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Statistical Analysis Plan for:

A Prospective Multicenter Open-label Randomized Controlled Trial of Agili-C vs. Surgical Standard of Care (SSOC) for the Treatment of Joint Surface Lesions of the Knee

Protocol Number CLN0021

Version 2.0

April 2020

This statistical analysis plan has been read and approved by:

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1. Introduction

1.1 Overview

This is a multicenter, 2:1 randomized, open-label, controlled clinical trial of the Agili-C™ device for the treatment of joint surface lesions of the knee. Subjects will be randomized to either the investigational Agili-C™ device or the surgical standard of care (SSOC) control group, with twice as many subjects allocated to the investigational device. The trial has a flexible sample size that will be determined adaptively using a "Goldilocks" strategy. A minimum of 250 subjects, and up to a maximum number of 500 subjects, will be randomized.

This is an adaptive trial design, with interim analyses which allow for early stopping of the trial for futility, or for early stopping of enrollment, but continuing follow-up, for expected success. The primary outcome, change from baseline in overall KOOS score will be assessed at 24 months. Table 1 presents the schedule of study activities.

Table 1.

Procedures	Screening Visit	Final Screening/ Procedure Visit	2 week Post-Procedure Visit (± 1.5 weeks)	3 $^{\mu}$, 6^ months post procedure (± 12 weeks, 12 and 18 Months Post-Procedure Visit (± 16 weeks)	24 Months Post-Procedure Visit (± 16 weeks)	Annual Post-24 months Visit$^{\$}$ (12 months ± 16 weeks)	Unscheduled Visit
Number of Visit	Visit 1	Visit 2	Visit 3	Visits 4-7	Visit 8	Visits 9+	
Obtain Informed Consent	X						
Assignment of Subject Number	X						
Review Inclusion/ Exclusion criteria	X	X (intra operative)					
BMI	X$^{@}$						
Medical History	X						
Baseline MRI	X*						
MRI according to CartiHeal protocol				X**	X**		X***
Defect Fill Evaluation according to MRI, off-site				X$^{**,\infty}$	X**		
Baseline standing X- ray (AP & Lateral)	X*						
Weight bearing AP & Lateral X-ray			X$^{\#}$	X$^{\infty}$	X		X***
IKDC Knee Examination form 2000 (Surgeon)	X			X$^{\infty}$	X		X
OA Classification Kellgren-Lawrence score, off-site	X						
ICRS Cartilage Injury Standard Evaluation Form 2000 (Subject)	X						
ICRS Knee History	X						

Registration (Surgeon)							
SF-12 v2	X			X$^{\infty}$	X	X	
Procedures	**Screening Visit**	**Final Screening/ Procedure Visit**	**2 week Post-Procedure Visit (± 1.5 weeks)**	**3 $^{\mu}$, 6^ months post procedure (± 12 weeks, 12 and 18 Months Post-Procedure Visit (± 16 weeks)**	**24 Months Post-Procedure Visit (± 16 weeks)**	**Annual Post-24 months Visit$^{\$}$ (12 months ± 16 weeks)**	**Unscheduled Visit**
2000 IKDC Subjective Knee Evaluation Form	X			X$^{\infty}$	X	X	
KOOS Subscales	X			X$^{\infty}$	X	X	
Tegner score	X			X$^{\infty}$	X	X	
mICRS cartilage injury mapping and classification		X					
Arthroscopy and randomization		X					
Analgesic, anti-inflammatory and prescription medicine recording	X	X	X	X	X	X	X
AEs/SAEs		X	X	X	X	X	X
Tissue biopsy with histology							X****
Video recording		X					X

@ # * performed at 12 and 24 months. Additionally, MRI will be performed at 3 and 6 months to an initial cohort of at least 25 patients per study groups Weight and Height, only at screening X-ray may be performed lying down or standing, per patient comfort Screening MRI and X-ray must not be older than 1 year** MRI and Defect Fill evaluation is

*** MRI and X-ray will be performed according to PI decision **** According to PI decision if surgery is performed. The biopsy will be sent to a central lab.

$ Annual visit until last patient out $^{\mu}$ The 3-month visit may take place ±2 weeks ^ The 6-month visit may take place ±12 weeks

$^{\infty}$ Not applicable for the 3 months visit

2 Study Objectives

The study objective is to evaluate the superiority of the Agili-C™ device versus SSOC. The underlying clinical hypothesis is that the Agili-C™ implant is superior to SSOC according to the average overall KOOS score (Pain, Symptoms, QOL, ADL, & Sports) at 24 months relative to baseline.

3 Study Design

This is a prospective, multicenter, open-label, randomized, and controlled trial of Agili-C™ vs. SSOC for the repair of joint surface lesions. Eligible subjects will be randomized intra-operatively into either Agili-C™ or SSOC. Agili-C™ implantations will be performed via an arthrotomy or mini-arthrotomy procedure, using a designated surgical toolset. In SSOC, microfracture and debridement procedures will be performed arthroscopically according to standard practice. Follow-up will be performed at 2 weeks and 3, 6, 12, 18 and 24 months post-procedure to evaluate the patient's knee condition and clinical health. Questionnaires will be completed at baseline and at 6, 12, 18 and 24 months, and yearly thereafter until the last patient exits the study at 24 months. Standing Anterior-Posterior (A/P) and Lateral knee X-rays will be taken at 2 weeks and at 6, 12, 18 and 24 months post procedure. MRI according to specific protocol will be performed at 12 and 24 months. Additionally, MRI will be performed at 3 and 6 months for an initial cohort of at least 25 patients per study group.

Up to a total of 30 active centers in and outside the United States will participate in the trial. The sample size will range from a minimum of 250 subject to a maximum of 500 subjects. An adaptive trial design will be used which will allow early stopping of the trial for futility, or early stopping of enrollment, but continuing follow-up, for expected success.

4 Endpoints

4.1 Primary Endpoint

The primary endpoint is the change from baseline to 24 months in the average overall KOOS score (Pain, Symptoms, QOL, ADL & Sports). The overall KOOS score ranges from 0 to 100, where higher values represent better outcomes. In addition to the 24-month visit, average overall KOOS will also be measured at intermediate visits at 6 months, 12 months, and 18 months post-baseline.

4.2 Confirmatory Secondary Efficacy Endpoints

The trial will have 4 confirmatory secondary endpoints for labeling purposes:

- Change from baseline to 24 months in KOOS Pain subscore
- Change from baseline to 24 months in KOOS QOL subscore
- Change from baseline to 24 months in KOOS ADL subscore
- Overall KOOS responder rate (defined as an increase from baseline to 24 months of ≥30 points on overall KOOS)

4.3 Secondary Efficacy Endpoints

Secondary endpoints will include:

- Percentage of Articular Defect Fill according to MRI at 12 and 24 months
- Change from baseline in average overall KOOS score (Pain, Symptoms, QOL, ADL & Sports) at 6, 12, and 18 Months
- Change from baseline in IKDC Subjective Knee Evaluation at 12, 18, and 24 Months
- Change from baseline in Tegner score at 12, 18, and 24 Months
- Change from baseline QOL as measured by SF-12 v2 at 6, 12, 18, and 24 Months
- Change from baseline to 24 months in the average overall KOOS score (Pain, Symptoms, QOL, ADL & Sports) in patients with chondral lesions
- Change from baseline to 24 months in the average overall KOOS score (Pain, Symptoms, QOL, ADL & Sports) in patients with osteochondral lesions
- Change from baseline to 24 months in the average overall KOOS score (Pain, Symptoms,

QOL, ADL & Sports) in patients with single lesion

- Change from baseline to 24 months in the average overall KOOS score (Pain, Symptoms, QOL, ADL & Sports) in patients with multiple lesions
- Change from baseline to 24 months in the average overall KOOS score (Pain, Symptoms, QOL, ADL & Sports) in patients without osteoarthritis (K/L 0-1)
- Change from baseline to 24 months in the average overall KOOS score (Pain, Symptoms, QOL, ADL & Sports) in patients with osteoarthritis (K/L 2-3)
- Change from baseline to 24 months in the average overall KOOS score (Pain, Symptoms, QOL, ADL & Sports) in patients with total lesion(s) size $\leq 3cm^2$
- Change from baseline to 24 months in the average overall KOOS score (Pain, Symptoms, QOL, ADL & Sports) in patients with total lesion(s) size $>3cm^2$
- Change from baseline to 24 months in the average overall KOOS score (Pain, Symptoms, QOL, ADL & Sports) in patients with previous ligament reconstruction
- Change from baseline to 24 months in the average overall KOOS score (Pain, Symptoms, QOL, ADL & Sports) in patients without previous ligament reconstruction
- Change from baseline to 24 months in the average overall KOOS score (Pain, Symptoms, QOL, ADL & Sports) in patients with intact meniscus
- Change from baseline to 24 months in the average overall KOOS score (Pain, Symptoms, QOL, ADL & Sports) in patients with previous partial meniscectomy
- Change from baseline to 24 months in the average overall KOOS score (Pain, Symptoms, QOL, ADL & Sports) in patients with concomitant partial meniscectomy
- Change from baseline to 24 months in the average overall KOOS score (Pain, Symptoms, QOL, ADL & Sports) in active patients
- Change from baseline to 24 months in the average overall KOOS score (Pain, Symptoms, QOL, ADL & Sports) in non-active patients

4.4 Safety Endpoint

Adverse events, including serious adverse events, reoperations and revisions, up to 24 months.

5 Treatment Failure Definition

- For both Agili-C™ & SSOC groups: any secondary invasive treatment in the treated joint, regardless if related or unrelated to the original treatment, will be considered a treatment failure. Invasive interventions include: open procedure, mini-open procedure, arthroscopic procedure and intra articular injections, such as: HA, PRP, stem cells and steroids.
- Additionally, for the Agili-C™ arm: failure to implant the device in indicated patients will be considered a treatment failure. However, failure to implant the device in contraindicated patients/conditions will not be considered a treatment failure.

6 Randomization

Subjects will be randomized to either receive the Agili-C™ device or the control arm SSOC in a 2:1 ratio. Subjects will be randomized by site using variable block sizes of 3 and 6.

7 Interim Analyses

Details for the interim analyses, decision criteria, models, imputation procedures, simulations and operating characteristics for the design are included in the Adaptive Design Report attached as Appendix 1. The interim analyses will be conducted by an independent statistician and reviewed by the Endpoint Adjudication Committee (EAC).

The interim analyses, as described in Appendix 1, include only the primary endpoint - change from baseline to 24 months in average overall KOOS score. For the EAC review, we will also summarize and test the first confirmatory secondary endpoint - change from baseline to 24 months in KOOS Pain subscore, using a Bayesian posterior probability of superiority. For this secondary confirmatory endpoint, the interim analysis will NOT include a longitudinal model to multiply impute incomplete observations. However, similarly to the primary outcome, we will consider any treatment failures to have the change from baseline to 24 months Pain subscore replaced with their baseline value. At the earlier interim analyses, there may be only a few

subjects that have reached 24-months of follow-up. If fewer than 30 subjects have completed follow-up at an interim analysis, no testing of the first confirmatory secondary endpoint will be performed and only descriptive statistics will be provided to the EAC.

Additional descriptive summaries of safety outcomes and other secondary outcomes may be included in the interim analysis reports reviewed by the EAC as supplemental information. No testing will be performed on these other endpoints; only summaries will be presented.

8 Sample Size

Sample size justification is provided in the Adaptive Design Report attached as Appendix 1.
The sample size selection procedure was selected to obtain approximately 80% power for 2:1 randomization with an alternative hypothesis corresponding to an 8-point improvement in 24 month KOOS, and assuming a 15% treatment failure rate in each study arm (thus the 8 point difference is prior to baseline imputation for treatment failures). The standard deviation in each study arm was assumed to be 23.

Details of the operating characteristics of the model, including simulations justifying the type I error rate of 2.5%, can be found in the Adaptive Design Report in Appendix 1.

9 Statistical Analyses

9.1 Analysis Populations

9.1.1 Full Analysis Set Population

The full analysis set (FAS) will consist of all treated subjects in the Agili-C™ arm and all treated subjects in the SSOC arm, for whom there is a valid overall KOOS score at baseline and at least one valid overall KOOS score post-baseline. A treated subject is defined as any subject who was randomized to any of the groups, and is not defined as a subject with major entry violation (as defined below).

In the FAS population, subjects who are treatment failures (as defined in Section 5.0) will have their 24-month KOOS score imputed as their baseline KOOS score. Thus, the treatment failure imputation will provide at least one valid overall KOOS score post-baseline and these subjects will be included in the primary analysis FAS population.

For all analyses performed on the FAS population, subjects will be analyzed according to the treatment arm to which they were randomized (regardless of the treatment actually received).

Consistent with ICH-E9, subjects with major entry violations will be excluded from FAS. Major entry violation is defined by having the potential to affect trial results and the decision of whether an entry violation is considered major will be performed by the Medical Director according to the following parameter - enrolment of subject with severe exclusion criteria, such as:

1. Bony defect depth deeper than 8mm
2. Uncontained lesion - lack of vital bone wall, at least 2mm thick, completely surrounding the lesion
3. Inability to position the implant 2mm recessed relative to the articular surface
4. Articular cartilage lesions in the tibia or the patella, ICRS grades IVa or above
5. Systemic cartilage and/or bone disorder

9.1.2 Safety Population

The safety population will consist of all patients for whom treatment with either Agili-C™ or SSOC was performed, including patients with major entry violations.

9.1.3 Per Protocol (PP) Population

The PP analysis set is the subset of FAS including subjects with no major protocol violations and with valid observations on the primary endpoint (average overall KOOS) at 12 months, at least.

9.2 General Considerations

For continuous endpoints, the descriptive statistics include: number of non-missing observations, mean, median, standard deviation, minimum and maximum. For categorical endpoints, the count and percentage will be given.

9.3 Primary Analysis

The primary analysis will be conducted on the FAS population. Complete analysis details may be found in the Adaptive Design Report in Appendix 1.

In addition to the primary Bayesian analysis, the data will be listed and summarized with descriptive statistics by arm.

The primary analysis will be repeated on the PP population.

9.3.1 Sensitivity Analyses

As noted in the appendix, a multiple imputation procedure will be used to address missing data in the primary analysis.

Several sensitivity analyses will also be provided.

- Tipping point. For each value X from the worst observed control subject to the best observed control subject, and for each value Y from the worst observed Agili-C subject to the best Agili-C subject, the primary analysis will be calculated imputing all missing Control subjects as X and all Agili-C subjects as Y, producing a grid over all plausible values for the control and Agili-C subjects. This grid includes a worst case scenario, where all control subjects are imputed with the best observed control value and all Agili-C patients imputed as the worst observed Agili-C patient. The grid also includes a best case scenario, imputing controls as the worst control patient and Agili-C patients as the best observed Agili-C patients. The tipping point curve can be observed looking in the grid for the required values of (X,Y) that result in primary analysis success.

9.4 Confirmatory Secondary Analyses

This trial has 4 confirmatory secondary endpoints that, for the final analysis, will be tested on the FAS population hierarchically in the order presented below to preserve overall Type I Error = 0.05.

The following three pairs of confirmatory hypotheses, relating to continuous endpoints, will be tested similarly to the primary endpoint final analysis as described in the preceding section:

Confirmatory I

H_0: Change in KOOS Pain (Agili-C^{TM}) at 24M $\leq$ Change in KOOS Pain (SSOC) at 24M

H_1: Change in KOOS Pain (Agili-C^{TM}) at 24M $>$ Change in KOOS Pain (SSOC) at 24M

Confirmatory II

H_0: Change in KOOS QOL (Agili-C^{TM}) at 24M $\leq$ Change in KOOS QOL (SSOC) at 24M

H_1: Change in KOOS QOL (Agili-C^{TM}) at 24M $>$ Change in KOOS QOL (SSOC) at 24M

Confirmatory III

H_0: Change in KOOS ADL (Agili-C^{TM}) at 24M $\leq$ Change in KOOS ADL (SSOC) at 24M

H_1: Change in KOOS ADL (Agili-C^{TM}) at 24M $>$ Change in KOOS ADL (SSOC) at 24M

Confirmatory IV

H_0: Response Rate (Agili-C^{TM}) at 24M $\leq$ Response Rate (SSOC) at 24M

H_1: Response Rate (Agili-C^{TM}) at 24M $>$ Response Rate (SSOC) at 24M

For Confirmatory Endpoints I-III, testing will be performed by calculating the posterior probabilities of superiority in a manner similar to the primary endpoint. (See Adaptive Design Report in the Appendix for Details). A confirmatory secondary endpoint will be considered a success if the posterior probability exceeds 0.975. Like the primary endpoint final analysis, treatment failures will have their outcome replaced with their baseline value. And for this final analysis, all subjects will have completed follow-up. However, subjects that drop out will be multiply imputed using the longitudinal model with weakly informative priors on all parameters (see Section 9).

For Confirmatory IV, the analysis will be similar, but adjusted for the dichotomous nature of the data. Let p_0 and p1 be the responder rates at 24 months for SSOC and Agili-C, respectively. We test the hypothesis

$H_0: p_1 = p_0$ vs. $H_A: p_1 > p_0$

We model the responder rate independently for each arm using non-informative priors, $p_j \sim$ Beta(0.5, 0.5) for arm j. Success corresponds to posterior probability $Pr(p_1 > p_0 \mid Data) > 0.975$. For this analysis, treatment failures will be imputed as non-responders. Subjects with missing data due to drop out will be handled using multiple imputation, as described in Section 9.

The analyses for the Confirmatory Secondary Endpoints will be repeated on the PP population.

9.5 Additional Secondary Analyses

All secondary analyses in this section will be performed on both the FAS and PP populations. Treatment failures will be imputed as baseline for continuous endpoints, and will be imputed as the worst outcome for categorical outcomes (e.g. non-responder).

Missing data due to dropouts will not be imputed for these secondary analyses.

9.5.1 Percentage of Articular Defect Fill according to MRI at 12 and 24 months

The number and percentage of subjects with Articular Defect Fill according to MRI will be summarized by arm and visit (12 and 24 months). The percentages between arms will be compared at each visit with a two-sided Chi Square test with significance alpha = 0.05.

9.5.2 Analysis of Secondary Endpoints over time

The following endpoints will be analyzed by 1) providing descriptive statistics by arm and visit, 2) graphically summarize the endpoint by treatment arm at each visit using box plots to visually inspect the time trend, and 3) performing a repeated measures analysis using a mixed effects model with terms for treatment, visit, and treatment-by-visit interaction. In the model we will use the values recorded at each visit, including the baseline visit.

The test for the treatment by visit interaction will be considered significant if the p-value is less than 0.05. No adjustments will be made for multiplicity, and results will be interpreted with caution due to the multiple tests.

The following secondary efficacy endpoints will be analyzed in this way:

- Change from baseline in average overall KOOS score (Pain, Symptoms, QOL, ADL & Sports) at 6, 12, and 18 Months
- Change from baseline in IKDC Subjective Knee Evaluation at 12, 18, and 24 Months
- Change from baseline in Tegner score at 12, 18, and 24 Months
- Change from baseline QOL as measured by SF-12 v2 at 6, 12, 18, and 24 Months

9.5.3 Subgroup Analyses on the Primary Endpoint

The primary endpoint (change from baseline to 24 months in the average overall KOOS score (Pain, Symptoms, QOL, ADL & Sports) will be analyzed in the following subgroups:

- Lesion type (chondral or osteochondral)
- Number of lesions (single or multiple)
- Level of osteoarthritis (K/L score 0-1 or 2-3)
- Lesion size (total lesion size $\leq 3cm^2$ or $>3cm^2$)
- Previous ligament reconstruction (with or without)
- Meniscus status (intact, previous partial meniscectomy, concomitant meniscectomy)
- Activity status (active or inactive)

For each of the categories above, summary statistics will be provided for the primary endpoint by arm and subgroup. Within each subgroup, the means of the two treatment arms will be compared using a Bayesian analysis similar to that for the Primary analysis; however, no imputation of dropouts will be performed.

9.6 Safety Analyses

Safety analyses will be conducted on the safety analysis set and will include all AEs, SAEs and USADEs.

The following summaries will be provided:

- An overall summary of the number and percentage of patients and AEs by SOC (System Organ Class) and PT (Preferred Term).
- An overall summary of the number and percentage of patients and events of SAEs by SOC and PT
- An overall summary of the number and percentage of patients and events of USAEDs by SOC and PT
- An overall summary of the number and percentage of patients and events of AEs by SOC, PT and Severity.
- An overall summary of the number and percentage of patients and events of AEs by SOC, PT and Outcome.

Anticipated AEs, listed in the eCRF, will be described by their pre-specified terms as collected in the eCRF. AEs which are not pre-specified in the eCRF will be coded and aggregated using MedDRA (Medical Dictionary for Regulatory Activities) version 18.2.

The AEs will be summarized with frequency and percentage of total subjects and number of events, and will be summarized and presented by treatment group.

For the summaries of AEs, subjects who experience the same AE more than once will only be counted once for that event in the number of subjects, but all occurrences of the same event will be counted in the number of events.

The AEs related to the implant, the tool-set and the procedure will be summarized with frequency and percentage of total subjects and number of events by these categories and by their pre-specified terms as collected in the eCRF, when applicable.

9.6.1 Treatment Failure Rate

The Treatment Failure Rate will be summarized with the number and percentage of subjects experienced Treatment Failures (section 5.0). The percentages between arms will be compared with a two-sided Chi Square test with significance alpha = 0.05

9.7 Covariate Analyses

Covariate analyses will be done on the PP population for the primary and secondary confirmatory endpoints by including each covariate of interest in an MMRM model, for both treatment groups, with one MMRM model per covariate listed below. Each covariate will appear in one MMRM. The covariates are

- Age
- Gender
- BMI
- Lesion type (chondral or osteochondral)
- Number of lesions (single or multiple)
- Level of osteoarthritis (K/L score 0-1 or 2-3)
- Lesion size (total lesion size $\leq 3cm^2$ or $>3cm^2$)
- Previous ligament reconstruction (with or without)
- Meniscus status (intact, previous partial meniscectomy, concomitant meniscectomy)
- Activity status (active or inactive)

Note that the effect of interest is the Treatment x Covariate interaction term in the MMRM model, which will be tested using a 0.15 significance level.
Additionally, descriptive statistics will be provided by covariate level for categorical covariates.

For categorical covariates, we will perform an additional analysis, similar to the primary analysis, within each category of the covariate. From this analysis, the credible interval for the treatment effect will be reported for each category and assessed overlap.

9.8 Demographic and Baseline Characteristics

Demographics and baseline characteristics will be summarized descriptively for the PP, FAS and Safety sets, by treatment group and overall.

- Demographics: age (continuous and categorized), gender (categorical), ethnicity (categorical) and race (categorical)
- Baseline Characteristics include the following:
    - Body Weight Index (BMI)
    - Lesion type (chondral or osteochondral)
    - Number of lesions (single or multiple)
    - Level of osteoarthritis (K/L score 0-1 or 2-3)
    - Lesion size (total lesion size $\leq 3cm^2$ or $>3cm^2$)
    - Previous ligament reconstruction (with or without)
    - Meniscus status (intact, previous partial meniscectomy, concomitant meniscectomy)
    - Activity status (active or inactive)

9.9 Subject Disposition

The patient disposition will be summarized as follows and presented for each treatment group, when applicable, and overall. The percentages will be calculated based on the number of randomized patients, unless otherwise specified.

- The number (%) of patients who started screening process but were not enrolled (failed screening before enrollment) - % calculated from the all enrolled subjects, including the distribution of the reasons for failing the screening
- The number of enrolled patients
- The number (%) of patients randomized to the study (% calculated from the all enrolled subjects)
- The number (%) of patients with treatment or procedure failure (% calculated from the randomized subjects)
- The number (%) of patients in the different analysis sets (Safety, FAS and PP sets, (% calculated from the randomized subjects)
- The number (%) of patients who completed the study (% calculated from the randomized subjects)
- The number (%) of patients who discontinued the study prematurely including the distribution of reasons for premature discontinuations (% calculated from the randomized subjects)
- The number (%) of patients by visit (% calculated from the randomized subjects)

9.10 Poolability Analyses

Heterogeneity across sites and patient subgroups will be assessed with one-way analysis of variance. All poolability analyses will be performed on the FAS population. Treatment failures will be imputed with their baseline score. Missing data due to dropout will be imputed as last observation carried forward (LOCF).

If homogeneity is rejected, then an additional sensitivity analysis will be conducted based on a Bayesian hierarchical model (similar to a random effects model) with site and/or subgroup modeled as random effects, as appropriate.

Regardless of the result of the poolability analyses, data will be summarized by site and by subgroup.

9.11 Poolabiltity of Sites

The interaction between site and treatment on the poolability of KOOS will be compared using an ANOVA model. The model is

Y = Site + Treatment + (Site x Treatment)

Small sites with n < 6 will be combined into a single "other" site category.

9.12 Poolability of Geographical Regions

The interaction between region (U.S. and OUS) and treatment on the poolability of KOOS will be compared using an ANOVA model.

9.13 Poolability of Subgroups

The poolability of the patient subgroups will be assessed using the method described above. The following subgroups will be assessed (separately, with one ANOVA for each):

- HA type (to the extent that multiple HA types are used in the study)
- Unilateral vs Bilateral symptomatic knees
- Follow-up visits within the pre-COVID-19 specified window (24 Months Post- Procedure Visit ± 8 weeks) and Follow-up within the expanded window*, outside the initially specified window (24 Months Post- Procedure Visit ± 8-16 weeks)
- On-site and off-site assessments of KOOS subscales**

* Following a pandemic coronavirus outbreak that occurred in Q1, 2020 the time window of follow-up visits were extended in the following manner:

a. Six (6) months post-procedure ±12 weeks (instead of ±4 weeks)
b. Twelve (12), Eighteen (18), Twenty-four (24) months post-procedure ±16 weeks (instead of ±8 weeks)
c. Annual post 24 months visits ±16 weeks, until last patient reaches 24 months, (instead of current ±8 weeks)

** * Following a pandemic coronavirus outbreak that occurred in Q1, 2020 Subject off-site completion of the following Self-reported Questionnaires:

a. KOOS subscales
b. Tegner score
c. SF-12 Health Survey (v2)

d. 2000 IKDC Subjective Knee Evaluation Form

10 Missing Data

10.1 Within a KOOS Subscale Score:

Treatment of missing data within a KOOS scale measure:

1. KOOS Subscale Score:

   As per KOOS scale guideline, subscale scores will be computed based on observed items only if not more than 2 items are missing. Where more than two items are missing, the KOOS subscale score will be scored missing.

2. Overall KOOS Score:

   Overall KOOS Score will be defined as the average over the KOOS subscales, if not more than two subscales are missing. Where more than two KOOS subscales are missing, the Overall KOOS score will be scored missing.

10.2 Primary Analysis

At the primary (final) analysis, all subjects will have completed full follow-up time. Treatment failures will have their outcome replaced with their baseline value. If some subjects drop out and missing data is present after performing the steps mentioned above (if necessary), any remaining missing data will be handled through multiple imputation, however only weakly informative priors will be used for this final analysis, as follows:

$\alpha_t \sim N(0, 1)$ for t = 6, 12, 18 months

$\lambda_t^2 \sim IG(0.5, 312)$ for t = 6, 12, 18 months

$\tau^2 \sim IG(0.5, 312)$

See the adaptive design report in appendix 1 for full details of the model, as well as the informative prior distributions to be used at the interims.

10.3 Confirmatory Secondary Analyses

Missing data for the confirmatory secondary endpoints at the final analysis will be handled in a manner similar to the primary analysis. Treatment failures will have their outcome replaced with their baseline value. If necessary, we will next perform the steps for missing information with the KOOS subscale and overall KOOS score as described above. If missing data is still present due to subject drop out, the missing data will be handled through multiple imputation, using only weakly informative priors as in described above.

For Secondary Confirmatory Endpoint IV, the analysis method will differ slightly due to the dichotomous nature of the data. Treatment failures and dropouts will be imputed as described above for the continuous change from baseline endpoint. After imputation, the outcomes will be dichotomized for the purpose of testing the responder rate hypothesis.

10.4 Other Analyses

Additional secondary and safety data will not be subject to any imputation and will be summarized on an observed case basis.

10.5 Missing Data as a Result of the Coronavirus Outbreak

As described in 'FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Pandemic Guidance for Industry, Investigators, and Institutional Review Boards', March 2020, 'FDA recognizes that the COVID-19 pandemic may impact the conduct of clinical trials of medical products… FDA recognizes that protocol modifications may be required, and that there may be unavoidable protocol deviations due to COVID-19 illness and/or COVID-19 control measures'.

As of March 15, 2020, several sites have notified CartiHeal that on-site subjects follow-up visits are suspended, and that the ability to perform follow-up imaging (x-ray and MRI) is limited.

In order to ensure adequate oversight and minimize loss to follow-up of subjects, the following changes were applied:

1. Expansion of the follow-up visit windows to:
a. Six (6) months post-procedure ±12 weeks (instead of the ±4 weeks)
b. Twelve (12), Eighteen (18), Twenty-four (24) months post-procedure ±16 weeks (instead of ±8 weeks)
c. Annual post 24 months visits ± 16 weeks, until last patient reaches 24 months, (instead of ±8 weeks)

Subject off-site completion of Self-reported Questionnaires:
a. KOOS subscales
b. Tegner score
c. SF-12 Health Survey (v2)
d. 2000 IKDC Subjective Knee Evaluation Form
3. Virtual visits (telephone)/web to record medications, AEs and SAEs

4. Updates to the monitoring plan to allow for remote rather than in-person monitoring during the pandemic-related restrictions.

In case of missing data, despite the proactive measures that describe above, the rules that were described in 10.1-10.4 will be applied.