Statistical Analysis Plan

Title of Research:	Aerodentis Clinical Trial: Assessment of the Efficacy of Orthodontic Tooth Movement Using the Aerodentis System
UAB IRB Protocol #:	F160418007
Principal Investigator:	Dr. Chung How Kau, BDS, MScD, PhD.
Co-investigators:	Dr. Ejvis Lamani, DMD, PhD Dr. Terpsithea Christou, DDS
Sponsor:	Dror Orthodesign Ltd. 7 Hartom Street Jerusalem, Israel 9777507 972 (0) 74-700-6700

Statistical Considerations

Overview and Rationale for Primary Parameter

The aims of this trial are to assess the safety and efficacy of the Aerodentis system in producing tooth movement. Safety is measured by absence of root resorption while efficacy is typically measured by various parameters relating to tooth movement. Because tooth movement is highly variable between individuals, treatment success is not usually contingent on a specific amount of movement over time. To this end we specify the primary endpoint, achieving score <1mm in Little's index

Design

Historical controls will be utilized as a comparator group. This historical data will be generated using the same inclusion/exclusion criteria as the proposed prospective single arm study. The historical patient population will be derived from the study sites participating in this prospective study. The study inclusion/exclusion criteria will be applied to consecutive patients treated with clear correctors that have the potential for complete datasets (as defined by the study protocol).

The use of single arm, open label trial with historical controls is supported when a device technology is well developed and the subject of interest is well understood[1]. Orthodontic treatment of this patient population (i.e., use of mechanical force) is well developed and understood. In addition, the primary

[1] Draft Guidance for Industry, Clinical Investigators, and Food and Drug Administration Staff Design Considerations for Pivotal Clinical Investigations for Medical Devices, published August 15, 2011.

endpoints of success are Objective Performance Criteria (OPC) (use of impressions to objectively measure tooth movement and Little's index scoring and independent radiographic evaluation of tooth resorption). The effectiveness OPC in the treatment of this patient population is a summative Little's index score of <1.5mm. The safety OPC is to allow for no tooth root resorption. The use of this study design is supported both by proposed FDA Gudiance[5] and recent FDA approvals of devices with a high risk profile[2]

Safety Analysis Set

The safety analysis set will consist of all patients from whom dental plaster impressions were taken for the purpose of treatment with Aerodentis.

Full Analysis Set

Primary efficacy analysis will be assessed using the Full Analysis Set (FAS). The FAS will consist of patients from the intent to treat (ITT) cohort who started treatment and have at least one post-baseline assessment, and have no major protocol violation as determined by blind review.

Missing Data:

Missing data will be handled for imputation the primary endpoint data for FAS subjects. Subjects with no post-baseline assessment will be imputed as failures and will not be included in the FAS population. The MMRM model (Mixed-effect Model for Repeated Measures), which is based on MAR (missing at random) assumption will be applied to all the subjects of the FAS population. Sensitivity analyses will be applied for testing the effect of the imputation on the treatment effect. This will show the influence of the imputation on the study results.

Per Protocol Analysis Set

Efficacy analyses will also be done on the Per Protocol subset. Per Protocol subset include all FAS subjects who completed the study according to the protocol with no protocol deviations.

Missing Values: Only observed data will be used in the Per Protocol Analysis Set; i.e. missing data will not be imputed.

Endpoints

Safety

The safety endpoints are adverse events, whether or not treatment related. Included will be amount of root repsorption, measured by comparing x-rays before, mid-point and after treatment

Primary Efficacy

The primary endpoint will be to evaluate the degree of tooth movement. Treatment success will be defined using the Little's Index and when a score does not summative exceed 1.5mm (<1.5mm)

[2] Campbell, Greg Some Considerations for Medical Devices: Historical Controls and Performance Goals, FDA-NIH Science of Small Clinical Trials Course, November 27-28, 2012 https://www.google.com/url?sa=t&rct=j&q=&esrc=s&source=web&cd=15&cad=rja&ved=0CEIQFjAEOAo&url=https%3A%2F%2Fevents-support.com%2FDocuments%2FCampbell.pdf&ei=OL4dUvnoLMK9sAT7-YGgDw&usg=AFQjCNGQWAFNwDj6XKq5ZVay8hssRm9lzA&bvm=bv.51156542,d.cWc

This is a reasonable endpoint as the results are comparable to other successful aligner studies. In addition, studies to long term stability have used 2mm or less as an acceptable outcome of success post orthodontic treatment,

Invisalign® treatment in the anterior region: were the predicted tooth movements achieved? **Krieger E**[1], **Seiferth J**, **Marinello I**, **Jung BA**, **Wriedt S**, **Jacobs C**, **Wehrbein H**.
http://www.ncbi.nlm.nih.gov/pubmed/22890691

How well does Invisalign work? A prospective clinical study evaluating the efficacy of tooth movement with Invisalign. **Kravitz** 2009
http://www.ncbi.nlm.nih.gov/pubmed/19121497

Semin Orthod. 1999 Sep;5(3):191-204.
Stability and relapse of mandibular anterior alignment: University of Washington studies.
Little RM.

Br J Orthod. 1990 Aug;17(3):235-41.
Stability and relapse of dental arch alignment.
Little RM1.

Sample Size Considerations
The planned sample size is 40 subjects. The tested group will include 40 subjects.

Study Hypotheses
We will have demonstrated success if the summative Little's index score will achieve score <1.5mm.

Statistical Analysis
All measured variables and derived parameters will be tabulated by descriptive statistics.

For categorical variables summary tables will be provided giving sample size, absolute and relative frequency and 95% CI (Confidence Interval) for proportions.

For continuous variables summary tables will be provided giving sample size, arithmetic mean, standard deviation, median, minimum and maximum and 95% CI (Confidence Interval) for means of variables.

Complete individual listings of all data represented in the CRF will be provided as an appendix. All calculated and derived variables will be listed as well.

All tests will be two-tailed, and a p value of 5% or less will be considered statistically significant.
All statistical analyses will be performed and data appendices will be created using the SAS® system Version 9.1.3 or higher.

The effects of noncompliance, dropouts, and covariates on treatment will be assessed to determine the impact on the general applicability of results from this study.