NCT Number: NCT03190369

STATISTICAL ANALYSIS PLAN

A 26-week, Multicenter, Double-blind, Randomized, Placebo-controlled Parallel Group Study to Evaluate the Efficacy and Safety of a Single Dose of 6 mL of hylan G-F 20 (Synvisc-One®) in Chinese Patients With Symptomatic Osteoarthritis of the Knee

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

AE:	adverse event
AESI:	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA:	analysis of covariance
AST	aspartate aminotransferase
AT:	all-treated
ATC	anatomic Therapeutic Chemical
COGA:	clinical observer global assessment
eCRF:	electronic case report form
EQ-5D:	euroQol five dimensions
GEE:	generalized estimating equation
GGT	gamma-glutamyl transpeptidase
HRQOL	Health-Related Quality of Life
IA:	intra-articular
IMP:	investigational medicinal product
IVRS:	interactive voice response system
LOCF:	last observation carry forward
MAR	missing at random
MedDRA	medical Dictionary for Regulatory Activities
mITT:	modified intent-to-treat
NRS:	numerical rating scale
OA:	osteoarthritis
OC:	observed case
PBS:	phosphate buffered saline
PCSA:	potentially clinically significant abnormality
PQ:	patient questionnaire
PT:	preferred term
PTGA:	patient global assessment
SAE:	serious adverse event
SAIR:	severe acute inflammatory reaction
SAP:	statistical analysis plan
SD:	standard deviation
SOC:	system-organ-class
TEAE:	treatment emergent adverse event
WOMAC:	western Ontario and McMaster Universities Osteoarthritis Index

1 OVERVIEW AND INVESTIGATIONAL PLAN

1.1 STUDY DESIGN AND RANDOMIZATION

This is a 26-week, multicenter, double-blind, randomized, placebo-controlled parallel group study to evaluate the efficacy and safety of a single dose of 6 mL of hylan G-F 20 (Synvisc-One) injected IA into the knee in Chinese patients with symptomatic OA of the knee.

A screening and wash-out period may last for up to 14 days, depending on the half-life of the medications (please refer to Appendix C of the protocol), followed by an 8-day baseline period including the treatment day (Day 1). Overall, up to 21 days are allowed between signing informed consent (at screening visit) and the randomization (Day 1).The study observation period starts at randomization and lasts until the end of the study. IMP or placebo will be injected IA into knee of the randomized patients on Day 1. Randomized patients who had either IMP or placebo will be invited for 7 post treatment observation visits, up to Week 26 (see Section 1.2).

The randomization ratio of hylan G-F 20: placebo is 1:1.

Approximately 422 patients (211 patients per treatment group) will be recruited and randomized.

1.2 OBJECTIVES

1.2.1 Primary objectives

The primary objective of this study is to evaluate the efficacy of a single 6-mL IA injection of Hylan G-F 20 measured by Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) Numerical Rating Scale (NRS) 3.1 A1 score (1), over 26 weeks, in Chinese patients with symptomatic osteoarthritis (OA) of the knee.

1.2.2 Secondary objectives

The secondary objectives of this study are:

- To evaluate the efficacy of a single 6-mL IA injection of Hylan G-F 20 measured by 7-day average score of WOMAC A1 pain subscore in comparison to an IA placebo injection over 26 weeks.

- To evaluate the efficacy of a single 6-mL IA injection of Hylan G-F 20 measured by WOMAC A, patient global assessment (PTGA) and clinical observer global assessment (COGA) in comparison to an IA placebo injection over 26 weeks.

- To evaluate the response rate of a single 6-mL IA injection of Hylan G-F 20 in comparison to an IA placebo injection over 26 weeks. Response is defined as WOMAC A1 ≥2-point improvement from baseline on NRS.

- To evaluate the safety of a single 6-mL IA injection of Hylan G-F 20 in comparison to an IA placebo injection over 26 weeks.

1.2.3 Tertiary efficacy and other objectives

The tertiary and other objectives of this study are:

- To evaluate changes from baseline at Week 4, 8, 12, 16, 20, and 26 measured by WOMAC A1, WOMAC A, B, C and total, as well as PTGA, COGA and 7-day average score of WOMAC A1 pain subscore, in comparison with IA placebo injection.

- To evaluate the amount and days of permitted pain rescue medication use at Week 4, 8, 12, 16, 20, and 26 recorded by patient diary.

- To explore changes in patient quality of life from baseline after a single 6-mL IA injection of Hylan G-F 20 treatment at Week 4, 8, 12, 16, 20 and 26 by using EuroQol five dimensions (EQ-5D) questionnaire.

1.3 DETERMINATION OF SAMPLE SIZE

The sample size calculations are based on the primary efficacy variable of WOMAC A1 over 26 weeks, with the following assumptions:

- A common SD of [redacted] on the NRS scale
- [redacted] (on the NRS scale) mean difference in treatment effect of Hylan G-F 20 on the change from baseline in WOMAC A1 over 26 weeks, compared to placebo
- A t-test at a 2-sided 5% significance level with 90% power

The estimated treatment effect and SD are based on the observed treatment effect and SD for the WOMAC A1 over 26 weeks in US pivotal study (SOUND study) for a subgroup by excluding patients with symptomatic OA of another lower limb joint. Based on the above assumptions, 211 patients per treatment group, thus 422 patients in total will be randomized for this study.

As the ANCOVA model will be used for primary analysis, the power should be somewhat higher due to reduced estimate variability versus the t-test.

Calculations were made using nQuery Advisor 6.01.

1.4 STUDY PLAN

The study consists a Screening period (Day -21 to -8, including necessary medication washout period), 8-day baseline (including the treatment day (Day 1)) evaluations and a 26-week follow-up period.

A screening and wash-out period may last for up to 14 days, depending on the half-life of the medications (please refer to Appendix C), followed by an 8-day baseline period including the treatment day (Day 1). Overall, up to 21 days are allowed between signing informed consent (at screening visit) and the randomization (Day 1). In case eligibility criteria are not met, the patient may be re-screened and will follow the same procedure as described in the flow chart from screening visit to Day 1. A new patient number will be allocated. The study observation period starts at randomization and lasts until the end of the study. IMP or placebo will be injected IA into knee of the randomized patients on Day 1.

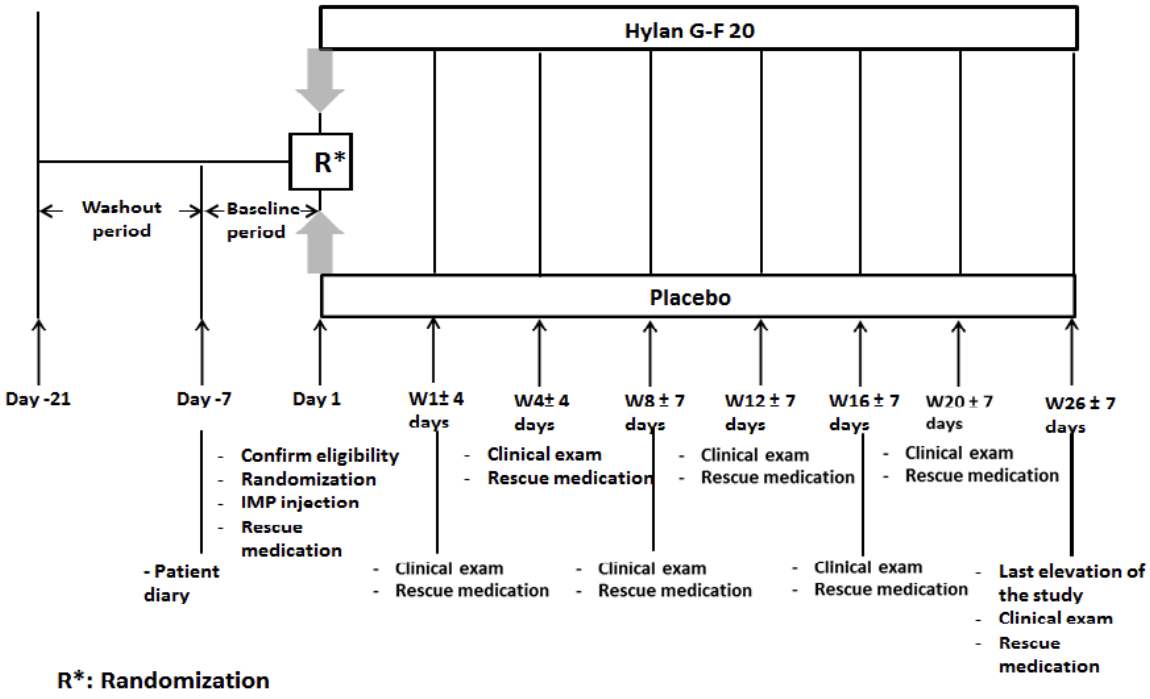
Approximately 422 patients are to be randomized in this study, in a 1:1 ratio, to receive either Hylan G-F20 or control (phosphate buffered saline) on Study Day 1 of the 26-week study period. Injection procedure details are given in protocol section 8. The patient and evaluator are blinded to investigative study treatment.

All patients are to have 7 site visits (Week 1, 4, 8, 12, 16, 20, 26, see Appendix A) during the on treatment period. Assessments of OA symptoms (WOMAC, PTGA), COGA and assessments of safety are performed at baseline visit and at specified time points over the 26-week study period.

Acetaminophen for target knee OA pain (rescue medication) for causes other than target knee pain (eg, flu, headache, non-target joint pain) are permitted during the study (see protocol Section 8.8.3), but must not be taken within 48 hours prior to a study visit (ie, within 2 days of a site visit), so as to not interfere with any patient-rated assessments. If acetaminophen is taken within the 48 hours period above, then the study visit must be rescheduled within the time window specified in Appendix A in the SAP.

The end of the study is defined as the last patient last visit planned per protocol, including the follow-up visit.

A schematic of the study design (protocol Figure 1) is copied here:



1.5 MODIFICATIONS TO THE STATISTICAL SECTION OF THE PROTOCOL

The protocol history table below gives the timing, rationale, and key details of major changes to the protocol statistical section.

Table 1 - Protocol amendment statistical changes

Amendment Number	Date Approved	Rationale	Description of statistical changes
1.0(electronic 3.0)	17-Feb-2017	Pain study has lower probability of success in general. Analyses of newly added endpoints will better interpret the study outcomes.	Adding a secondary endpoint, difference between treatment groups in change from baseline over 26 weeks in 7-day average WOMAC A1; Adding tertiary efficacy endpoints, including the differences between treatment groups in: • changes from baseline at Week 4, 8, 12, 16, 20, and 26 in 7-day average WOMAC A1 • changes from baseline at Week 4, 8, 12, 16, 20, and 26 measured by WOMAC A1, WOMAC A, B, C and total, as well as PTGA and COGA • the amount and days of permitted pain rescue medication use at Week 4, 8, 12, 16, 20, and 26. and Quality of life variables include: • changes of quality of life from baseline at Week 4, 8, 12, 16, 20, and 26 in EQ-5D scores.

1.6 STATISTICAL MODIFICATIONS MADE IN THE STATISTICAL ANALYSIS PLAN

Not applicable.

2 STATISTICAL AND ANALYTICAL PROCEDURES

2.1 ANALYSIS ENDPOINTS

2.1.1 Demographic and baseline characteristics

The baseline value is generally defined as the last available value before randomization.

All baseline safety and efficacy parameters are presented along with the on-treatment summary statistics in the safety and efficacy sections (Section 2.4.5 and Section 2.4.4).

Demographic characteristics

Demographic variables are gender (Male, Female), age in years (quantitative and qualitative variable: ≤60 and >60 years), race (American Indian or Alaska Native, Asian, Black, Native Hawaiian or Other Pacific Islander, White, Unknown), baseline BMI.

Medical or surgical history

Medical (or surgical) history includes information on the eCRF relating to any prior or existing medical conditions/surgical procedures involving the following categories: Infectious Diseases, Allergic, Metabolic/Endocrine/Nutritional, Haematopoietic, Musculoskeletal, Dermatological, Head, Ears, Eyes, Nose, and Throat (HEENT), Breasts, Respiratory, Cardiovascular, Gastrointestinal/Hepatic, Genitourinary/Renal, Neurological, and Psychiatric/Psychosocial.

The patient will be asked to provide a relevant medical history with specific dates. Those conditions and/or procedures reported will be compared to the inclusion and exclusion criteria for the study. Specific attention is paid to the patient's previous history with respect to exclusionary conditions, procedures, and surgeries.

This information will be coded using the version of Medical Dictionary for Regulatory Activities (MedDRA) currently in effect at Sanofi at the time of database lock.

Disease characteristics at baseline

Specific disease history includes target knee (Right, Left), X-ray used as a diagnostic tool (yes, no), the Modified Kellgren-Lawrence Numerical Grading System (2) grade for the target knee (grade 0, grade I, grade II, grade III and grade IV).

Vital signs

Vital signs at baseline are temperature, heart rate, and systolic and diastolic blood pressure.

Any technical details related to computation, dates, and imputation for missing dates are described in Section 2.5.

2.1.2 Prior or concomitant medications

All medications will be coded using the World Health Organization-Drug Dictionary (WHO-DD) using the version currently in effect at Sanofi at the time of database lock.

- Prior medications are those the patient used 26 weeks prior to first investigational medicinal product (IMP) injection. Prior medications can be discontinued before first administration or can be ongoing during treatment phase.
- Concomitant medications are any treatments received by the patient concomitantly to the IMP, from randomization to the end of treatment. A given medication can be classified both as a prior medication and as a concomitant medication.

Acetaminophen (rescue medication) are permitted for causes other than target knee OA pain (eg, flu, headache, non- target joint pain) during the study, but must not be taken within 48 hours prior to a study visit, so as to not interfere with any patient-rated assessments. Information on acetaminophen will be captured in the eCRF and should include the date, medication strength, dose (eg, number of tablets per day), dosage form, and whether or not it was taken for target knee OA pain. On an as-needed basis in a tiered manner, the following therapies will be allowed as **rescue medication**: 1) Acetaminophen (500 mg), 2) Acetaminophen (325 mg)/oxycodone (5 mg), or 3) Acetaminophen (325 mg)/tramadol (37.5 mg).

Any technical details related to computation, dates, imputation for missing dates are described in Section 2.5.

2.1.3 Efficacy endpoints

The baseline value for efficacy endpoints is defined as the last available value prior to the IMP administration or last available value on or before the date of randomization if not treated, unless otherwise specified.

WOMAC scores

The WOMAC NRS 3.1 questionnaire is a self-administered, health status measure used to probe symptoms of pain (WOMAC A), stiffness (WOMAC B), and function (WOMAC C) in patients with OA of the knee (1, 3). The questionnaire consists of 24 questions relating to the patient's assessment of his/her target joint pain (5 questions), stiffness (2 questions), and physical function (17 questions). An 11-point NRS ranging from 0 (None) to 10 (Extreme) will be used to capture the patient's response to each of the questions. All responses will be recorded directly on the paper patient questionnaire (PQ), and the PQ will serve as source documentation. The patient was asked to check the box that indicated his/her amount of target joint pain, amount of stiffness, and degree of difficulty completing tasks within the past 48 hours.

The WOMAC A consists of 5 questions assessing pain symptoms while walking, using stairs, at night while in bed, sitting or lying, and standing.

The WOMAC A1 is a single question within the WOMAC A that specifically assesses target knee pain while walking on a flat surface.

The WOMAC B consists of 2 questions assessing severity of stiffness that occurs after a period of inactivity later that same day.

The WOMAC C consists of 17 questions assessing physical function while performing the following activities: stair rise, rise from sitting, standing, bending, walking, getting in/out of a car, putting on/taking off socks, rising from bed, lying in bed, getting in/out of bath, sitting, getting on/off toilet, heavy household duties, and light household duties.

The WOMAC total score is computed as the sum of the available components of the 3 subscores: WOMAC A, WOMAC B and WOMAC C. The raw total WOMAC score ranges from 0 to 240, since the sums for the components of the 3 subscores range from 0 to 50 for the WOMAC A, 0 to 20 for the WOMAC B, and 0 to 170 for the WOMAC C. The total WOMAC score will be set to missing if any of the WOMAC subscores are set to missing as defined above. The raw total WOMAC score will be standardized to the 0 to 10 scale by dividing by 24.

Patient Global Self-Assessment (PTGA)

The patient's global self-assessment of target knee OA condition is the response on an 11-point NRS (0 = best possible to 10 = worst possible) to the question "Considering all the ways that the arthritis of your target knee affects you, select one response below for how you are doing at the present time." The patient's response will be recorded directly on the PQ, and the PQ will serve as the source documentation.

Clinical Observer Global Assessment (COGA)

The physician performs a global assessment of the patient's target knee OA using the 11-point NRS pain intensity rating scale (0 = best possible to 10 = worst possible) in response to the question "Considering all the ways that the arthritis of the patient's target knee affects him/her, select one response below for how you feel the patient is doing at the present time." The same physician will complete this assessment for all patients at a site and record in the eCRF and this will serve as the source documentation.

2.1.3.1 Primary efficacy endpoint(s)

The primary efficacy endpoint is change from baseline in WOMAC A1 over 26 weeks for hylan G-F 20 compared to placebo.

2.1.3.2 Secondary efficacy endpoint(s)

Secondary efficacy endpoints include the differences between treatment groups in:

- Change from baseline over 26 weeks in 7-day average walking pain score (measured by daily WOMAC A1, 7-day average WOMAC A1), WOMAC A, B, C and total, as well as PTGA, and COGA
- Percentages of positive responders over 26 weeks, where response is defined as a ≥2-point improvement from baseline in the WOMAC A1 NRS

2.1.4 Safety endpoints

The safety analysis will be based on the reported adverse events and other safety information, including vital signs.

Observation period

The observation period will be divided into 2 periods:

- The pre-treatment period is defined as the time between when the patients give informed consent and the injection of IMP.
- The on-treatment period is defined as the time from the injection of the IMP up to Week 26 follow up visit.

The treatment-emergent adverse event period will only include the on-treatment period.

2.1.4.1 Adverse events variables

Adverse event observation period

- Pretreatment adverse events are adverse events that developed or worsened or became serious during the pretreatment period
- Treatment-emergent adverse events are adverse events that developed or worsened or became serious during the treatment-emergent adverse event period

All adverse events (including serious adverse events) will be coded to a lower-level term (LLT), preferred term (PT), high-level term (HLT), high-level group term (HLGT), and associated primary system organ class (SOC) using the version of Medical Dictionary for Regulatory Activities (MedDRA) currently in effect at Sanofi at the time of database lock.

Adverse event of special interest (AESI)

- Anaphylaxis
- Foreign Body Reaction
- Pseudosepsis
- Severe acute inflammatory reaction (SAIR)
- Joint infection
- Injection site allergy
- Drug allergy
- Pregnancy

2.1.4.2 Deaths

The deaths observation period are per the observation periods defined above.

- Death on-study: deaths occurring during the treatment-emergent adverse event period

2.1.4.3 Laboratory safety variables

Not applicable.

2.1.4.4 Vital signs variables

Vital signs include: temperature, heart rate, and systolic and diastolic blood pressure.

2.1.5 Tertiary efficacy endpoints and other endpoint

2.1.5.1 Tertiary efficacy endpoints

Tertiary efficacy endpoints include the differences between treatment groups in:

- Changes from baseline at Week 4, 8, 12, 16, 20, and 26 in 7-day average WOMAC A1
- Changes from baseline at Week 4, 8, 12, 16, 20, and 26 measured by WOMAC A1, WOMAC A, B, C and total, as well as PTGA and COGA
- The amount and days of permitted pain rescue medication use at Week 4, 8, 12, 16, 20, and 26.

2.1.5.2 Quality of life variables

Changes of quality of life from baseline at Week 4, 8, 12, 16, 20, and 26 in EQ-5D scores.

Patients' health status will be assessed using the EQ-5D-5L questionnaire which includes 5 levels of severity in each of the five dimensions: no problems, slight problems, moderate problems, severe problems, and extreme problems (4, 5).

2.2 DISPOSITION OF PATIENTS

This section describes patient disposition for both patient study status and the patient analysis populations.

Screened patients are defined as any patients who met the inclusion criteria and signed the informed consent.

Randomized patients consist of all patients with a signed informed consent form who have had a treatment kit number allocated and recorded in the IVRS/IWRS database, and regardless of whether the treatment kit was used or not.

For patient study status, the total number of patients in each of the following categories will be presented in the clinical study report using a flowchart diagram or summary table:

- Screened patients
- Screen failure patients and reasons for screen failure
- nonrandomized but treated patients
- Randomized patients
- Randomized but not treated patients and reason for not being treated
- Randomized and treated patients
- Patients who complete the 26-week on treatment period as per protocol
- Patients who discontinued study participation by main reason for study discontinuation
- Status at last study contact

For all categories of patients (except for the screened and nonrandomized categories) percentages will be calculated using the number of randomized patients as the denominator divided by the number of exposed patients. Reasons for study discontinuation will be supplied in tables giving numbers and percentages by treatment group.

A patient is considered lost to follow-up at the end of the study if he/she is not assessed at the last protocol planned visit and if the time from the last successful contact to the last protocol planned visit is greater than 7 days.

All critical or major deviations potentially impacting efficacy analyses, randomization, and drug-dispensing irregularities, and other major or critical deviations will be summarized in tables giving numbers and percentages of deviations by treatment group.

Additionally, the analysis populations for safety and efficacy will be summarized in a table by number of patients on the randomized population.

- Efficacy population: modified intent-to-treat (mITT) population
- Safety population: all-treated population

2.2.1 Randomization and drug dispensing irregularities

Randomization and drug-dispensing irregularities occur whenever:

1. A randomization is not in accordance with the protocol-defined randomization method, such as a) an ineligible patient is randomized, b) a patient is randomized twice.

   OR

2. A patient is dispensed an IMP kit not allocated by the protocol-defined randomization, such as a) a patient is dispensed a different treatment kit than as randomized (which may or may not contain the correct-as-randomized IMP), or b) a nonrandomized patient is treated with IMP reserved for randomized patients.

Randomization and drug-dispensing irregularities will be monitored throughout the study and reviewed on an ongoing basis.

All randomization and drug-dispensing irregularities will be documented in the clinical study report. If the number of irregularities is large enough to make a tabular summary useful, the irregularities will be categorized and summarized among randomized patients (number and percentages). Nonrandomized, treated patients will be described separately.

2.3 ANALYSIS POPULATIONS

Patients treated without being randomized will not be considered randomized and will not be included in any efficacy population.

The randomized population includes any patient who has been allocated to a randomized treatment regardless of whether the treatment kit was used.

For any patient randomized more than once, only the data associated with the first randomization will be used in any analysis population. The safety experience associated with any later randomization will be assessed separately.

The safety experience of patients treated and not randomized will be reported separately, and these patients will not be in the safety population.

2.3.1 Efficacy populations

2.3.1.1 Modified intent-to-treat population

The modified intent-to-treat population: mITT population contains all randomized and treated patients, as randomized. Patients will be analyzed in the treatment group to which they are randomized.

The mITT population is the primary analysis population and will be used for the analyses of all efficacy variables.

2.3.2 Safety population

The safety population is defined as:

- Randomized population who actually received at least 1 injection or part of an injection of Hylan G-F 20 or placebo. It is used for safety analysis, where observations will be summarized based on the treatment actually received

In addition:

- Nonrandomized but treated patients will not be part of the safety population; however, their safety data will be presented separately
- Randomized patients for whom it is unclear whether they took the IMP will be included in the safety population as randomized
- For patients receiving randomized more than once, the safety experience associated with any later randomization will be assessed separately.

2.3.3 Other analysis population

None.

2.4 STATISTICAL METHODS

Continuous data will be summarized using the number of available data, mean, standard deviation (SD), median, minimum, and maximum for each treatment group. Categorical and ordinal data will be summarized using the number and percentage of patients in each treatment group. Missing data will not be categorized in the summaries.

2.4.1 Demographics and baseline characteristics

Parameters will be summarized on the randomized population analyzed in the treatment group to which they were randomized. Analyses for the safety population will be included in the appendices if the size of the safety population is different (>10%) from the size of that in the primary analysis population for any treatment group.

Parameters described in Section 2.1.1 will be summarized by treatment group and overall treatment groups using descriptive statistics.

Medical or surgical history as recorded on the eCRF will be summarized by SOC and PT.

P-values on demographic and baseline characteristic data will not be calculated.

2.4.2 Prior or concomitant medications

The prior and concomitant medications will be presented on the safety population.

Medications will be summarized by treatment group according to the WHO-DD dictionary, considering the first digit of the anatomic category (ATC) class (anatomic category) and the first 3 digits of the ATC class (therapeutic category). All ATC codes corresponding to a medication will be summarized, and patients will be counted once in each ATC category (anatomic or therapeutic) linked to the medication. Therefore patients may be counted several time for the same medication.

The table for prior medications will be sorted by decreasing frequency of ATC followed by all other therapeutic classes based on the overall incidence across treatment groups. In case of equal frequency regarding ATCs (anatomic or therapeutic categories), alphabetical order will be used.

The tables for concomitant medications will be sorted by decreasing frequency of ATC followed by all other therapeutic classes based on the incidence in the treatment group. In case of equal frequency regarding ATCs (anatomic or therapeutic categories), alphabetical order will be used.

2.4.3 Extent of investigational medicinal product exposure and compliance

The extent of IMP exposure will be assessed and summarized by actual treatment within the safety population (Section 2.3.2).

2.4.3.1 Extent of investigational medicinal product exposure

The extent of IMP exposure will be assessed by actual dose information.

Dose information will be summarized descriptively (number, mean, SD, median, minimum and maximum) for the volume administered of the IMP by treatment group.

Fluid or effusion withdrawn will also be summarized in a similar manner as dose information.

2.4.3.2 Compliance

No compliance analysis will be done for this study.

2.4.4 Analyses of efficacy endpoints

2.4.4.1 Analysis of primary efficacy endpoint(s)

The statistical test for the primary efficacy endpoint, the mean change from baseline measure of pain relief (WOMAC A1) between Hylan G-F 20 and placebo over 26 weeks, will be 2-sided at α level of 0.05.

For the primary efficacy endpoint, the following null hypothesis and alternative will be tested:

H0: Hylan G-F 20 is not superior to placebo

H1: Hylan G-F 20 is superior to placebo

The primary effectiveness analysis will be performed on the mITT population and will be based on repeated-measures Analysis of Covariance (ANCOVA) that will be used to test for differences in treatment efficacy, as quantified by the change from baseline in WOMAC A1 over 26 weeks between Hylan G-F 20 and placebo. The repeated measures ANCOVA model is equivalent to mixed model for repeated measures (MMRM) and will include terms for treatment, site, visit and visit-by-treatment interaction, as well as the baseline WOMAC A1 score as a covariate.

The difference between Hylan G-F 20 group and placebo group and its corresponding 95% confidence interval will be estimated within the framework of ANCOVA. An unstructured variance-covariance structure will be used to model the within-patient errors. If this model fails to converge, the following structures will be tested in this order: Toeplitz (equal variances and a separate correlation for each level of separation between the time points), AR (1) (first-order autoregressive, equal variances and exponentially decreasing correlations), CS (compound symmetry, equal variances and equal pairwise correlations across fixed time points). The first (co)variance structure yielding convergence will be used as the primary analysis.

The Kenward-Roger approximation will be used to estimate denominator degrees of freedom. Outcomes between patients are assumed to be independent. The primary comparison will be the contrast between Hylan G-F20 and control over 26 weeks. An example of the SAS code is provided below (note time is modeled with the visit variable):

SAS Display 1 Code for Continuous Endpoints

```
proc mixed data = data method = ml;
class patid randgrp site visit;
model y_chg = site baseline randgrp visit visit*randgrp / ddfm=kr;
repeated visit / type = un subject = patid;
lsmeans randgrp randgrp*visit / cl diff at baseline= baseline;
run;

where:
randgrp = Hylan G-F20, control
site    = site number
visit   = numerical visit weeks (4,8,12,16,20,26)
baseline= patient's baseline WOMAC A1 score
y_chg   = change from baseline WOMAC A1 value (WOMAC A1 value at post-baseline
          visit assessment minus the baseline value)

TYPE =
 UN  = unstructured covariance
 CS  = compound symmetry covariance
AR(1)= first-order autoregressive covariance
TOEP = Toeplitz covariance
```

Subgroup analysis

Descriptive analyses will be performed on the primary efficacy endpoint to summarize the treatment effects across subgroups for the following baseline characteristics as needed and will be considered as exploratory.

- Age groups (≤60, >60 years)
- BMI category (<=25, >25)
- Baseline WOMAC A1 score (5, 6-7, 8)

Sensitivity analysis

Sensitivity analyses will be performed using multiple imputation (MI) methods based on pattern mixture models (6) as appropriate.

First, a repeated measures Normal model will be fitted to the data using a Bayesian approach, with non-informative priors for the mean and variance-covariance matrix to provide a joint posterior for the parameters in the model. The repeated measures Normal model will include separate mean profiles for each treatment group and the same covariates as those in the primary analysis. Independent samples will then be drawn from the posterior distributions for the mean and variance-covariance matrix to provide inputs into an imputation model.

For each subject with missing data, these sampled values of the parameters for mean vectors and the variance-covariance matrices specify a joint distribution for their observed and unobserved outcome data. The post-withdrawal part of each pattern-specific distribution will be modelled using the approaches discussed below.

Based on this imputation model, a single set of data will be sampled for the missing data based on the distribution for the subject's missing data conditional upon their observed data.

Each imputed data set will then be analyzed using the same repeated measures analysis of ANCOVA and resulting treatment differences over 26 weeks and their standard errors will then be combined to produce valid statistical inference based on t-tests using the SAS PROC MIANALYZE. Least-squares mean change from baseline over 26 weeks for each treatment group will be calculated and displayed with their associated standard errors. Estimated treatment differences along with corresponding 95% confidence intervals and p-values will also be presented. These analyses will also be performed at each scheduled post-base visit.

The post-withdrawal part of each pattern-specific distribution will be modelled using the following approaches:

- Missing at Random (MAR) Approach: The means and variance-covariances following withdrawal are chosen to reflect the subject's own treatment group. This approach will provide similar results to using a mixed effects model where the unstructured covariance matrix is estimated separately for each treatment group.
- Copy Reference (CR) Approach: The whole distribution of Hylan G-F20 group even prior to withdrawal is assumed to be the same as the control group. This mimics the case where those withdrawing are in effect non-responders. If a patient on Hylan G-F20 is above the control group mean then this positive residual will feed through into subsequent observations, to a degree determined by the correlation in the control group. The patient's profile will slowly decay back towards the mean for the control group at later visits. For the control group, this is equivalent to the MAR approach above.

It is important to note that the CR approach is conservative and constructed to attenuate the treatment difference estimated from the primary analysis.

2.4.4.2 Analyses of secondary efficacy endpoints

As with the primary effectiveness analysis, the secondary effectiveness analyses will be performed on the mITT population as well.

For the analysis of the change from baseline in 7-day average WOMAC A1, WOMAC A, PTGA, and COGA, repeated-measures ANCOVA will be used as described in the description of the primary effectiveness analysis.

For the analysis of WOMAC A1 responders (≥2 point improvement on NRS Scale) generalized estimating equations (GEE) modeling will be used. Each responder (yes/no) endpoint evaluated at multiple post-baseline visits will be analyzed using GEE for binary outcomes. A GEE model will be fitted to the responder data and will include terms for baseline measure, site, visit, treatment group and a visit-by-treatment group interaction. Hypothesis testing will be performed using least squares means based on the linear predictor of the model.

For the analysis of the percentages of positive responders, patients who discontinued the study prior to the Week 26 assessment due to either target knee-related AEs or due to lack of efficacy were classified as non-responders in the efficacy analysis. Patients who discontinued the study for other reasons had their responder status imputed using the LOCF method. The LOCF was used for all responder analyses, but not for the analysis of other parameters. No replacement on any missing or invalid data was made for the safety analyses.

No sensitivity analyses are planned for secondary efficacy endpoints in this study.

2.4.4.3 Multiplicity issues

The overall Type I Error will be set at 5%. The primary effectiveness endpoint will be tested at the 5% significance level.

The analyses of secondary effectiveness variables will be interpreted according to the Hochberg Step-Up (7) Procedure with the overall alpha set at the 0.05 level. The procedure will be implemented as follows:

The observed p-values will be sorted in descending order p1 >…>pm.

Term	Interpretation	Value
i	The current positioning the evaluation order	
m	The total number of comparisons	5
q	The overall level of type I error rate for the family of tests	0.05
pi	An individual observed p-value in the ith position	
qi	Significance level of the ith comparison	

For each evaluation *i* the largest p-value remaining in the set to be evaluated pi is compared to the significance level for that comparison (q/i). If pi is less than the significance level, it and all other p-values remaining in the set are declared statistically significant and the evaluation process stops. If this condition is not met, then the current pi is declared, “not statistically significant” and the remaining set of observed p-values is evaluated at the next value of “*i*”. If the last p-value (pm)

fails at the level of q/m, then all comparisons are declared to be not statistically significant. With 5 secondary endpoints, the evaluation will be conducted according to the following table:

i	qi less than	interpretation
1	0.0500	All five tests declared significant
2	0.0250	P2, p3, p4 and p5 declared significant
3	0.0167	P3, p4 and p5 declared significant
4	0.0125	P4 and p5 declared significant
5	0.0100	P5 declared significant

2.4.4.4 Analyses of tertiary efficacy endpoints and other endpoints

The analyses of tertiary efficacy endpoints and other endpoints will be presented with unadjusted p-values and considered exploratory. As with the primary effectiveness analysis, the tertiary effectiveness analyses and analyses of other endpoints will be performed on the mITT population as well.

For the analyses of the change from baseline in WOMAC A1, 7-day average WOMAC A1, WOMAC A, PTGA and COGA at Week 4, 8, 12, 16, 20, and the change from baseline in WOMAC B, C and total and quality of life at Week 4, 8, 12, 16, 20, 26, the same repeated-measures ANCOVA model as described in the primary analysis will be used. The changes from baseline to each visit for each parameter will be calculated. Means and adjust means of each treatment group will be provided, as well as adjusted mean and associated two-sided 95% CI of the difference between treatment groups.

For the change from baseline in the amount and days of permitted pain rescue medication at each post-baseline visit, the Wilcoxon Mann Whitney test will be performed.

2.4.5 Analyses of safety data

The summary of safety results will be presented by treatment groups.

General common rules

All safety analyses will be performed on the safety population as defined in Section 2.3.2, unless otherwise specified, using the following common rules:

- Safety data in patients who do not belong to the safety population (eg, exposed but not randomized) will be listed separately
- The baseline value is defined generally as the last available value before randomization.
- The potentially clinically significant abnormality (PCSA) values are defined as abnormal values considered medically important by the Sponsor according to predefined criteria/thresholds based on literature review and defined by the Sponsor for clinical laboratory tests and vital signs.
- PCSA criteria will determine which patients had at least 1 PCSA during the treatment-emergent adverse event period, taking into account all evaluations performed during the

treatment-emergent adverse event period, including nonscheduled or repeated evaluations. The number of all such patients will be the numerator for the on-treatment PCSA percentage

- The treatment-emergent PCSA denominator by group for a given parameter will be based on the number of patients assessed for that given parameter in the treatment-emergent adverse event period by treatment group on the safety population.
- For quantitative safety parameters based on reading measurements, descriptive statistics will be used to summarize results and change from baseline values by visit and treatment group.
- The analysis of the safety variables will be essentially descriptive and no systematic testing is planned. Relative risks versus placebo and their 95% confidence intervals may be provided, if relevant
- selected safety analyses will be summarized by age, gender subgroups, and any pertinent subgroups as appropriate

2.4.5.1 Analyses of adverse events

Generalities

The primary focus of adverse event reporting will be on treatment-emergent adverse events. Pre-treatment adverse events will be described separately.

If an adverse event date/time of onset (occurrence, worsening, or becoming serious) is incomplete, an imputation algorithm will be used to classify the adverse event as pretreatment or treatment-emergent. The algorithm for imputing date/time of onset will be conservative and will classify an adverse event as treatment emergent unless there is definitive information to determine it is pre-treatment. Details on classification of adverse events with missing or partial onset dates are provided in Section 2.5.3.

Adverse event incidence tables will present by SOC and PT, sorted in alphabetical order for each treatment group, the number (n) and percentage (%) of patients experiencing an adverse event. Multiple occurrences of the same event in the same patient will be counted only once in the tables within a treatment phase. The denominator for computation of percentages is the safety population within each treatment group.

Sorting within tables ensures the same presentation for the set of all adverse events within the observation period (pretreatment and treatment-emergent). For that purpose, the table of all treatment-emergent adverse events presented by SOC and PT sorted by the internationally agreed SOC order and decreasing frequency of PTs within SOCs will define the presentation order for all other tables unless otherwise specified. Sorting will be based on results for the experimental treatment arm.

Analysis of all treatment-emergent adverse events

The following treatment-emergent adverse event summaries will be generated for the safety population.

- Overview of treatment-emergent adverse events, summarizing number (%) of patients with any
  - Treatment-emergent adverse event
  - Adverse event of special interest
  - Serious treatment-emergent adverse event
  - Treatment-emergent adverse event leading to death
  - Treatment-emergent adverse event leading to permanent study discontinuation
- All treatment-emergent adverse events by primary SOC and PT, showing the number (%) of patients with at least 1 treatment-emergent adverse event, sorted by the internationally agreed SOC order and by decreasing incidence of PTs within each SOC. This sorting order will be applied to all other tables, unless otherwise specified
- All treatment-emergent adverse events regardless of relationship and related by primary SOC, and PT, showing the number (%) of patients with at least 1 treatment-emergent adverse event, sorted by the internationally agreed SOC order. The PT level will be presented in alphabetical order
- All treatment-emergent adverse events by maximal severity, presented by primary SOC and PT, showing the number (%) of patients with at least 1 treatment-emergent adverse event by severity (ie, mild, moderate, or severe), sorted by the sorting order defined above

Analysis of all treatment emergent serious adverse event(s)

- All treatment-emergent serious adverse events by primary SOC, and PT, showing the number (%) of patients with at least 1 serious treatment-emergent adverse event, sorted by the internationally agreed SOC order. The PT level will be presented in alphabetical order
- All treatment-emergent serious adverse events regardless of relationship and related to IMP, by primary SOC, and PT, showing the number (%) of patients with at least 1 treatment-emergent serious adverse event, sorted by the internationally agreed SOC order. The PT levels will be presented in alphabetical order

Analysis of all treatment-emergent adverse event(s) leading to study discontinuation

- All treatment-emergent adverse events leading to study discontinuation, by primary SOC and PT, showing the number (%) of patients sorted by the internationally agreed SOC order. The PT level will be presented in alphabetical order
- PTs within each SMQ

Analysis of adverse event of special interest

- All adverse event of special interest by primary SOC and PT, showing the number (%) of patients sorted by the internationally agreed SOC order and decreasing incidence of PTs within each SOC

Analysis of pretreatment adverse events

- All pretreatment adverse events by primary SOC and PT, showing the number (%) of patients sorted by the internationally agreed SOC order and decreasing incidence of PTs within each SOC

2.4.5.2 Deaths

Any adverse events leading to death will be presented as a listing, indicating the study period (pretreatment or treatment-emergency period).

2.4.5.3 Analyses of laboratory variables

Not applicable.

2.4.5.4 Analyses of vital sign variables

The summary statistics (including number, mean, median, standard deviation, minimum and maximum) of all vital signs variables (central laboratory values and changes from baseline) will be calculated for each visit or study assessment (baseline, each post-baseline time point) by treatment group.

2.4.6 Analyses of quality of life

The analyses of quality of has been described in Section 2.4.4.4.

2.5 DATA HANDLING CONVENTIONS

2.5.1 General conventions

The following formulas will be used for computation of parameters.

Demographic formulas

Age in years = integer part of ((date of informed consent - date of birth)/365.25)

Vital signs formulas

BMI = weight in kilograms divided by height in meters squared

Prior or concomitant medications and therapeutic procedures derivation

Prior medications are those the patient used 26 weeks prior to first investigational medicinal product (IMP) injection. Prior medications can be discontinued before first administration or can be ongoing during treatment phase.

Concomitant medications are any treatments received by the patient concomitantly to the IMP, from randomization to the end of treatment.

A given medication can be classified both as a prior medication and as a concomitant medication.

2.5.2 Data handling conventions for secondary efficacy variables

For 7-day average WOMAC A1, the baseline value is defined as the average of the WOMAC A1 scores recorded 7 days prior to the first IMP administration (WOMAC A1 score recorded on Day 1 included). The 7-day average WOMAC A1 will be set as missing if 3 or more of the 7 WOMAC A1 scores were missing.

The analyses for change from baseline over 26 weeks for 7-day average WOMAC A1, WOMAC A, PTGA, and COGA are similar to the analyses for the primary effectiveness endpoint (SAP Section 2.4.4.1).

2.5.3 Missing data

For the analysis of the percentages of positive responders, patients who discontinue the study prior to the Week 26 assessment due to either target knee-related AEs or due to lack of effectiveness will be classified as non-responders (no=0) in the effectiveness analysis. Patients who discontinue the study for other reasons will have the responder status imputed using the LOCF method as follows: If a patient is a responder (yes=1) or a non-responder (no=0) at a given visit, but at the next visit the patient does not have the data necessary to determine responder/non-responder status, then at the second visit the individual values from a previous visit will not be carried forward but the responder/non-responder determination of the previous visit will be carried forward. Small amounts of intermediate missing data will also be handled by this LOCF method.

For categorical variables, patients with missing data are not included in calculations of percentages unless otherwise specified. When relevant, the number of patients with missing data is presented.

Handling of medication missing/partial dates

No imputation of medication start/end dates or times will be performed. If a medication date or time is missing or partially missing and it cannot be determined whether it was taken prior or concomitantly, it will be considered a prior, concomitant.

Handling of adverse events with missing or partial date/time of onset

Missing or partial adverse event onset dates and times will be imputed so that if the partial adverse event onset date/time information does not indicate that the adverse event started prior to treatment or after the treatment-emergent adverse event period, the adverse event will be classified as treatment-emergent.

TEAEs are events with start dates on or after the date of injection. If the onset date of the AE is partially or completely missing and the stop date of the AE does not indicate that it occurred prior to the injection, then the determination of treatment-emergent status will be based on the following:

- If the adverse event start year is after the year of the injection date, then the AE is treatment emergent; else,
- If the adverse event start year is the same as the year of the injection date and
  - the start month is missing, then the AE is treatment emergent; else if
  - the start month is present and is the same or after the month of the injection, then the AE is treatment-emergent; else,
- If the start date is completely missing, then the AE is treatment-emergent.

No imputation of adverse event end dates/times will be performed. These data imputations are for categorization purpose only and will not be used in listings.

Handling of adverse events when date and time of investigational medicinal product administration is missing

When the date and time of the injection is missing, all adverse events that occurred on or after the day of randomization should be considered as treatment-emergent adverse events.

Handling of missing assessment of relationship of adverse events to investigational medicinal product

If the assessment of the relationship to IMP is missing, then the relationship to IMP has to be assumed and the adverse event considered as such in the frequency tables of possibly related adverse events, but no imputation should be done at the data level.

Handling of missing severity of adverse events

If the severity is missing for 1 of the treatment-emergent occurrences of an adverse event, the maximal severity on the remaining occurrences will be considered. If the severity is missing for all the occurrences, a “missing” category will be added in the summary table.

Handling of potentially clinically significant abnormalities

Not applicable.

2.5.4 Windows for time points

The time window for a given visit is defined in the protocol Schedule of Events, included in SAP Appendix A.

The statistical analysis visit windows (see SAP Section 2.5.5 for unscheduled visits) are defined below:

Visit number	Scheduled visit	Scheduled Visit Window, in Study days	Analysis Visit Window, in Study days
1	Screening	Study Day -21 to -8	-21 to -8
2	Baseline	Study Day -7 to 1	-7 to 1
3	Randomization	Study Day 1	1
4	Week 1	Study Day 7 ± 4 days	2 to 17
5	Week 4	Study Day 28 ± 4 days	18 to 42
6	Week 8	Study Day 56 ± 7 days	43 to 72
7	Week 12	Study Day 84 ± 7 days	73 to 96
8	Week 16	Study Day 112 ± 7 days	97 to 126
9	Week 20	Study Day 140 ± 7 days	127 to 161
10	Week 26	Study Day 182 ± 7 days	162 to 196

If multiple valid values of a variable exist within an analysis window, the nearest one from the targeted study day will be selected. If the difference is a tie, the value after the targeted study day will be used. If multiple valid values of a variable exist within the same day, the first value of the day will be selected when time is available, or the scheduled visit will be selected.

2.5.5 Unscheduled visits

Unscheduled visit measurements of laboratory data, vital signs will not be included in the by-visit summaries, but will be used for computation of baseline.

Unscheduled and early withdrawal visit assessments for effectiveness measures will be assigned to the nearest scheduled visit using the windowing scheme defined in SAP Section 2.5.4.

If only one record is within an analysis visit window, the data from that record will be used in the summary statistics and by visit analyses. If more than one record is within the same analysis visit window, the following rules will be applied:

- If one record from regularly scheduled visit and one or more records from unscheduled visits fall in the same analysis visit window, then the record from the regularly scheduled visit will be used.

- If one record from regularly scheduled visit and an early withdrawal visit fall in the same analysis visit window, then the record from the early withdrawal visit will be used in the current analysis visit and the regularly scheduled visit will not be used.

- If no regularly scheduled visit and more than one record from unscheduled visits fall in the same analysis visit window, if there is an early withdrawal visit then the early withdrawal visit will be used; otherwise the unscheduled visit closest to the middle of the interval will be used.

2.5.6 Pooling of centers for statistical analyses

Not applicable.

2.5.7 Statistical technical issues

Not applicable.

3 INTERIM ANALYSIS

No interim analysis is planned for this study.

4 DATABASE LOCK

The database is planned to be locked at 4 weeks after last patient last visit.

5 SOFTWARE DOCUMENTATION

All summaries and statistical analyses will be generated using SAS version 9.4 or higher.

6 REFERENCES

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2. Kellgren JH, Lawrence JS. Radiological assessment of osteoarthritis. Ann Rheum Dis. 1957;16(4):494-502.

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4. Herdman M, Gudex C, Lloyd A, Janssen MF, Kind P, Parkin D, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Qual Life Res. 2011;20(10):1727-36.

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7. Hochberg Y. A sharper Bonferroni procedure for multiple tests of significance. Biometrika.1988;75(4):800-2.

7 LIST OF APPENDICES

Appendix A: Schedule of Study Events

Appendix B: Summary of statistical analyses

Appendix C: Potentially clinically significant abnormalities criteria

Appendix A Schedule of Study Events

	Screening and Washout	Baseline (Treatment on Day 1)		Follow-up						
VISIT	1		2	3	4	5	6	7	8	9
DAY	Day -21 to Day -8[a]	Day -7 to Day -1	Day 1	Week 1 (±4 days)	Week 4 (±4 days)	Week 8 (±7 days)	Week 12 (±7 days)	Week 16 (±7 days)	Week 20 (±7 days)	Week 26[b] (±7 days)
Informed Consent[c]	X									
Inclusion Criteria & Exclusion criteria	X		X							
Randomization			X							
Patient demography & Baseline Characteristics	X									
Height & Weight	X									
Vital Signs	X		X							X
Medical History	X									
Physical examination[d]	X									X
Liver function test and biochemistry[e]	X									
Urinary Pregnancy Test[f]			X							X
Radiograph	X[g]									
WOMAC (NRS)	X		X		X	X	X	X	X	X
PTGA			X		X	X	X	X	X	X
COGA[h]			X		X	X	X	X	X	X
EQ-5D			X		X	X	X	X	X	X
Prohibited Medication Washout[i]	X									
Administration of IMP			X							
Withhold Intake of Permitted Pain Medications for 48 Hours			X	X	X	X	X	X	X	X
Paper diary dispensation& training	X									
Paper diary collection (reviewed at each on-site visit)		X	X	X	X	X	X	X	X	X
Rescue Medication Monitoring			X	X	X	X	X	X	X	X
AE/SAE recording	←----------									----------→
Concomitant Medications/Therapies	X		X	X	X	X	X	X	X	X

a. Screening visit may occur up to 21 days prior to Day 1, to allow for medication washout.
b. Any patients withdrawing prematurely must complete all Week 26 assessments at their last study visit.
c. Written informed consent will be obtained prior to any study-specific procedures, including washout of any prohibited medications.
d. Including inguinal region of the target knee (adenopathy).
e. Total bilirubin (and, in case of values above the normal range, differentiation in conjugated and nonconjugated bilirubin), aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), gamma-glutamyl transpeptidase (GGT). Biochemistry tests include fasting glycemia, serum electrolytes and serum creatinine.
f. Females of childbearing potential only. A woman is considered of reproductive potential (WOCBP), i.e., fertile,

following menarche and until becoming postmenopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy.

g. An X-ray is only required at screening visit if the patient has not had a valid X-ray within3 months prior to screening visit

h. The evaluator's COGA assessment must be performed following the patient's completion of questionnaires.

i. Assessment of prohibited medication must occur prior to administration of study drug. WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index; NRS: Numerical Rating Scale; PTGA: Patient global assessment; COGA: Clinical observer global assessment; EQ-5D: EuroQol five dimensions; IMP: investigational medicinal product; AE: adverse event; SAE: serious adverse event

Appendix B Summary of statistical analyses

EFFICACY ANALYSIS

Endpoint	***Analysis population***	***Primary analysis***	***Supportive analysis***	***Subgroup analysis***	***Other analyses***
Primary endpoint					
the mean change from baseline in WOMAC A1 between Hylan G-F 20 and placebo over 26 weeks	*mITT*	*repeated-measures Analysis of Covariance (ANCOVA)*	*multiple imputation (MI) methods based on pattern mixture models*	*Yes Subgroups: age, BMI category, baseline WOMAC A1 score, etc.*	*No*
Secondary endpoints					
the change from baseline in 7-day average WOMAC A1, WOMAC A, PTGA, and COGA	*mITT*	*repeated-measures Analysis of Covariance (ANCOVA)*	*No*	*Yes*	*No*
WOMAC A1 responders		*generalized estimating equations (GEE) modeling*	*No*	*No*	*No*
tertiary endpoints					
the change from baseline in WOMAC A1, 7-day average WOMAC A1, WOMAC A, B, C and total, PTGA, COGA and quality of life	*mITT*	*repeated-measures Analysis of Covariance (ANCOVA)*	*No*	*No*	*No*
the change from baseline in the amount and days of permitted pain rescue medication		*Wilcoxon Mann Whitney test*	*No*	*No*	*No*

Endpoint	Analysis population	Primary analysis	Supportive analysis	Subgroup analysis	Other analyses

m ITT =modified intent-to-treat;

SAFETY ANALYSES

Endpoint	Analysis population	Primary analysis	Supportive analysis	Subgroup analysis	Other analyses
Adverse events	*Safety*	*Follow safety guidelines*	*No*	*No*	*No*

Appendix C Potentially clinically significant abnormalities criteria

For phase 2/3 studies (oncology excepted)

(from BTD-009536-version 3.0-21-MAY-2014)

Vital signs		
HR	≤50 bpm and decrease from baseline ≥20 bpm ≥120 bpm and increase from baseline≥20 bpm	To be applied for all positions (including missing) except STANDING.
SBP	≤95 mmHg and decrease from baseline ≥20mmHg ≥160 mmHg and increase from baseline ≥20 mmHg	To be applied for all positions (including missing) except STANDING.
DBP	≤45 mmHg and decrease from baseline ≥10 mmHg ≥110 mmHg and increase from baseline ≥10 mmHg	To be applied for all positions (including missing) except STANDING.

EFC12723 16.1.9 Statistical analysis plan

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm)
[redacted]	Clinical Approval	30-Jan-2019 22:27 GMT+0100
[redacted]	Clinical Approval	31-Jan-2019 04:18 GMT+0100