: NCT06539676

PROTOCOL NUMBER: 2000-CIP-0001

CLINICAL STUDY CODE: C-OR-24-017

Title: A prospective, two-armed, multicenter clinical study to evaluate efficacy, performance, and safety of Nighttime Aligners (worn 10-12 hours day or night) compared to Daytime Aligners (worn 20-22 hours day/night)

Sponsor: Straight Smile, LLC
(a Dentsply Sirona company, doing business as Byte)
1556 20th Street, Suite A
Santa Monica, CA 90404, U.S.A.
1-866-765-2327

Investigational Product: Nighttime Aligners

Investigational Sites: Multi-center clinical study with up to 15 sites in the US.
See separate study specific investigational site list.

Revision: 1

REVISION HISTORY

Rev.	Change By	Description of Change	Rationale for Change
0	Louis Erazo	Initial draft	Draft for FDA pre-sub
1	Freja Freedman	Initial release	New

LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse event
DD	Device deficiencies
SAE	Serious adverse event
CFR	Code of Federal Regulations
eCRF	Electronic case report form
EDC	Electronic data capture
ERP	Enterprise resource planning
DSM	Digital Study Model
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
IC	Informed Consent
ICH	International Conference on Harmonization
IP	Investigational Product (equivalent with Investigational device)
IRB	Institutional Review Board
NSR	Non-significant risk
PAR	Peer Assessment Rating
CoCR	Center of Clinical Research
US	United States

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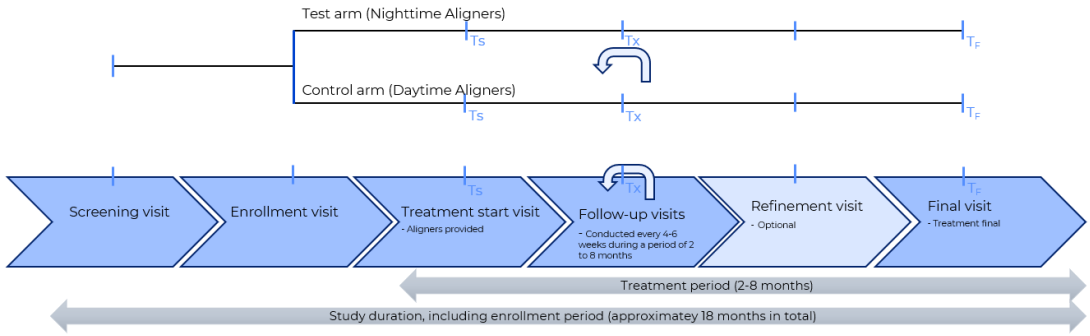
TABLE OF CONTENTS

PROTOCOL SYNOPSIS

TITLE	A Prospective, multi-center Clinical Study to Support Substantial Equivalence of Safety and Effectiveness of Nighttime Aligners (worn 10-12 hours day or night)
DESIGN	Multi-site, two-armed, prospective, controlled clinical study
STUDY LOCATION	United States
SUBJECT POPULATION	Permanent dentition (i.e., all second molars), ages 12 and up
SAMPLE SIZE	The study will enroll up to 100 subjects [50 per treatment arm] to have a minimum of 23 fully evaluable subjects per treatment arm at end of treatment
NUMBER OF SITES	Up to 15 investigational sites
STUDY DURATION	18 months, inclusive of enrollment period, where typical treatment duration is 6-8 months
TEST	Treatment arm 1 – Test group Nighttime Aligners (worn 10-12 hours per day or night)
CONTROL	Treatment arm 2 – Control group Daytime Aligners (worn 20-22 hours day/night)
OBJECTIVE	This clinical study is designed to provide Straight Smile, LLC and Dentsply Sirona data to support substantial equivalence, including safety and efficacy, of wearing Nighttime Aligners for 10-12 continuous hours per day (or night). The expressed movements demonstrated by the Nighttime Aligners (investigational/test group) will be compared to the expressed movements demonstrated by the Daytime Aligners (control group), which are worn for 20-22-hours per day/night.
CLINICAL STUDY PROCEDURE	The flowchart below provides an overview of the clinical study. For visit-specific procedures, see section 8: Visit and procedure plan.

	
EFFECTIVENESS ASSESSMENTS	Efficacy of Nighttime Aligners (worn 10-12 hours per day or night) will be assessed by demonstrating no statistically significant difference between expressed tooth movement versus programmed tooth movement at the end of treatment when compared to the Daytime aligners (worn 20-22 hours day/night). Quantification and comparison of expressed and programmed tooth movements will be conducted using Peer Assessment Rating (PAR) index to measure orthodontic treatment need and outcome, using the built-in weighted PAR analysis tool of 3Shape Ortho System software.
SAFETY ASSESSMENTS	The primary safety endpoint of the study will be the incidence of (device or dental) related AEs associated with the planned investigational treatment, as well as the occurrence of SAEs. Additionally, safety will be assessed through a post-treatment questionnaire administered to the subject asking about subject perceived comfort during treatment. Results will be quantified using a visual analogue scale. Both numerical values and a Wong Baker face scale will be used.
INCLUSION CRITERIA	For inclusion in this clinical study subjects must meet all of the following criteria: 1. Subject willing to participate in the clinical study and able to understand the content of the clinical study. 2. Subject must have permanent dentition (i.e. all second molars). 3. Subject must be 12 years of age or older. 4. Subject must be able to provide and sign consent for themselves, without requiring consent to be given by a legally authorized representative. Parental consent is also required for all participants who are not of the legal age to provide consent themselves (based on participant state of residence). 5. The subject requires correction of teeth without planned extrusive movements on either or both arches.

	6. The subject has no greater than 5 mm of crowding and/or spacing (based on estimation by Investigator). 7. The subject does not require planned correction of molar tooth positions, posterior bite or molar classic relationship corrections. Subjects with Class II or Class III malocclusions requiring posterior bite / class correction are not eligible. 8. Subjects without prior orthodontic treatment within the past 18 months. 9. Subjects who are periodontally stable. 10. Subjects without a known history of plastic allergies. 11. Subjects who have not had or do not require tooth extractions in preparation for orthodontic treatment with aligners. 12. Subjects with a treatment plan that does not include the use of elastics.
EXCLUSION CRITERIA	Any of the following is regarded as a criterion for exclusion from the clinical study: 1. Unlikely to be able to comply with clinical study procedures according to Investigator's judgement. 2. Unable or unwilling to return for follow-up visits. 3. Previous enrolment in the present clinical study. 4. Involvement in the planning and conduct of the clinical study (applies to both Sponsor personnel and the clinical study site) 5. Participation in another clinical study that may interfere with the present clinical study. 6. Subjects who have active carries, where there is no plan to correct them prior to the start of aligner therapy. 7. Other dental or clinical pathologies, which in the judgment of the Investigator, deem the candidates inappropriate for participation in the study (e.g. clinically significant periodontal disease or gingivitis, interproximal decay, etc.). 8. The subject require interproximal reduction or attachments to obtain a corrected malocclusion. 9. In addition to the criteria listed above, this product is contraindicated for use in adult and adolescent subjects presenting with the following dental conditions: • Active periodontal disease • Severe open bite or severe overjet

	• Tooth malocclusion requiring surgical correction • Subject with mixed dentition • Subject with a skeletally narrow jaw • Dental prosthetics/implants or significant number of missing teeth 10. Known pregnancy, pregnancy tests will be performed as per local requirements.

1. STUDY OBJECTIVES

1.1 Primary Objective:

The primary efficacy objective of this study is the comparison between groups of the quantification of actual vs planned tooth movements. Changes in tooth position from pre-treatment baseline to end of treatment results will be measured for both Daytime Aligners (control) and Nighttime Aligners (test).

The safety objective of the study will be the incidence of (device or dental) related AEs associated with the planned investigational treatment, in comparison to the incidence of AEs associated with control treatment.

1.2 Secondary Objectives:

The secondary efficacy objective of this study will be to assess overall dentist and subject satisfaction with the treatment.

Safety will also be assessed through subject questionnaire during and after treatment.

2. BACKGROUND AND RATIONALE

2.1 Background:

2.1.1 Orthodontic clear aligners have become increasingly popular since the advent by Align Technologies in 1998. The esthetics and comfort of using clear aligners instead of traditional wire and bracket braces have greatly contributed to their adoption for orthodontic treatment around the world. Applying slow, continuous force to a subject's teeth is the premise behind clear aligners being safe and effective at treating malocclusions.

2.1.2 The aligner system positions teeth by way of continuous gentle force and this system has been applied to the Daytime Aligners which are indicated for the treatment of tooth malocclusion in subjects with permanent dentition (i.e. second molars). The Daytime Aligners (worn 20-22 hours per day) have been available in the US market since 2019 and were initially cleared by the US FDA under pre-market notification K180346. Recently, design changes to the aligners were subsequently cleared by the US FDA under pre-market notifications K230199.

2.1.3 Nighttime Aligners have not been cleared by the US FDA, and the purpose of this clinical study is, in part, to gain valid scientific evidence for device safety and efficacy to support US FDA pre-market clearance for the device system. These aligners are to be worn by the subject continuously for 10-12 hours per day (or night). When worn while sleeping, the therapy complements the circadian rhythm of bone remodeling and metabolism for tooth movement (Qin 2019, Luo 2021).

2.2 **Rationale:**

2.2.1 Nighttime Aligners program smaller incremental tooth movements into each aligner tray/stage allowing for activation of biological cascade governing orthodontic tooth movement (Krishnan 2006, Kumasako-Haga 2019), with an added advantage of intermittent force resulting in reduced root resorption (Ozkalavci 2018). Movements of molar teeth and extrusive tooth movements are not eligible in the treatment plans for these aligners.

2.2.2 This clinical study is designed to provide Straight Smile (doing business as Byte) and Dentsply Sirona data to support performance, efficacy and safety of wearing Nighttime Aligners for 10-12 continuous hours per day (or night). The expressed movements demonstrated by the Nighttime Aligners (investigational/test group) will be compared to the expressed movements demonstrated by the Daytime Aligners (control group), which are worn for 20-22-hours per day. Both control and investigational groups are for subjects with mild malocclusion.

2.2.3 This clinical study involves no more than minimal risk (as defined in 21 CFR 50.3(k) or 56.102(i)) to the subjects. Based on this assessment, the IRB will be asked to make a determination that the clinical study does not pose more than minimal risk to the study subjects (non-significant risk) and thus the clinical study is considered to have abbreviated IDE requirements and does not require FDA approval of the study (21 CFR 8.12.2(b)).

- This request is made in part by reviewing the recommendations provided by the Office of Good Clinical Practice, Office of Special Medical Programs, Office of the Commissioner Food and Drug US FDA in the document “Information Sheet Guidance for IRBs, Clinical Investigators, and Sponsors: Significant Risk and Non-significant Risk Medical Device Studies”.

  (https://www.fda.gov/regulatory-information/search-fda-guidance-documents/significant-risk-and-nonsignificant-risk-medical-device-studies)

3. REFERENCES

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4. STUDY DESIGN

The clinical study is a multi-center, controlled, prospective study enrolling on a convenience basis.

The study period for each study subject shall end when the subject discontinues use of the investigational or control devices (i.e., withdraws from the study or completes aligner treatment under the study time frame).

All study subjects will be provided with removable retainers after completion of aligner therapy.

This study shall be carried out in compliance with FDA regulations and Good Clinical Practices (GCP), including but not limited to the Protection of Human Subjects, Informed Consent, Institutional Review Boards, and the Obligations of Clinical Investigators and Sponsors.

4.1 Population

This study will seek to enroll subjects who are clinically eligible candidates for aligner therapy as outlined in the inclusion/exclusion criteria and are interested in voluntarily participating in this study. Only subjects with permanent dentition (i.e., all second molars) will be screened for enrollment in the study (this is consistent with the intended use statement for the Daytime Aligners [control]).

The clinical study shall be conducted only in the United States.

4.2 Number of Subjects

The study shall prospectively enroll up to 100 subjects (50 per treatment arm) on a convenience basis, with a minimum of 50 eligible subjects per treatment arm. A minimum of 23 fully evaluable, compliant, and viable subjects completing treatment in each study treatment arm is required.

4.3 Study Duration

4.3.1 The study, as a whole is expected to run for up to 18 months, inclusive of the enrollment period.

4.3.2 The minimum planned orthodontic treatment period per subject will be 2 months.

4.3.3 The maximum planned orthodontic treatment period per subject will be 8 months, unless a refinement is required.

4.3.4 Study subjects will remain on-study until treatment with the final investigational or control device is complete or if the subject wishes to no longer participate in the study (withdraws consent) or Severe non-compliance to protocol as judged by the Investigator and/or Sponsor causing the subject to be withdrawn from the study.

5. SELECTION AND ENROLLMENT OF STUDY SUBJECTS

5.1 Inclusion Criteria

For inclusion in this clinical study subjects must meet <u>all</u> of the following criteria:

1. Subject willing to participate in the clinical study and able to understand the content of the clinical study.
2. Subject must have permanent dentition (i.e. all second molars).
3. Subject must be 12 years of age or older.
4. Subject must be able to provide and sign consent for themselves, without requiring consent to be given by a legally authorized representative. Parental consent is also required for all participants who are not of the legal age to provide consent themselves (based on participant state of residence).

5. The subject requires correction of teeth without planned extrusive movements on either or both arches.
6. The subject has no greater than 5 mm of crowding and/or spacing (based on estimation by Investigator).
7. The subject does not require planned correction of molar tooth positions, posterior bite or molar classic relationship corrections. Subjects with Class II or Class III malocclusions requiring posterior bite / class correction are not eligible.
8. Subjects without prior orthodontic treatment within the past 18 months.
9. Subjects who are periodontally stable.
10. Subjects without a known history of plastic allergies.
11. Subjects who have not had or do not require tooth extractions in preparation for orthodontic treatment with aligners.
12. Subjects with a treatment plan that does not include the use of elastics.

5.2 **Exclusion Criteria**

Any of the following is regarded as a criterion for exclusion from the clinical study:

1. Unlikely to be able to comply with clinical study procedures according to Investigator's judgement.
2. Unable or unwilling to return for follow-up visits.
3. Previous enrolment in the present clinical study.
4. Involvement in the planning and conduct of the clinical study (applies to both Sponsor personnel and the clinical study site)
5. Participation in another clinical study that may interfere with the present clinical study.
6. Subjects who have active carries, where there is no plan to correct them prior to the start of aligner therapy.
7. Other dental or clinical pathologies, which in the judgment of the Investigator, deem the candidates inappropriate for participation in the study (e.g. clinically significant periodontal disease or gingivitis, interproximal decay, etc.).
8. The subject require interproximal reduction or attachments to obtain a corrected malocclusion.
9. In addition to the criteria listed above, this product is contraindicated for use in adult and adolescent subjects presenting with the following dental conditions:
    - Active periodontal disease

- Severe open bite or severe overjet
- Tooth malocclusion requiring surgical correction
- Subject with mixed dentition
- Subject with a skeletally narrow jaw
- Dental prosthetics/implants or significant number of missing teeth

10. Known pregnancy, pregnancy tests will be performed as per local requirements.

5.3 Screening and Enrollment Procedures

5.3.1 Subjects seeking orthodontic treatment through the Byte+ network of dentists will be pre-screened for enrollment.

5.3.2 Subjects shall meet all inclusion and none of the exclusion criteria. Subject scanned will be invited to participate in the study. If they agree and consent to participate, they will be included and subsequently enrolled in this study.

5.3.3 Subjects will be enrolled on a convenience basis by their voluntary selection to participate in a clinical study after first expressing interest in aligner therapy.

- Consented subjects will be assigned a unique subject identification number randomly generated by the ERP system. This number will be used as the primary identifier on all study related documents. In addition subject will receive a subject Id when enrolled in the study. Subject IDs are unique to each individual subject and cannot be changed.

All screening activities shall be documented in the screening Log, including but not limited to the determination of eligibility for each screened subject Any protected health information shall be de-identified. The Sponsor shall be able to review protected health information upon request for the purpose of study data monitoring.

5.4 Subject Consent/Assent Procedure

5.4.1 Subjects will be fully informed of the nature of the study, the risks involved in participating in the study, and the procedures that will need to be followed during the study period.

5.4.2 The Investigator shall explain the terms of the clinical study, objectives of the research being conducted, benefits and risks of participation, benefits and risks of not participating, duration of the study, possible continuation of treatment after the study ends, subject responsibilities, subject compliance, and subject expectations.

5.4.3 It is important that the Investigator discusses alternative and traditional (non-research) treatments available, as well as the risks and benefits of those options.

5.4.4 All subjects are required to go through the formal consent process and sign and date the consent form prior to participating as a study subject in this study.

5.4.5 Informed Consent is required prior to participation in this study. Eligible subjects, 18 years of age or older, who are willing to participate in the study will read and sign the written, study specific Informed Consent Form prior to undergoing any study-specific procedures.

5.4.6 Assent: Eligible subjects under the age of 18 require parental consent to participate in this study, in addition to the subject's consent for participation. Eligible subjects under the age of 18 will require a parent or legal guardian's approval via the study specific Informed Consent Form prior to undergoing any study-specific procedures.

5.4.7 Each subject will receive a copy of their signed Informed Consent Form.

5.4.8 The study Informed Consent Form does not replace any consent-for-treatment agreement the Investigator currently requires to accept and begin treatment.

- The enrolled subject (or parent/legal guardian's if applicable) will be offered a rebate for their participation in this study. The subject will receive a rebate on their aligner order following enrollment in the study, and an additional rebate upon compliant and successful completion of aligner therapy under this study protocol. Providing discounts or payments to clinical study subjects in exchange for their participation is a common and, in general, acceptable practice. These actions are not considered a benefit that would be part of the weighing of benefits or risks; it is a recruitment incentive.
- If the subject is removed from the study by the Sponsor or Investigator due to non-compliance to the study protocol, they will not be eligible for the second rebate, attained at the end of the study.

6. INVESTIGATIONAL DEVICE

6.1 Device Description

6.1.1 All investigational and control aligner devices will be made using FDA cleared plastic materials [Essix ACE (PETG), K062828].

6.1.2 Nighttime Aligners are indicated for the treatment of tooth malocclusion in subjects with permanent dentition (i.e., second molars). The aligner system positions teeth by way of continuous gentle force. These aligners

are to be worn by the subjects continuously for 10-12 hours per day (or night); aligners may be removed for small periods of time while eating, drinking or brushing. Subjects will wear each aligner tray for 1-2 weeks, or as instructed by their dentist. When worn while sleeping, the therapy complements the circadian rhythm of bone remodeling and metabolism for tooth movement. Smaller incremental tooth movements are programmed into each aligner tray/stage allowing for activation of biological cascade governing orthodontic tooth movement, with an added advantage of intermittent force resulting in reduced root resorption. Nighttime aligners (investigational) are made with material that is 0.35-0.40 inch thick and the planned tooth movement rate is 20% less than that of the Daytime Aligners (control).

Tooth movement treatment planning constraints of Nighttime Aligners (investigational):

Movement Type	**Translate [B/L] (mm)**	**Torque / Incline (°)**	**Tip (°)**	**Rotate (°)**	**Intrude (mm)**	**Extrude (mm)**
Per aligner	*0.25 mm*	*1 °*	*1 °*	*1.6 °*	*0.1 mm*	*N/A*
Tooth	**Totals per treatment plan**					
Incisors	5	25	25	45	2.5	N/A
Laterals	5	25	25	45	2.5	N/A
Canines	3	25	25	35	2.5	N/A
Premolars	2	10	10	10	1	N/A
Molars*	N/A	N/A	N/A	N/A	N/A	N/A

**Movements of molar teeth are not in the treatment plans for these aligners.*

6.1.3 Daytime Aligners are indicated for the treatment of tooth malocclusion in subjects with permanent dentition (i.e., second molars). The aligner system positions teeth by way of continuous gentle force. These aligners are to be worn by the subject 20-22 hours per day and night; aligners may be removed for small periods of time while eating, drinking or brushing.

Subjects will wear each aligner tray for 1-2 weeks, or as instructed by their dentist. When worn while sleeping, the therapy complements the circadian rhythm of bone remodeling and metabolism for tooth movement. Smaller incremental tooth movements are programmed into each aligner tray/stage allowing for activation of biological cascade governing orthodontic tooth movement, with an added advantage of intermittent force resulting in reduced root resorption. Daytime aligners (control) are made with material that is 0.30-0.35 inch thick and the planned tooth movement rate is 20% more than that of the Nighttime Aligners (investigational).

Tooth movement treatment planning constraints of Daytime Aligners (control):

Movement Type	**Translate [B/L] (mm)**	**Torque / Incline (°)**	**Tip (°)**	**Rotate (°)**	**Intrude (mm)**	**Extrude* (mm)**
Per aligner	*0.3 mm*	*1 °*	*1 °*	*2 °*	*0.1 mm*	*N/A*
Tooth	**Totals per treatment plan**					
Incisors	5	25	25	45	2.5	N/A
Laterals	5	25	25	45	2.5	N/A
Canines	3	25	25	35	2.5	N/A
Premolars	2	10	10	10	1	N/A
Molars*	N/A	N/A	N/A	N/A	N/A	N/A

**Extrusive and molar movements are allowable with standard, Daytime Aligners, however, for the purposes of this study, they will not be allowed.*

6.2 Accountability of Investigational Product (IP)

All investigational and control devices must be accounted for.

6.2.1 Accountability of all investigational and control devices provided to the Investigator shall be documented by the Sponsor and the Investigator.

6.2.2 Accountability of all investigational and control devices provided to the subject shall be documented by the Investigator.

6.2.3 The documentation shall provide lot/batch/serial numbers and any pertinent tracking or traceability information provided on product labels or packaging.

6.2.4 This information shall be maintained in the clinical trial master file for the life of investigational device.

6.2.5 Used investigational and control devices will not be returned to the Sponsor.

6.2.6 Any unused investigational and control devices provided to subjects shall be returned to the Sponsor at the end of the study, at the expense of the Sponsor.

6.3 Study Related Materials

6.3.1 All investigational materials provided to the Investigator shall be documented by the Sponsor.

6.3.2 All investigational materials provided to subject shall be documented by the Investigator.

6.3.3 All documents and study related materials required to conduct this study will be provided to each Investigator by the Sponsor. Additional materials may be sent upon request.

7. RISKS AND BENEFITS OF PARTICIPATION

7.1 Risks

7.1.1 The Sponsor has not identified any additional risks by participation in this clinical study. However, there are some risks that have an increased probability of occurrence with a reduced wear time aligner regimen including:

- Reduced wear time causes teeth to shift while aligner is not worn; treatment takes longer than expected → Treatment Delay
- Only wearing aligners for 10-12 hours per day can lead to greater subject discomfort when aligners are worn → Subject Discomfort

7.1.2 Additionally, there are risks associated with orthodontic treatment in general, including:

- Discomfort: There may be some discomfort due to wearing an aligner for the first time, as the mouth is very sensitive. As the teeth move, often some discomfort is to be expected, however this usually wears off in a couple of days after each aligner tray

change. Aligners may cause irritation to the surrounding cheeks and lips.

- Allergy: Although rare, some people may be allergic to the plastic in aligners. If the subject knows that they have a plastic allergy or sensitivity, they should notify the Investigator prior to starting aligner therapy. Subject with known allergies to plastic materials are not eligible to participate in this clinical study. If an allergy to the aligner occurs, the Sponsor and/or the Investigator may recommend that treatment be paused and continued using alternative methods.
- Cavities: The surface of teeth may become weaker, and may have more cavities. Excellent oral hygiene will help to prevent this from happening during treatment.
- Resorption: The roots of teeth may become shorter or weaker during treatment. The Sponsor and/or the Investigator may recommend that treatment be paused if this process called root resorption occurs.
- Tooth movement not tracking according to the prescribed treatment plan: This can be caused by several factors; the top factor being subject compliance in wearing aligners the required number of hours per day/night. Treatment time may take longer than expected, or final outcomes may be different than what was planned when aligners are not worn as prescribed.
- X-ray: Standard procedures will be used i.e., all attempts to limit X-ray exposure will be made during the clinical study, including proper shielding.

7.1.3 Accidental Disclosure of Personal Health Information: Although rare, there is a risk that personal health information may be disclosed to others who do not have the right to see it. The US HIPAA and EU GDPR privacy rules help your dentist and the Sponsor ensure they have the appropriate processes in place to prevent this from occurring.

7.2 **Benefits**

7.2.1 The investigational device being used in this study may help straighten the subject's teeth or improve their smile. While there are no guarantees the study of this product will provide a conclusive outcome.

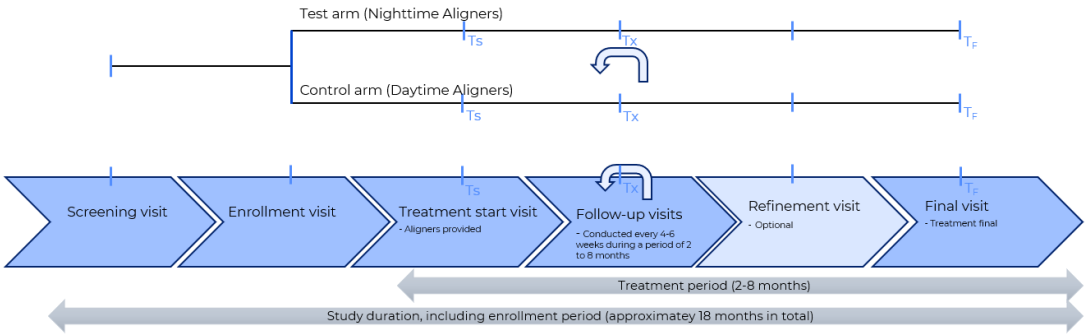
7.2.2 One benefit of the reduced wear time aligner therapy is aesthetics. Subjects are able to wear the aligners during periods when they are sleeping or otherwise at home; offering a more discrete option of therapy.

7.2.3 Another benefit of the reduced wear time aligner therapy is increased subject ease of using the device. Aligners must be removed prior to eating and drinking anything except cool water. The subject must also brush their

teeth prior to reinserting the aligners. If the aligners are only worn during sleep or times when the subject is not eating or drinking for a continuous 10-12 hours, subjects do not need to worry about this additional device/oral hygiene process.

7.2.4 Information from this study might help researchers develop a better orthodontic device that will help others in the future.

8. STUDY PROCEDURES



8.1 Screening

8.1.1 Subjects seeking orthodontic treatment will be screened through the Byte+ network of dental providers. Subjects who opt to receive orthodontic aligner treatment using the Byte® system will be screened for eligibility by the Investigator in the dental office. Screening will be based on potential study subject case complexity and eligibility.

8.1.2 Subjects will visit one of the Byte+ network dentists for an initial intraoral scan, x-ray (PAN, CBCT, CEPH and/or FMX), intraoral and extraoral photographs. An X-ray taken within a year from study visit may be used for treatment planning if deemed adequate by the Investigator.

8.1.3 Subjects will be screened based on the inclusion and exclusion criteria defined above.

8.1.4 Subjects will be informed that the investigational device is being studied for its safety and efficacy in achieving prescribed tooth movement per each individual subject's subject treatment plan and is not currently cleared by the FDA.

8.1.5 Informed consent (and parental consent for minors under the age of 18) will be obtained from the subject.

8.1.6 All subjects screened will be documented in the Screening Log maintained at each investigational site.

8.1.7 Once the treatment plan is created, the Byte+ account manager will ensure that the subject's prescribed tooth movements are within the constraints and criteria outlined within this study's inclusion/exclusion criteria.

- If the subject requires movements outside of the study's eligibility criteria, they can continue with their orthodontic treatment with Daytime aligners outside of the confines of this clinical study. In these cases, the Investigator will be informed by the digital lab as to why the subject is not eligible for the study; the Investigator in turn shall notify the subject and withdraw them from the study.

8.2 **Enrollment**

8.2.1 Subjects who meet the inclusion and exclusion criteria defined above are eligible to participate in this clinical study.

8.2.2 Eligible subjects who agree to participate in this study and meet the eligibility criteria will be informed that their case has been accepted into the study and they are eligible to participate.

8.2.3 Once a subject has been enrolled, the order will be placed in the Byte system and a treatment plan is created by the Byte digital lab, using the digital impression received and FDA cleared treatment planning software (refer to K230199), to stage the subject's orthodontic treatment.

8.2.4 Subjects will be assigned a unique subject identification number randomly generated by the ERP system. This number will be used as the primary identifier on all study related documents. In addition subject will receive a subject Id when enrolled in the study. Subject IDs are unique to each individual subject and cannot be changed.

8.2.5 All enrolled subjects will be documented in the Screening Log.

8.3 **Study Schedule**

Visit	Screening visit	Enrollment visit	Treatment start visit (T_S)	Follow-up visits (Tx - e.g. T1, T2 etc.)	Final visit (T_F)
Timepoint			Day 0	T_S + every 4-6 weeks during a 2-8 months period	T_S + 8 months
Informed Consent	X				
Subject eligibility	X	X[4]			
Demography	X				
Medical history[1]	X				
Concomitant medications	X		X	X	X
Oral examination	X				
X-ray[2]	X				X
Clinical photography[3]	X			X	X
Intraoral scan	X				X
Intraoral refinement scan				X[5]	
Treatment plan (.stl-file)[4]		X			
Subject questionnaire				X	X
Investigator questionnaire					X
Aligners provided			X	X	
Aligner instructions to subject			X		
AE/DD collection			X	X	X

[1] Relevant medical conditions.
[2] Treatment screening X-ray and Treatment final X-ray (e.g. (PAN, CBCT, CEPH, and/or FMX).
[3] Intraoral and extraoral photographs.
[4] Treatment plan generated through Byte portal (final eligibility verification).
[5] Refinement scan only applicable if deemed needed by the investigtor.

8.3.1 Once aligners are manufacturered, the first fifteen (15) aligner stages will be provided to the Investigator. Additional aligner stages in sets up to fifteen (15) are provided to the Investigator to continue treatment after completion of the first fifteen (15) sets.

8.3.2 The Investigator will provide the subject with aligners at treatment start and at monthly check-ins with the Investigator at clinic visits.

8.3.3 Once the aligner trays are received by the subject, they can start their treatment. The date the aligners are received will be recorded as the start date of each subject's participation (TS). The initial visit worksheet must be completed at this time.

8.3.4 The subject visits will be performed monthly (every 4-6 weeks). The Investigator will review the subject's treatment progress, confirm treatment plan and follow-up on any safety events. A visit worksheet must be completed at each visit (T_1, T_2, T_3, etc.).

8.3.5 The study aims to collect the following data at the following time points:

- Intraoral scans of the subject prior to the start of treatment (T_S) and end of treatment (T_F).
- X-ray (PAN, CBCT, CEPH, and/or FMX) prior to the start of treatment (T_S) and at the end of treatment final visit (T_F).
- Intraoral and extraoral photographs prior to the start of treatment (T_S), at every check-in visit, and end of treatment final visit (T_F).
- Completed visit worksheet at initial aligner visit (T_S), scheduled monthly check in visits (4-6 week intervals: T_1, T_2, T_3, T_4, etc.), and final aligner visit (T_F).
- Completed subject questionnaire at check in visits (4-6 week intervals: T_1, T_2, T_3, T_4, etc.),
- Subject post-treatment questionnaire at the end of the treatment (T_F).
- Relevant medical conditions and concomitant medication incl. trade name, dosage, route and start.
- AE/DD documentation

8.3.6 At the final aligner treatment visit (T_F), the dentist will complete a final visit worksheet and subject will complete the post-treatment questionnaire.

8.3.7 Each subject will receive removable retainers following completion of aligner therapy.

8.4 Subject Eligibility

8.4.1 Subject Eligibility, informed consent, and if applicable parental consent shall be documented and later transferred to the **eCRF**.

8.5 Subject Information

8.5.1 Subject demographic information including subject ID, age, gender, ethnicity and race will be collected and transferred to the corresponding **eCRF**.

8.6 Pre-Treatment Period

8.6.1 The following will be collected prior to aligner treatment, and are required for the treatment planning phase of aligner therapy:

- Intraoral scan
- X-ray (CBCT, CEPH, PAN and/or FMX)
- Intraoral and extraoral photographs

8.7 Treatment Start

8.7.1 The initial delivery of the investigational or control devices will be received by the subject (TS). A visit worksheet is required for the initial aligner visit. Visit worksheet data will be transferred to the eCRF.

- The subject will be directed on use and care of the investigational or control device during the treatment period.

8.8 In-Treatment Period

8.8.1 The subject will check in with the Investigator at their dental practice/office monthly (every 4-6 weeks).

- The Investigator will review the subject's treatment progress and provide feedback to the subject and the Sponsor related to compliance and tracking via completion of a visit worksheet at each visit (T1, T2, T3, etc.).
- The Investigator will also take subject progress intraoral and extraoral photographs at each check in visit and submit them to the Sponsor.
- In-treatment subject questionnaire

8.8.2 The Investigators and the Sponsor will assess the progression of investigational treatment through information subject submitted to the **eCRF**.

8.9 Treatment Final

8.9.1 The following will be collected at final treatment visit (T_F).

- Intraoral scan
- X-ray (CBCT, CEPH, PAN, and/or FMX)
- Intraoral and extraoral photographs
- Final visit worksheet (TF)
- Post-treatment subject questionnaire

8.9.2 Each subject will receive removable retainers following completion of aligner therapy.

8.9.3 Participation in this study ends for each subject when:

- Subjects complete treatment with the investigational or control device and the Investigator determine that a retainer can be ordered.

- When a subject withdraws their consent to continue participating in the study.
- If an Investigator removes a subject from the study due to ineligibility or non-compliance with study protocols.

8.10 Subject Discontinuation

8.10.1 The Investigator and/or the Sponsor may discontinuing a subject if severe non-compliance to the protocol. Subject may also be discontinued due to safety reasons as judged by the Investigator and/or Sponsor.

8.10.2 If a subject for any reason desires to no longer participate in the study or continue treatment, they are free to discontinue participation in the study, at any time and without providing a reason for the withdrawal. Discontinuation from the clinical study will not affect future treatment /care of the subject.

8.10.3 Subjects who discontinue should always be inquired about the reason(s) for their discontinuation and any potential safety issues. If possible, they should be seen and assessed by an Investigator. The termination section in the eCRF should be completed. Safety events should be followed up. Any study specific material provided to the subject should be collected.

9. ENDPOINTS

9.1 Primary Safety Endpoint

The primary safety endpoint of the study will be the incidence of (device or dental) related AEs and SAEs associated with the planned investigational treatment, compared to the incidence from treatment with the control device.

9.2 Secondary Safety Endpoint

The secondary safety endpoint of the study will be the subject self-reported values pertaining to pain/discomfort during treatment and comfort in wearing the aligners captured in the questionnaire. For this endpoint, a Visual Analogue Scale (VAS) with a Wong Baker face scale is used.

9.2.1 Subject comfort wearing aligners during treatment via visual analogue scales (VAS): This question is directed to the subject. “How comfortable were the aligners to wear during your treatment?” (VAS: 0 very comfortable - 10 very uncomfortable).

9.2.2 Subject pain associated with new tooth movements during treatment via visual analogue scales (VAS): This question is directed to the subject. “Did you experience any pain associated with new tooth movement?” (VAS: 0 no pain – 10 worst possible pain).

9.3 Primary Efficacy Endpoint

The primary effectiveness endpoint is the comparison between the treatment groups of the quantification of actual vs planned tooth movements using weighted Peer Assessment Rating (PAR) index.

- Planned percentage reduction in PAR Score (Planned Improvement of Malocclusion [PIM])

In addition comparison between treatment groups will also be performed for:

- Actual percentage reduction in PAR Score (Actual Improvement of Malocclusion [AIM])
- Percentage of Accuracy of Outcome

Quantification and comparison of expressed and programmed tooth movements will be conducted using to measure orthodontic treatment need and outcome, the built-in weighted PAR analysis tool of 3Shape Ortho System software (K152086).

9.3.1 The weighted PAR scores for each Digital Study Model (DSM) would be compared as follows:

- Planned percentage reduction in PAR Score (Planned Improvement of Malocclusion [PIM]) = PAR Score TS- PAR Score TP / PAR Score TS * 100
- Actual percentage reduction in PAR Score (Actual Improvement of Malocclusion [AIM]) = PAR Score TS- PAR Score TF / PAR Score TS * 100
- Percentage of Accuracy of Outcome = 100% - [(|PIM - AIM|/|AIM|) *100%]

9.4 Secondary Efficacy Endpoint

The secondary endpoint of this study will be to assess overall subject and dentist (Investigator) satisfaction with their treatment. This will be assessed through a questionnaire provided to both the dentist and the subject when treatment is completed. For this endpoint, a rating scale (1 very satisfied - 10 very unsatisfied) is used.

9.4.1 Doctor satisfaction with treatment results: “How satisfied are you with the results obtained?” (1 very satisfied - 10 very unsatisfied).

9.4.2 Subject satisfaction with treatment results: This question is directed to the subject “How satisfied are you with the results obtained?” (1 very satisfied - 10 very unsatisfied).

10. DEVIATIONS

10.1 Deviations

10.1.1 All deviations from this protocol will be reported in the study report. If it is necessary for the protocol to be amended, the amendment and/or a new version of the protocol (Substantial Amendment) must be notified to or approved by IRB before implementation. Local requirements must be followed. If a protocol amendment requires a change to a particular investigational site's ICF, then Sponsor and IRB must be notified. Approval of the revised ICF by Sponsor and by the IRB is required before the revised form is used. Sponsor will distribute amendments and new versions of the protocol to each Investigator and IRB. In general, a non-substantial amendment does not require a notification to or approval by IRB.

10.1.2 The Investigator is not allowed to deviate from the protocol except in case of emergency to protect a subject's rights, safety, and wellbeing. In such a case, the Investigator may proceed without prior approval from Sponsor or the IRB. However, the deviation should be documented and reported to Sponsor and the IRB as soon as possible.

10.1.3 Any protocol deviation that occurs, which is not approved by the Sponsor, will render the study subject ineligible for continued participation in this clinical study.

10.1.4 The Investigator should promptly report any protocol deviations to the Sponsor. It is the responsibility of the Sponsor to report all protocol deviations affecting study subject safety to the IRB in a timely manner.

11. ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

11.1 Adverse Event (AEs)

11.1.1 All adverse events must be reported to the divisional complaint officer and regulatory compliance.

11.1.2 All Adverse Events (AEs) will be documented and recorded by the Investigator in the eCRF throughout the study period.

- AE is defined as: Any untoward medical occurrence, unintended disease, effect or injury, or untoward clinical sign in a subject, whether related to the investigational product or not.
- For example, a rash, bleeding, or blistering appearing on the soft tissue in contact with the investigational device.
- Another example is clinically significant root resorption.

11.1.3 All adverse events shall be reported for that particular study subject's

appointment.

- This documentation should list the event, the cause of the event if known, consequences and resulting actions by the Investigator, or designee, and any other medically pertinent information.
- Where possible, a diagnosis rather than a list of symptoms should be given.
- The intensity to be recorded is the worst intensity experienced during the course of the event. The Investigator should complete all related information, including date(s) of onset, severity, corrective therapies given, outcome, and professional opinion as to whether the AE had a relationship to the investigational device.

11.1.4 The Center of Clinical Research (CoCR) team must make the determination of relationship to the investigational device for each recorded AE in the corresponding **eCRF**. The CoCR should decide whether there is a reasonable possibility that the event may have been caused by the investigational device.

11.1.5 If there is any valid reason, even if undetermined or untested, for suspecting a possible cause-and-effect relationship between the investigational device and the occurrence of the AE, then the AE should be considered “possibly” or “probably related”.

11.1.6 Otherwise, if no valid reason exists for suggesting a relationship, then the AE should be classified as “unrelated”. The following guidance may also be helpful:

- Unrelated: There is no medical evidence to suggest that the AE is related to the investigational device. The AE can be readily explained by the subject’s underlying medical condition or concomitant therapy or lacks a plausible temporal relationship to investigational device.
- Possibly Related: A direct cause and effect relationship between the investigational device and the AE has not been demonstrated, but there is a reasonable possibility that the AE was caused by the investigational device.
- Probably Related: The AE is likely related to the investigational device. This category applies when the experience most likely seems to be related to the investigational device but there is a modest suspicion that it could be related to other causes.
- Related: There is a direct cause and effect relationship between the AE and the investigational device.

11.1.7 The medical assessment of related AE severity will be determined by

using the following definitions:

- Mild: The AE is easily tolerated and does not interfere with usual activity.
- Moderate: The AE interferes with daily activity, but the subject is still able to function.
- Severe: The AE is incapacitating, and the subject is unable to work or complete usual activity, i.e. a serious injury has occurred.
- Life Threatening: The SAE places the subject, in the view of the Investigator, at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that had it occurred in a more severe form, might have caused death.

11.1.8 Outcome may be classified as resolved, ongoing, resolved with sequelae, or death.

- Unexpected severe or life threatening related events will be followed until resolved (the subject's health has returned to his/her baseline status or all variables have returned to normal), an outcome is reached, stabilization (the Investigator does not expect any further improvement or worsening of the AE), or the event is otherwise explained regardless of whether the subject is still participating in the study.
- Where appropriate, medical testing and examinations will be performed to document AE resolution.

11.1.9 The types of adverse events that are known to occur with orthodontic treatment include mild to moderate gum pain, inflammation, and redness; allergic reaction to plastic(s) or metal(s); and root resorption.

11.2 Serious Adverse Events (SAEs)

11.2.1 A SAE is any AE that results in any of the following outcomes:

- Death
- Immediate threat to life
- Hospitalization or prolongation of an existing hospitalization
- Persistent or significant disability/incapacity
- Congenital anomaly/birth defect

11.2.2 Important medical events that do not result in one of these outcomes, but based on appropriate medical judgment, are deemed to jeopardize the subject or require medical or surgical intervention to avert one of the listed outcomes, may also be considered SAEs at the Investigator's discretion.

- Allergic reactions are a known risk with clear aligners. Subjects with known plastic allergies have been excluded from this study.

As there may be some subjects enrolled who are unaware of a plastic allergy, allergic reactions will not be documented as SAEs. They should however be documented as Adverse Events (AE).

11.2.3 Any AE considered serious (SAE) according to the criteria above that occurs during the study must also be documented by the Investigator and recorded in the **eCRF**.All deaths and immediately life-threatening events, whether related or unrelated, will be recorded on the SAE Form and documented via the eCRF system within 24 hours of Investigators awareness.

11.2.4 All SAEs will be followed until satisfactory resolution has been reached, or until the Investigator deems the SAE to be chronic or the subject to be stable.

11.2.5 All SAEs must also be reported by the Sponsor as soon as possible to the IRB.

11.2.6 It is the responsibility of the device Sponsor to report the event as specified in 21 CFR Part 812.46. All SAEs designated as “unrelated” to the product will be reported to the FDA at least annually in a summary format by the Sponsor.

11.2.7 Subjects will be notified of any unexpected SAEs within the timelines specified by the U.S. CFR.

11.3 **Device Deficiencies (DDs)**

11.3.1 Device Deficiency (DD) is defined as: Inadequacy of a medical device with respect to its identity, quality, durability, reliability, usability, safety, or performance.

- Device deficiencies include malfunctions, use errors, and inadequacy in the information supplied by the manufacturer including labelling.
- This definition includes device deficiencies related to the investigational medical device or the comparator.

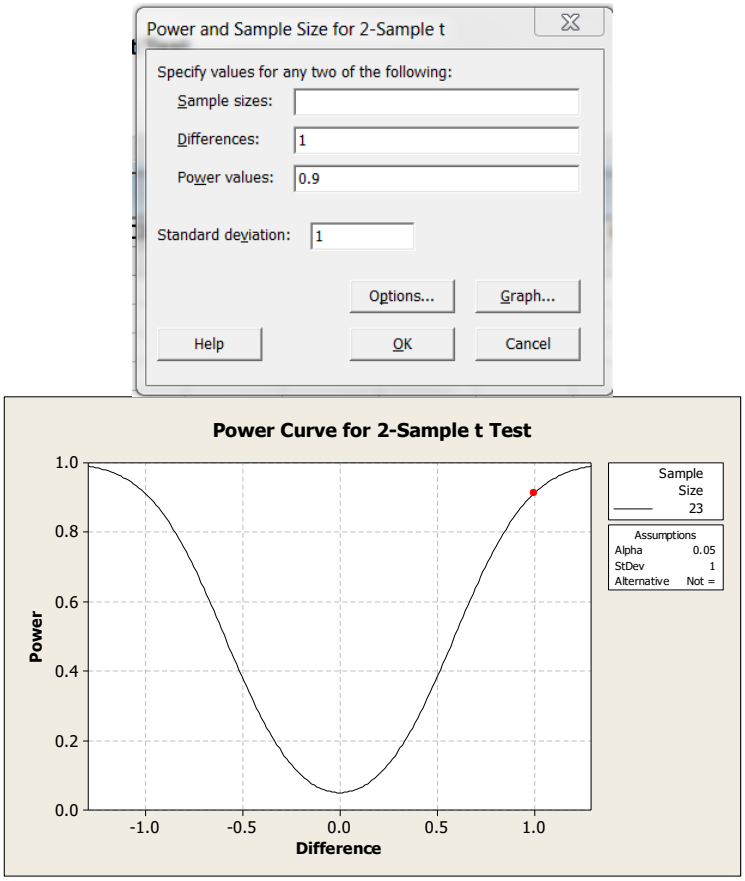
11.3.2 All DDs must be reported to the divisional complaint officer and regulatory compliance.

12. DATA AND STATISTICAL ANALYSIS

12.1 **Statistical Sample Size and Power (provided as an example)**

12.1.1 The current study is a controlled prospective study to determine the expressed movements demonstrated by investigational device, Nighttime Aligners for 10-12 continous hours per day/night compared to the control group, Daytime Aligners, which are worn for 20-22 hours per day.

12.1.2 Sample size calculations for this study were determined using statistical software Minitab to ensure proper powering. The desired sample size per arm is 23 based on power calculations previously developed by Dentsply Sirona. The desired level of power is 90%. The desired confidence is 95% ($p < 0.05$). Calculations are based on a standard deviation of 1, a power value of 0.9 and a detected difference of 1. The calculation also assumes a 2-sided, alpha = 0.05 level of significance.



12.2 **Data Analysis**

12.2.1 The Sponsor and Investigators are not blinded to the study data during the conduct of the trial, and may at periodic intervals analyze the data to assess study progress.

12.2.2 If nothing else is stated, descriptive statistics will be given for each variable in the clinical study and p-values may be complemented by confidence intervals as appropriate. When using the terminology descriptive statistics, it is meant that the number of subjects (N), mean, median, standard deviation (Sd), minimum (Min) and maximum (Max) values will be presented for continuous data and frequencies and percentages for categorical data.

12.2.3 All tooth movement data analyses will be performedusing 3Shape Ortho System (K152086).

12.2.4 Three .stl files from each subject would be used for the analysis:

- A pre-treatment STL file (TS) would be generated by scanning subject's pre-treatment intraoral scan taken before the start of treatment.
- A planned or programmed STL (TP) file would be obtained from Archform Orthodontic Software System (K213916) after planned or programmed tooth movements have been made based on the treatment plan finalized by the digital lab and study Investigators.
- The actual post-treatment STL file (TF) would be generated by scanning subject's post-treatment intraoral scan at the end of treatment.

12.2.5 Each STL file would convert into a Digital Study Model within the 3Shape Ortho System software to standardize the analysis.

12.2.6 Each DSM would be segmented using the "auto segmentation tool" of the software to demarcate each tooth separately.

12.2.7 This would be followed by Peer Assessment Rating (PAR) index to measure orthodontic treatment need and outcome (Richmond, 1992). This would be done using the built-in weighted PAR analysis tool of 3Shape Ortho System software. The PAR index will be performed by an external evaluator.

12.2.8 The weightage for each component of the PAR index would be set as: maxillary and mandibular anterior segment alignment x 1; buccal occlusion x 1; overjet x 6; overbite x 2; centerline x 4; following the ABO guidelines. The weighted PAR scores for each DSM would be compared as follows:

The PAR Score values for T_S, T_P, and T_F will be transferred to the eCRF and the following will be calculated:

- Planned percentage reduction in PAR Score (Planned Improvement of Malocclusion [PIM]) = PAR Score TS- PAR Score TP / PAR Score TS * 100
- Actual percentage reduction in PAR Score (Actual Improvement of Malocclusion [AIM]) = PAR Score TS- PAR Score TF / PAR Score TS * 100
- Percentage of Accuracy of Outcome = 100% - [(|PIM - AIM|/|AIM|) *100%]

Statistical analysis comparing the two treatment groups using the Wilcoxon rank sum test will pe performed. A two-sided p-value below

5% will be regarded as statistically significant. The null hypothesis of the study is that there is no difference between the two groups.

12.2.9 Additional comparisons between treatment groups may be performed and p-values presented using the Wilcoxon rank sum test. Wilcoxon signed rank test may be used for analysis within treatment groups over time.

12.2.10 Calculation of Spearman's rank correlation coefficients will be performed to elucidate the relationships between the accuracy of outcome with treatment duration, number of aligners, subject pain levels, and overall subject and doctor satisfaction for each group.

12.2.11 All methods used in this clinical study have been previously published and reviewed (Griffith 2021, Grünheid 2022). All data in this clinical study will be analyzed by an independent contractor to remove bias. Any adjustments or modifications to these methods will be duly documented and reported.

12.3 **Safety Analysis**

12.3.1 As this is a non-significant risk study, the Sponsor does not intend to use a Data Safety Monitoring Board for this clinical study.

12.3.2 Safety aspects of the investigational device will be evaluated in terms of related adverse events (AEs) and serious adverse events (SAEs) documented during the course of treatment beginning at the time of application of the device through the time of completion of the treatment period; i.e., the time of removal of the final treatment aligner.

12.3.3 Evaluation of adverse events will be based on the risk management file and known risks/harms documented by Sponsor for aligner systems (e.g. design / process FMEAs, harms libraries, historical complaint files and post-market surveillance data).

13. DATA COLLECTION AND MONITORING

13.1 **Source Documents & eCRFs**

13.1.1 Within the scope of this study, the Sponsor will record information related to the subject's treatment as outlined above. These data points shall be recorded and entered into the study specific **eCRF** by each investigational site participating in this clinical study.

13.1.2 During and at the end of the study, all data will be reviewed for completeness and accuracy against the data contained in the **eCRFs**.

13.1.3 A Monitoring Plan (MP) will be finalized prior to the first monitoring visit. The MP will describe the level of source data verification and tasks to be performed at monitoring visits, including frequency and intervals. A risk-based approach will be used when determining the extent and nature of monitoring activities. During the course of the clinical study, a monitor

from the Sponsor or representative will have regular contacts with the investigational site. The monitor or another Sponsor representative will also be available between visits if the Investigator or other personnel at the investigational site needs information and advice.

13.1.4 The Investigator is responsible to ensure that study information is recorded in the medical record, in accordance with national regulations and requirements. In general, the following information should be recorded in the medical record:

- Study code, and/or clinical study title.
- That informed consent for participating in the clinical study was obtained, and signature date.
- Diagnosis.
- All visits during the clinical study period including visit date.
- All AEs/ADEs/SADEs.
- Treatments and medications.
- Subject health service identification number, if applicable.

The Investigator is responsible for ensuring that source data, and data reported to the Sponsor, is attributable, legible, contemporaneous, original, accurate, and complete. The Investigator is responsible for providing the monitor, auditor, IRB, or RA if required, with access to all clinical investigational-related records, including source documents.

For data recorded directly in the eCRF, the eCRF is considered source data this should be documented on the source data specification form.

13.1.5 The Investigator should comply with the terms, conditions, and obligations of the Clinical Study Agreement (CSA). In the event of any discrepancy between the protocol and the CSA, the protocol shall prevail with respect to the conduct of the study and the treatment of subjects. For inconsistencies not related to the conduct of the clinical study or treatment of subjects, the terms of the CSA shall prevail over the protocol. The CSA should be finalized and signed before any study-related procedures, including subject enrollment, are performed at site. Should the Investigator break any obligations under the CSA and fail to remedy such a breach where it is capable of cure, Sponsor retains the right to disqualify the site from the clinical

13.2 **Case Report Forms (CRFs)**

13.2.1 All study data will be entered into the eCRF by personnel at the clinical study sites and signed by the site Investigator. Worksheets must be entered into **eCRF** within 48 hours of each visit.

13.2.2 When data has been reviewed and found to be clean, by CoCR, the data shall be locked in the **eCRF**.

13.2.3 Once data has been entered into the **eCRF** and locked, it cannot be modified by the personnel at the Investigational Sites unless unlocked by the CoCR.

13.3 **Data Entry and Management**

13.3.1 The handling of data, including data quality assurance, will comply with applicable regulatory guidelines (e.g.,ICH and GCP) and the Sponsor's operating procedures and work instructions. All steps and actions taken regarding data management and quality assurance will follow the Sponsor's policies and the data handling guidelines.

13.3.2 Completed CRFs will be verified and checked against source data, by CoCR, for completeness (i.e., source data verification), consistency, and legibility according to the study monitoring plan. In addition

- Edit checks will be implemented to ensure data quality and accuracy.
- Responses to requests for further clarification of data recorded in the eCRF will be documented, dated, and signed by the Investigator in the software.
- All adverse event terms recorded on the CRF will be collected and entered into the Sponsor's AE tracking system.

13.3.3 Data contained within the eCRFs will be exported from the Electronic Data Capture (EDC) system software Viedoc.

- When all study data has been entered, signed and locked and all queries are resolved Clean File will be declared and, the study database will be locked, and data will be exported for the purpose of statistical analysis and reporting.

13.4 **Data Monitoring**

13.4.1 The CoCR shall review the data entered into the eCRFs to ensure that it is accurate and corresponds with the information contained in the Source Documents.

13.4.2 Only personnel at the Study sites shall have access to modify data entered into the eCRFs and corresponding study database(s).

13.4.3 CoCR will query the personnel at the Investigational Site for any unclarities that are identified during data review and source data verification.

13.4.4 The queries are solved by personnel at the Investigational Site and approved by CoCR.

13.4.5 All eCRF data changes, updates and query handling is tracked in the EDC

software audit trail.

14. QUALITY ASSURANCE

14.1 Responsibilities

14.1.1 The Sponsor and Investigators must agree to conduct the study in accordance with the applicable regulations and Good Clinical Practice (GCP) guidelines.

14.1.2 Sponsor Study Director is responsible for signing this clinical protocol and all protocol amendments. The Sponsor Study Director is also responsible for ensuring that all study personnel are adequately trained and that the required material(s) are sent to each subject in a timely fashion. Sponsor Study Director is also responsible for ensuring the completion of the clinical study report at the conclusion of the study. CoCR shall assist in statistical analyses associated with the protocol.

- Sponsor responsibilities include the creation and oversight of protocol development, data monitoring, maintaining GCP conduct of the study, and the submission of final study report(s) to the FDA. Additionally,
- Sponsor shall conduct a timely evaluation of any unanticipated adverse device event.
- Sponsor who determines that an unanticipated adverse device event presents an unreasonable risk to subjects shall terminate all investigations or parts of investigations presenting that risk as soon as possible. Termination shall occur not later than 5 working days after the Sponsor makes this determination and not later than 15 working days after the Sponsor first received notice of the event.
- If the study is halted due to a safety concern, the Sponsor will submit the safety information to the FDA and will receive IRB approval prior to restarting the study.

14.2 Training

14.2.1 All Sponsor and site personnel involved in the execution of this clinical study shall be appropriately trained prior to participating in any study related tasks.

15. DOCUMENTATION REQUIREMENTS

15.1 Enrolled Subjects:

15.1.1 The original consent form, along with detailed information on the subject, will be kept at site. A copy of the signed informed consent will be provided to the subject.

15.1.2 In order to protect confidentiality of the study subjects, any information that could identify the individual, such as name, initials or address, will not be included in the eCRF nor the data set provided for analysis. This also include any files uploaded to the EDC system such as photos, scan files or x-rays. All eCRF data in the EDC system is pseudonymized.

15.1.3 Each subject must agree to allow CoCR team to view any and all relevant source documentation to aid in study related monitoring and data analysis.

15.2 Sponsor:

15.2.1 Study results shall be documented and approved in a final report. The report shall summarize the study data, present the results of the conducted statistical analysis, and document the conclusion of the study.

15.2.2 All data collected during the execution of this clinical study shall be maintained by the Sponsor in the clinical trial master file.

15.2.3 These records are accessible to Sponsor staff and regulatory agencies for review upon request.

15.3 Investigator:

15.3.1 All data collected at the clinical study site shall be maintained by the Investigator in the Investigator site file (ISF).

15.4 Record Retention:

15.4.1 Sponsor will be responsible for long-term storage of the clinical trial master file in accordance with applicable local laws. Clinical study data will be securely stored at Sponsor, with restricted access. Data will be retained at Sponsor for 15 years after the last device was placed on the market.

15.4.2 The medical records of clinical study subjects must be retained in accordance with local legislation and in accordance with the maximum period of time permitted by the clinic. The Investigator shall retain all clinical study records during the study and for the period required by applicable regulatory requirements or for at least 10 years after the premature termination or completion of the clinical study, whichever ever is the longest. The Investigator must take measures to prevent accidental or premature destruction of the records. The Investigator should contact Sponsor prior to destruction of any records or reports pertaining to the

clinical study to ensure they no longer need to be retained. In addition, if the Investigator leaves the hospital, he/she should provide Sponsor with the name and address of the person who will take over the responsibility for the clinical study-related records. If the records are transferred to another person/party, the transfer should be documented at the clinical study site or at Sponsor.

16. SUBJECT RIGHTS AND CONFIDENTIALITY

16.1 IRB Review

16.1.1 This protocol and each subsequent revision shall be reviewed and approved by an Institutional Review Board prior to initiation.

16.1.2 All associated consent, assent, and advertising materials associated with the protocol shall be reviewed and approved by the same IRB prior to use.

16.1.3 The Investigator is responsible for submitting amendments, and updated ICFs, to IRB and approval(s) must be obtained prior to implementation at site. Any additional requirements by the IRB should be met.

16.2 Insurance

16.2.1 The Sponsor is responsible for ensuring adequate insurance coverage of any injuries to subject(s) caused by the Aligner.

16.3 Protected Health Information & Subject Confidentiality

16.3.1 Subjects will be assigned a unique subject identification number during enrollment generated by the ERP system at the time of placing the subject's orthodontic treatment order.

- This number will be used as the primary identifier on all study related documents. In addition subject will receive a subject Id when enrolled in the study.

16.3.2 Each investigational site shall maintain a Screening Log. All enrolled subjects are included in the Subject Id log that links each subject to their assigned subject identification number.

- The Sponsor shall have access to this information solely for the purposes of data monitoring.

16.3.3 No personal identification information such as subject's first or last name, initials, social security number shall be included in study related documents.

- In cases where records containing protected health information must be sent to the Sponsor, FDA, or other agency, it will be appropriately de-identified to ensure that subject's privacy is maintained in accordance with the Health Insurance Portability and Accountability Act (HIPAA) and EU GDPR.

16.4 **Subject Withdrawal**

16.4.1 During the informed consent process, eligible study subjects will be advised that they are free to withdraw their consent to participate in the study at any time, without prejudice by the Sponsor.

16.4.2 Every reasonable effort should be made to ensure that each subject complies with the protocol and completes all study visits. However, a subject may withdraw or be withdrawn from participation if:

- The subject withdraws consent,
- CoCR or study Investigators recommend discontinuation in the interest of the subject's safety (i.e., AE-related) or because of significant and irremediable protocol non-compliance,
- There is a report of a SAE that warrants discontinuation,
- The subject is lost to follow-up, or
- The Sponsor or the Institutional Review Board (IRB) terminates the clinical trial.

16.4.3 Data for subjects that are withdrawn from the study, but have already completed a portion of the trial, will be retained and used in the statistical analyses described in this protocol.

16.4.4 Withdrawals from the study shall be documented, with the primary reason for withdrawal recorded by the Investigator.

17. ASSOCIATED DOCUMENTS

1. Nighttime Aligners Instructions for Use (Investigator)
2. Nighttime Aligners Instruction for Use (Subject)
3. Daytime Aligners Instructions for Use (Investigator)
4. Daytime Aligners Instructions for Use (Subject)

18. SIGNATURES

I agree to the terms of the Clinical Study Protocol.

Approval of Study Protocol	
Nick Sarnoff *VP, Byte*	Date (DD/MMM/YYYY)
Jay Khorsandi *Study Director*	Date (DD/MMM/YYYY)
Scott Lurgio *Quality Assurance & Regulatory*	Date (DD/MMM/YYYY)
Gretchen Heasley *Regulatory Affairs*	Date (DD/MMM/YYYY)
Bharat Patel *Research & Development*	Date (DD/MMM/YYYY)
AnnaKarin Lundgren *Director Center of Clinical Research*	Date (DD/MMM/YYYY)