NCT Number: NCT03190369

AMENDED CLINICAL TRIAL PROTOCOL NO. 01

Local for China

COMPOUND: Synvisc-One®/hylan G-F 20/GZ402662

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

STUDY NUMBER: EFC12723

STUDY NAME: C-SOUND

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CLINICAL TRIAL SUMMARY

COMPOUND: Hylan G-F 20 (Synvisc-One®)	**STUDY No: EFC12723** **STUDY NAME: C-SOUND**
TITLE	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
INVESTIGATOR/TRIAL LOCATION	China
PHASE OF DEVELOPMENT	3
STUDY OBJECTIVE(S)	**Primary objective:** To evaluate the efficacy of a single 6-mL intra-articular (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, over 26 weeks, in Chinese patients with symptomatic osteoarthritis (OA) of the knee. **Secondary objective(s):** 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 injectionof 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. **Tertiary efficacy objectives and other objective(s):** • 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.
STUDY DESIGN	This is a multicenter, double-blind, randomized, placebo-controlled, parallel group study. Eligible patients will be randomized in a 1:1 ratio to receive a 6-mL IA injection of Hylan G-F 20 (Group 1), or a 6 mL IA placebo injection of phosphate-buffered saline (PBS) (Group 2) on Day 1. Follow-up period will be 26 weeks.

STUDY POPULATION **Main selection criteria**	**Inclusion criteria** Chinese patient with OA of the target knee joint I 01. Between 40 to 80 (included) years of age at randomization I 02. Symptomatic OA of the target knee joint with WOMAC A1 NRS score of ≥4.0 and ≤8.0 as recorded in baseline period I 03. Confirmed by standard X-rays performed within 3 months prior to screening visit: modified Kellgren-Lawrence Numerical Grading System of Grade I-III (1) in the target knee joint I 04. Defined according to the American College of Rheumatology (ACR) Criteria (2) I 05. With failure to respond adequately to conservative non-pharmacologic therapy and/or simple analgesics, such as acetaminophen I 06. Patient is willing and able to provide signed informed consent prior to any study related procedures being performed **Exclusion criteria** E 01. Patient with painDETECT Questionnaire score >18 at screening visit E 02. Patient with moderately severe or severe depression as indicated by Patient Health Questionnaire-9 (PHQ-9) total score of ≥15 or a score of >0 on item # 9 at screening visit E 03. Patient with severe anxiety as indicated by Generalized Anxiety Disorder 7-item (GAD-7) score of ≥15 at screening visit E 04. Patient does not record a minimum of 5 days' worth of diary data within the 7 days before the treatment day (Day 1) E 05. Patient with severe insomnia as indicated by Insomnia Severity Index (ISI) Questionnaire score >22 at screening visit E 06. Patient is not ambulatory (assistive device allowed if used 4 weeks or more prior to screening visit) E 07. The score of contralateral knee pain (if present) >3.0 NRS at screening visit. E 08. Ipsilateral hip OA E 09. Patient with alanine aminotransferase (ALT)/ aspartate aminotransferase (AST) ≥3 x the upper limit of normal (ULN) and/or bilirubin ≥1.5 x ULN E 10. Female of childbearing potential who is unwilling to use effective contraceptive method throughout the duration of the study E 11. Female who is pregnant or lactating E 12. Patient with active knee joint infections or skin diseases or infections in the area of the injection site of the target knee joint E 13. Patient with systemic corticosteroids within 12 weeks prior to screening visit E 14. Patient with injection of IA corticosteroids in the target knee joint within 26 weeks prior to screening visit E 15. Patient has visco- supplementation injection in any joint, including the target knee joint, within 26 weeks prior to screening visit E 16. Patient with concomitant inflammatory disease or other condition that affects the joints (eg, rheumatoid arthritis, metabolic bone disease, psoriatic arthritis, gouty arthritis, symptomatic chondrocalcinosis, osteonecrosis or active infection) E 17. Patient with secondary OA of the target knee joint due to acute

		disease or trauma within 5 years prior to screening visit
	E 18.	Patient with significant valgus/varus deformities, ligamentous laxity, or meniscal instability
	E 19.	Patient with any major surgery, arthroplasty or arthroscopy in the target knee joint or another joint/joints in the lower extremity within 26 weeks prior to screening visit, or planned surgery in the lower extremities throughout the duration of the study
	E 20.	Patient with septic arthritis in any joint within 12 weeks prior to screening visit
	E 21.	Patient with any significant chronic skin disorder that could interfere with evaluation of the injection site
	E 22.	Concurrent chronic pain conditions with pain score >3.0 NRS at screening, or peripheral or central neuropathy that may affect sensation of the target knee area, including but not limited to back pain, hip pain, disc herniation, sciatica, diabetic neuropathy, post-stroke pain or fibromyalgia
	E 23.	Patient with active malignancy or treatment for malignancy within 5 years prior to screening visit, except non-melanoma skin cancer
	E 24.	Patient with active asthma that may require periodic treatment with systemic steroids during the study period
	E 25.	Patient with a venous or lymphatic stasis in the leg
	E 26.	Patient with claudication or peripheral vascular disease
	E 27.	Patient with oral or parental anticoagulant therapy or with high doses of platelet anti-aggregant therapy; however, acetyl salicylic acid (ASA) at doses ≤325 mg/day is allowed
	E 28.	Patient is not willing to withhold intake of permitted pain medications for 48 hours prior to all study visits
	E 29.	Started the use of glucosamine, chondroitin sulfate, diacerhein, or avocado/soya extracts within 2 months prior to Screening
	E 30.	Patient used an investigational drug, device or biologic within 12 weeks prior to screening visit
	E 31.	Patient not able to read and understand the language and content of the study material, understand the requirements for follow-up visits, and not willing to provide information at the scheduled evaluations
	E 32.	Patient with other factors assessed by the Investigator that may limit the ability of the patient to perform necessary study evaluations eg, active alcohol abuse, active drug abuse, planned relocation, significant psychiatric or neurological disorder (eg, Parkinsonism, Alzheimers, or other similar chronic and progressive neurological diseases…)
	E 33.	Investigator, sub-investigator, pharmacist, study coordinator, other study staff or relatives to the staff who is directly involved in the conduct of the protocol
	E 34.	Patient with any significant medical condition, including clinically significant coagulopathy, that the Investigator feels would interfere with study safety and efficacy evaluations and study participation
	E 35.	Patient with a known history of hypersentivity to lidocaine, acetaminophen, oxycodone or tramadol
	E 36.	Patient with a known history of hypersensitivity to avian protein or any components of hyaluronan-based injection devices

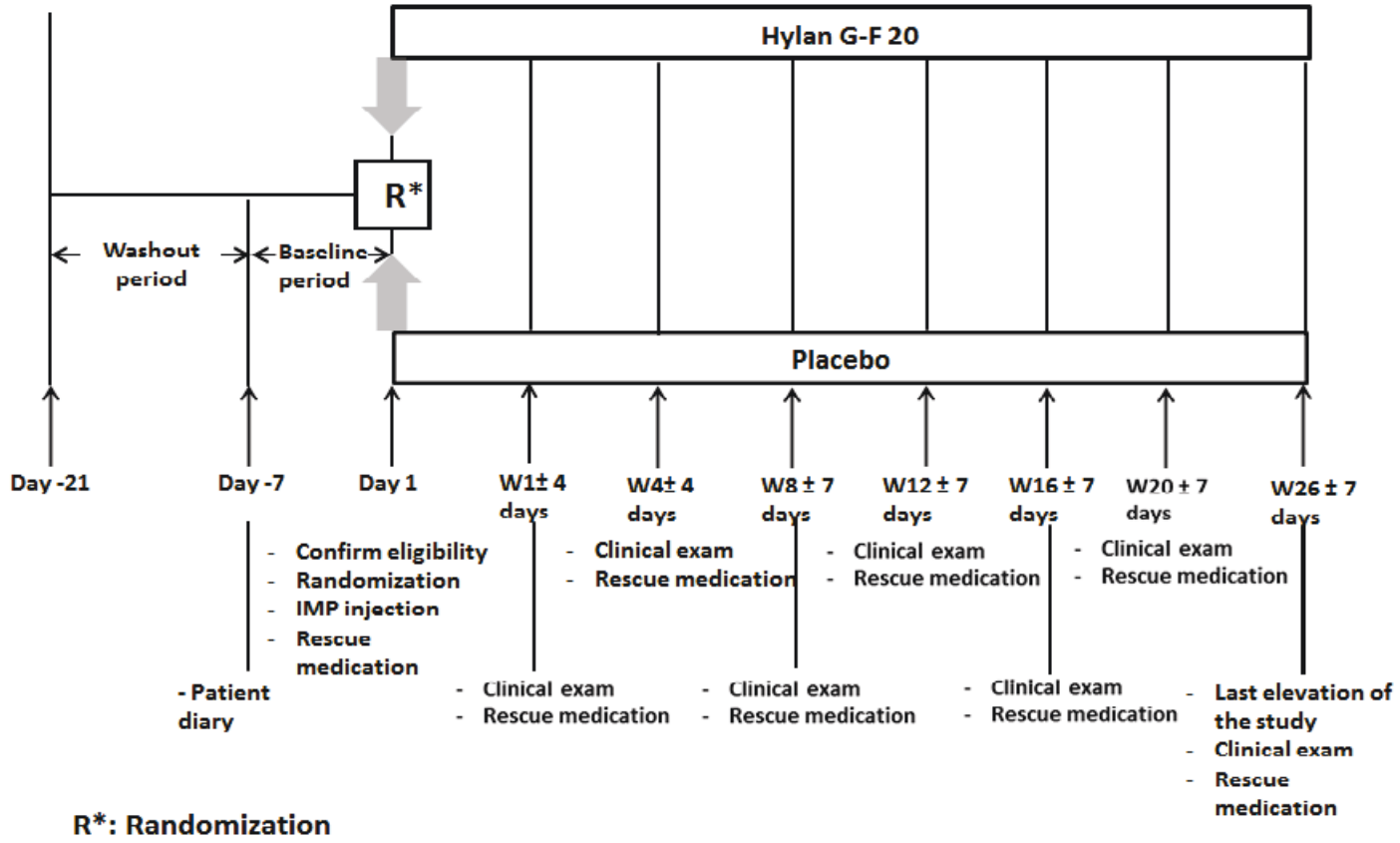
Total expected number of patients	Approximately 422 patients (211 patients per group) will be randomized. Patients who had been randomized and prematurely withdraw from the study will not be replaced.
STUDY TREATMENT(s)	
Investigational medicinal product(s) **Formulation**	Hylan G-F 20 or matching placebo Pre-filled syringe
Route(s) of administration	IA injection
Dose regimen	Group 1: At Day 1, patients randomized to active treatment will receive a 6-mL IA injection of Hylan G-F 20, containing 48 mg of hylan polymer in buffered physiological sodium chloride solution (pH 7.2 ±0.3), in the target knee. Group 2: At Day 1, patients randomized to placebo treatment will receive a 6-mL IA injection of PBS in the target knee. Study medication will be provided in blinded patient kits, and injection will be administered by a qualified injector other than the blinded evaluator. Before injection, qualified injector must examine, disinfect and anaesthetize (if required) the injection site, followed by arthrocentesis.
Noninvestigational medicinal product(s) (if applicable) **Formulation**	Rescue medication: Acetaminophen (first line), Acetaminophen/tramadol, or acetaminophen/oxycodone Tablet
Route(s) of administration	Oral
Dose regimen	Throughout the study, patients may receive acetaminophen at doses up to 3000 mg/day as a rescue medication for exacerbations of OA symptoms in the target knee. The Investigator should consider the use of rescue medication other than acetaminophen on a case-by-case basis, ie, in case of unbearable pain and based on the risk of acetaminophen overdose. Rescue medication will be considered on an as-needed: • Acetaminophen as first line (up to 3000 mg/day); • If ineffective, after stopping acetaminophen, acetaminophen 325 mg combined with tramadol hydrochloride 37.5 mg, up to 1 tablet 6 times daily. Or • If ineffective, after stopping acetaminophen, acetaminophen 325 mg combined with oxycodone 5 mg, up to 1 tablet 4 times daily. However, rescue medication must not be taken within 48 hours prior to any study visit.
ENDPOINT(S)	**Primary endpoint** • Change from baseline in WOMAC A1 over 26 weeks for hylan G-F 20 compared to placebo. **Secondary 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), WOMAC A, 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. Safety will be assessed by evaluation of the incidence of treatment emergent adverse events (TEAEs) and changes in standard safety parameters (eg, vital signs) from screening visit through the last follow up visit. **Tertiary efficacy endpoints and other endpoint(s):** 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 walking pain score (measured by daily 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. 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.
ASSESSMENT SCHEDULE	After providing informed consent, each patient will undergo screening visit assessments to determine study eligibility. Eligible patients will enter the wash-out period, during which time a patient will washout from prohibited pain and OA medications (ie, those with a half-life >5 hours, please refer to Appendix C). The wash-out period may last for up to 14 days, depending on the half-life of the medications. Following completion of the wash-out period, a patient will initiate baseline (Day-7 to Day-1) daily pain reporting using a patient diary. A patient's eligibility for participation in the study will be reevaluated at Day 1 to confirm that the patient continues to meet all study eligibility criteria. Study medication will be administrated at 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. Follow-up for efficacy and safety will be done at Week 1, 4, 8, 12, 16, 20, and 26.
STATISTICAL CONSIDERATIONS	Sample size determination: Four hundred and twenty two patients (211 patients per treatment group) will be randomized. The following assumptions were made to compute the sample size: *a* 90% power *b* α=0.05 *c* Standard deviation (SD) of [redacted] on the NRS scale *d* [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. The estimated treatment effect and SD are based on the observed treatment effect and SD for the change from baseline in 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. Analysis population: Efficacy population: modified intent-to-treat (mITT) population contains all randomized patients who have at least a baseline measurement of WOMAC A1, as randomized. Safety population: Treated population contains all randomized patients who receive any study treatment, as treated.

	Primary analysis: The primary efficacy 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 control. The ANCOVA model will include terms for treatment, site, visit and visit-by-treatment interaction, as well as the baseline WOMAC A1 as a covariate. Analysis of secondary endpoints: As with the primary efficacy analysis, the secondary efficacy analyses will be performed on the mITT population. For the analysis of the change from baseline in WOMAC A, PTGA, and COGA, similar repeated-measures ANCOVA will be used as described in the description of the primary efficacy analysis by including terms for treatment, site, visit and visit-by-treatment interaction, as well as the corresponding baseline as a covariate. For the analysis of WOMAC A1 responders ($\geq$2 point difference 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 efficacy analysis, the baseline is defined as the last available value prior to the first investigational medicinal product (IMP) administration after or on the randomization day. 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 adverse event (AE) 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 last observation carry forward (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. TEAE period for safety analysis is defined as the time from first dose of IMP on or after randomization to Week 26.
DURATION OF STUDY PERIOD (per patient)	Duration will be 29 weeks at maximum. The 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. Overall, there will be up to 21 days between signing informed consent (at screening visit) and the randomization (Day 1). Treatment will be administered on Day 1, and follow-up period will be 26 weeks.

1 FLOW CHARTS

1.1 GRAPHICAL STUDY DESIGN



1.2 STUDY FLOW CHART

	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

	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)**
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), ie, 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.

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3 LIST OF ABBREVIATIONS

ACR:	American College of Rheumatology
AE:	adverse event
AESI:	adverse event of special interest
ALT:	alanine aminotransferase
ANCOVA:	analysis of covariance
ASA:	acetyl salicylic acid
AST:	aspartate aminotransferase
AT:	all-treated
CME:	chief medical evaluators
COGA:	clinical observer global assessment
CSR:	clinical study report
CV:	curriculum vitae
DRF:	discrepancy resolution form
eCRF:	electronic case report form
EMEA:	European Medicines Agency
EQ-5D:	EuroQol five dimensions
FDA:	Food and Drug Administration
GAD-7:	generalized anxiety disorder 7-item
GCP:	good clinical practice
GEE:	generalized estimating equation
GPE:	Global Pharmacovigilance & Epidemiology
HLGT:	High level group term
HLT:	high level term
IA:	intra-articular
IB:	investigator's brochure
IMP:	investigational medicinal product
ISI:	insomnia severity index
IVRS:	interactive voice response system
LLT:	low level term
LOCF:	last observation carry forward
mITT:	modified intent-to-treat
NIMP:	non-investigational medicinal product
NRS:	numerical rating scale
OA:	osteoarthritis
OARSI:	Osteoarthritis Research Society International
OC:	observed case
OPD:	outpatient department
PBS:	phosphate buffered saline
PCSA:	potentially clinically significant abnormality
PHQ-9:	Patient Health Questionnaire-9
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
SFDA:	State Food and Drug Administration
SOC:	system-organ-class
SSRI:	selective serotonin re-uptake inhibitor
TCM:	traditional Chinese medicine
TEAE:	treatment emergent adverse event
ULN:	upper limit of normal
WOMAC:	Western Ontario and McMaster Universities Osteoarthritis Index

4 INTRODUCTION AND RATIONALE

Hylan G-F 20 is a high molecular weight, cross-linked derivative of hyaluronan (extract of chicken comb) viscosupplement that temporarily supplements the elastoviscosity of the synovial fluid in the joint. It is currently marketed in multiple countries under the trade names Synvisc® and/or Synvisc-One®. These 2 products are identical in composition, but differ in their approved injection regimen. Synvisc-One (hylan G-F 20) combines the three 2-mL (16 mg hylan polymer) IA injections of Synvisc into a single 6-mL (48 mg hylan polymer) IA injection. Details of the product please refer to Investigator's Brochure (IB). Synvisc was approved as a medical device by State Food and Drug Administration (SFDA) in 2001. It is indicated to control OA knee pain. Per SFDA Announcement Number 81 in 2009, hyaluronan products for arthritis treatment should be regulated as medicinal products instead of medical devices. Hence Synvisc is currently in the middle of transition process to be registered as a medicinal product.

This study will evaluate the benefits and risks of 6-mL hylan G-F 20 (Synvisc-One) in Chinese patients with symptomatic OA of the knee. Knee OA diagnosis criteria follow ACR Criteria (2). For which is in line with Chinese Orthopedic Association Criteria (3). Efficacy of 6-mL hylan G-F 20 will be measured by WOMAC NRS Version 3.1 A1 in comparison with matching placebo over 26 weeks.

WOMAC OA index was developed to simultaneous assess pain and function (4, 5). This is because pain and function are interdependent and may not even be separable in principle. WOMAC A1 is subscore of WOMAC, which measures walking pain. It is selected as the primary endpoint in this study as it encompasses motion (pain while walking on a flat surface) and a reasonable time period (the previous 48 hours) during which natural fluctuations in OA pain can be captured. More importantly, walking pain (WOMAC A1) is thought to be the most relevant pain subscore for the mild to moderate knee OA population of interest in this study whereas the other WOMAC A questions such as pain when going up/down stairs (WOMAC A2), at night while in bed (WOMAC A3), pain sitting or lying (WOMAC A4), or pain when standing upright (WOMAC A5) are thought to be more relevant to a more severe end-stage population (6, 7). As further support, Osteoarthritis Research Society International (OARSI) has recently stated in a report to the U.S. Food and Drug Administration (FDA) that WOMAC A1 has the strongest rationale for such local (intra-articular visco-supplement) treatments and for this target population (mild to moderate knee OA pain) (8).

As secondary objectives, efficacy will also be measured in comparison with matching placebo by WOMAC NRS A, PTGA and COGA over 26 weeks.

The dose and regimen employed in this study, as well as that of US/EU pivotal study (SYNV00704, SOUND study), is decided based on a pilot study (SYNV00502) (9, 10). SYNV00502 evaluated several combinations of higher single dose volumes (4 and 6 mL) and a reduced number of injections (1 or 2). In SYNV00502, all treatment regimens resulted in statistically significant improvement from baseline to Week 24 in all endpoints for all treatment regimens. In particular, the 1 x 6-mL treatment group was ranked either first or second in 5 of the 6 endpoints (Patient Pain, WOMAC A, WOMAC B, WOMAC C, Patient Global, and Physician

Global). In this treatment group, there was no serious safety concerns related to this dose regimen.

SOUND study is a double-blind, placebo-controlled study demonstrated that a single injection of 6 mL of hylan G-F 20 is safe and effective in providing symptomatic relief up to 26 weeks in patients with primary knee OA. There was a statistically significant estimated treatment difference (-0.15, p = 0.047) between the treatment group and control group for the primary efficacy endpoint of this study, the change from baseline over the course of the 26-week study using the patient's assessment of his/her pain (WOMAC LK 3.1 A). Overall, SOUND study confirms a favorable risk/benefit profile of a single injection of 6 mL of hylan G-F 20 in patients with symptomatic primary OA of the knee. Design of this study utilizes the same design of SOUND study to confirm efficacy and safety in Chinese population.

FDA recommends OA trial duration for demonstration of symptom improvement should be at least 3 months (11). Similarly, European Medicines Agency (EMEA) suggests maintenance of improvement should be evaluated normally after at least 3 months for medicinal products with a quick onset of action claiming acute symptom relief. For this study, in line with these Guidelines and treatment effect observed in previous studies, will observe symptom improvement for 26 weeks (12).

In this study, placebo is chosen as the comparator based on suggestion from FDA and EMEA Guidance. FDA Guidance indicates the persuasiveness of trials showing a difference is generally greater than that of equivalence trials, so it is highly desirable for a claim to be demonstrated in at least one trial showing superiority of the test product to placebo control (11). EMEA also recommends therapeutic confirmation studies should have a randomized, double blind, parallel group design. Efficacy of products claiming improvement in symptoms is generally established by means of placebo controlled trials (12).

Rationale for the selection of study population

Severe mental disorders as well as neuropathic pain will impact the measurement of effectiveness at target knee joint (13). To exclude patients with clear neuropathic OA pain in target knee joint as well as severe major mental disorders, four questionnaires painDETECT, Patient Health Questionnaire-9 [PHQ-9], Generalized Anxiety Disorder 7-item [GAD-7], and Insomnia Severity Index [ISI]) are used in the exclusion criteria (described in Section 7.2.1 and Appendix D).

5 STUDY OBJECTIVES

5.1 PRIMARY

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 WOMAC NRS 3.1 A1, in comparison to an IA placebo injection over 26 weeks, in Chinese patients with symptomatic OA of the knee.

5.2 SECONDARY

The secondary objectives 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 sub-score 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,PTGA and 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, relative to an IA placebo injection over 26 weeks.

5.3 TERTIARY EFFICACY AND OTHER

- 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.

6 STUDY DESIGN

6.1 DESCRIPTION OF THE PROTOCOL

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.

6.2 DURATION OF STUDY PARTICIPATION

6.2.1 Duration of study participation for each patient

A period of approximately 17 months is anticipated from the time the first patient enrollment to the completion of the last patient visit (last patient out). Individual patient participation lasts up to 29 weeks.

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).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).

6.2.2 Determination of end of clinical trial (all patients)

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

7 SELECTION OF PATIENTS

7.1 INCLUSION CRITERIA

Chinese patient with OA of the target knee joint

I 01. Between 40 to 80 (included) years of age at randomization

I 02. Symptomatic OA of the target knee joint with WOMAC A1 NRS score of ≥4.0 and ≤8.0 as recorded in base line period

I 03. Confirmed by standard X-rays performed within 3 months prior to screening visit: modified Kellgren-Lawrence Numerical Grading System of Grade I-III (1) in the target knee joint[1]

I 04. Defined according to the ACR Criteria (2)

I 05. With failure to respond adequately to conservative non-pharmacologic therapy and/or simple analgesics, such as acetaminophen

I 06. Patient is willing and able to provide signed informed consent prior to any study related procedures being performed

7.2 EXCLUSION CRITERIA

7.2.1 Exclusion criteria related to study methodology

E 01. Patient with painDETECT Questionnaire score >18 at screening visit (Appendix D)

E 02. Patient with moderately severe or severe depression as indicated by PHQ-9 total score of ≥15 or a score of >0 on item # 9 at screening visit (Appendix D)

E 03. Patient with severe anxiety as indicated by GAD-7 score of ≥15 at screening visit (Appendix D)

E 04. Patient does not record a minimum of 5 days' worth of diary data within the 7 days before the treatment day (Day 1)

E 05. Patient with severe insomnia as indicated by ISI Questionnaire score >22 at screening visit (Appendix D)

[1] Anterioposterior view: weightbearing (extension or semi-flexion) + profile and a femoro-patellar view at 30° classical.

E 06. Patient is not ambulatory (assistive device allowed if used 4 weeks or more prior to screening visit)

E 07. The score of contralateral knee pain (if present) >3.0 NRS at screening visit

E 08. Ipsilateral hip OA

E 09. Patient with ALT/AST ≥3 × ULN and/or bilirubin ≥1.5 × ULN

E 10. Female of childbearing potential who is unwilling to use effective contraceptive method throughout the duration of the study.

E 11. Female who is pregnant or lactating

E 12. Patient with active knee joint infections or skin diseases or infections in the area of the injection site of the target knee joint

E 13. Patient with systemic corticosteroids within12 weeks prior to screening visit

E 14. Patient with injection of IA corticosteroids in the target knee joint within 26 weeks prior to screening visit

E 15. Patient has visco-supplementation injection in any joint, including the target knee joint, within 26 weeks prior to screening visit

E 16. Patient with concomitant inflammatory disease or other condition that affects the joints (eg, rheumatoid arthritis, metabolic bone disease, psoriatic arthritis, gouty arthritis, symptomatic chondrocalcinosis, osteonecrosis or active infection)

E 17. Patient with secondary OA of the target knee joint due to acute disease or trauma within 5 years prior to screening visit

E 18. Patient with significant valgus/varus deformities, ligamentous laxity, or meniscal instability

E 19. Patient with any major surgery, arthroplasty or arthroscopy in the target knee joint or another joint/joints in the lower extremity within 26 weeks prior to screening visit, or planned surgery in the lower extremities throughout the duration of the study

E 20. Patient with septic arthritis in any joint within 12 weeks prior to screening visit

E 21. Patient with any significant chronic skin disorder that could interfere with evaluation of the injection site

E 22. Concurrent chronic pain conditions with pain score >3.0 NRS at screening, or peripheral or central neuropathy that may affect sensation of the target knee area, including but not limited to back pain, hip pain, disc herniation, sciatica, diabetic neuropathy, post-stroke pain or fibromyalgia

E 23. Patient with active malignancy or treatment for malignancy within 5 years prior to screening visit, except non-melanoma skin cancer

E 24. Patient with active asthma that may require periodic treatment with systemic steroids during the study period

E 25. Patient with a venous or lymphatic stasis in the leg

E 26. Patient with claudication or peripheral vascular disease

E 27. Patient with oral or parental anticoagulant therapy or with high doses of platelet anti-aggregant therapy; however, acetyl salicylic acid (ASA) at doses ≤325 mg/day is allowed

E 28. Patient is not willing to withhold intake of permitted pain medications for 48 hours prior to all study visits

E 29. Started the use of glucosamine, chondroitin sulfate, diacerhein, or avocado/soya extracts within 2 months prior to Screening

E 30. Patient used an investigational drug, device or biologic within 12 weeks prior to screening visit

E 31. Patient not able to read and understand the language and content of the study material, understand the requirements for follow-up visits, and not willing to provide information at the scheduled evaluations

E 32. Patient with other factors assessed by the Investigator that may limit the ability of the patient to perform necessary study evaluations eg, active alcohol abuse, active drug abuse, planned relocation, significant psychiatric or neurological disorder (eg, Parkinsonism, Alzheimers, or other similar chronic and progressive neurological diseases…)

E 33. Investigator, sub-investigator, pharmacist, study coordinator, other study staff or relatives to the staff who is directly involved in the conduct of the protocol

E 34. Patient with any significant medical condition, including clinically significant coagulopathy, that the Investigator feels would interfere with study safety and efficacy evaluations and study participation

7.2.2 Exclusion criteria related to the active comparator and/or mandatory background therapies

E 35. Patient with a known history of hypersentivity to lidocaine, acetaminophen, oxycodone or tramadol

7.2.3 Exclusion criteria related to the current knowledge of Sanofi compound

E 36. Patient with a known history of hypersensitivity to avian protein or any components of hyaluronan-based injection devices

8 STUDY TREATMENTS

8.1 INVESTIGATIONAL MEDICINAL PRODUCT(S)

The IMP evaluated in this study is Synvisc-One (hylan G-F 20), which is a sterile, non-pyrogenic, elastoviscous fluid containing hylan polysaccharide hydrated in physiological saline. Hylan is a cross-linked derivative of hyaluronan, a natural polysaccharide (glycosaminoglycan) responsible for the elastoviscosity of synovial fluid. Synvisc-One consists of 2 different hylans. Hylan A is a water-soluble hyaluronan derivative (hylan A fluid). Hylan B is a water-insoluble hylan derivative, which forms a hydrated gel in aqueous solvents (hylan B gel). Hylan A fluid constitutes 80% (per volume) and hylan B gel slurry 20% (per volume) of the final hylan G-F 20 fluid. Hylan B is produced by chemically crosslinking hylan molecules to form a molecular network (14, 15, 16). It is a water-insoluble, viscoelastic hydrated gel. One milliliter of Synvisc-One contains 8 mg hylan polymer. The hydration fluid is isotonic physiological sodium chloride solution.

Investigational medicinal product will be provided in prefilled syringes, volume of 6 mL, containing 48 mg of hylan polymer in buffered physiological sodium chloride solution (pH 7.2±0.3)

The equal volume placebo is PBS, which has the same formulation as the hydration fluid in Synvisc-One (buffered physiological sodium chloride solution, pH 7.2).

8.1.1 Study Treatment Preparation

A technician should be trained by study standard training before his/her first injection.

Both Synvisc-One and Placebo (PBS) are supplied in a pre-filled syringe. Therefore, no study treatment preparation is required for this clinical study protocol.

Each syringe is intended for single use. The contents of the syringe must be used immediately after the syringe has been removed from its packaging.

Twist the tip cap before pulling it off, as this will minimize product leakage.

8.1.2 General Instructions for Injection

For the injection visit (Treatment Study Day 1), the study staff should ensure that the injection room is properly prepared prior to patient arrival. The facility must be prepared by the Unblinded Injector to ensure patient blinding before the patient enters the injection room. Preparation includes: having the interactive voice response system (IVRS) assigned patient kit (see Section 8.4) and all necessary supplies available; having a surgical/anesthesia drape in place to obscure the patient's view of the supplies; and ensuring the kit contents is not visible to the patient.

The Synvisc-One or placebo injection will be performed by a qualified professional. Before injection, qualified injector must examine, disinfect and anaesthetize (if required) the injection site, followed by arthrocentesis. Strict aseptic technique and universal precautions must be followed. The Unblinded Injector should use the injection approach of lateral supra-patellar or lateral mid-patellar according to instructions and training provided by the Sponsor (17). Deviations from these injection procedure guidelines must be documented.

8.1.3 Precautions for Joint Injection

Prior to each injection, the Investigator must examine the injection site for any of the following signs or symptoms:

1. Tense effusions
2. Clinically significant redness or tenderness (such as overlying cellulitis), and/or
3. Any medically significant condition that could compromise patient safety or study integrity

If any of these signs or symptoms is present, the Investigator must not carry out the procedure.

8.1.4 Injection Site Preparation

The injection site should be disinfected carefully according to standard medical practice.

Disinfectants containing quaternary ammonium salts are not permitted, because hyaluronan can precipitate in their presence. A surgical/anesthesia drape will obscure the patient's view of the injection procedure and injection supplies to maintain blinding.

8.1.5 Anaesthetization of the Injection Site

Anaesthetization of the injection site is not required. However, the Unblinded Injector may administer at his/her discretion a topical (eg, ethyl chloride) or subcutaneous anesthetic (eg, lidocaine).

8.1.6 Arthrocentesis

Arthrocentesis will be performed prior to every injection. Only 18- to 20-gauge needles are to be used for this study. Strict aseptic administration technique must be followed. The injection approach should be either lateral supra-patellar or lateral mid-patellar. Gentle aspiration will be performed in an attempt to ascertain if the needle has been placed within the joint space.

Any fluid or effusion will be withdrawn and the volume of the fluid/effusion will be recorded. Leaving the needle in the joint space, the syringe will be removed and replaced by a pre-filled syringe containing either Synvisc-One or Placebo (PBS). Care must be taken when manipulating the luer lock so as not to agitate or remove the needle or to incorrectly attach the next syringe (eg, could cause leakage). Refer to Section 8.1.7 for further administration instructions.

8.1.7 Injection of Synvisc-One or Placebo

Remove the pre-filled 10-mL syringe from its packaging and use only if the packaging has not been opened or damaged. Notify the Sponsor promptly if the packaging is not intact (see Section 10.4.6). After the syringe has been removed from its packaging, immediately attach it to the 18- or 20-gauge needle that has been positioned in the joint; special care should be taken to ensure that the Unblinded Injector removes the tip cap from the syringe using aseptic technique before attaching to the needle.

Synvisc-One or Placebo (PBS) should NOT be injected extra-articularly, into the synovial tissues, into the capsule, or into the bursae. Each 10 mL syringe contains 6 mL of Synvisc-One or 6 mL of Placebo (PBS). Inject 6 mL into the target knee over 3 to 4 minutes, and then remove the needle and syringe.

If 6 mL of Synvisc-One or Placebo (PBS) cannot be injected, the reason must be documented. The total volume injected must be calculated and documented.

All procedures will be carefully documented in the patient notes and appropriate electronic Case Report Form (eCRF).

8.1.8 Post injection Procedures

After withdrawing the needle from the joint space, light pressure should be applied to the injection site, followed by application of a simple adhesive bandage. The patient should be encouraged to rest the injected joint for 24 hours. Patients are allowed to return to work that day but strenuous activity and driving for long distances in the 24 hours after injection is not recommended. Typically there could be pain associated with the procedure. For postinjection pain management, it is recommended that patients rest and ice the injection site.

All pharmacological and nonpharmacologinal treatments taken by the patient for post-injection pain must be captured in the eCRF.

All AEs occurring after the informed consent has been signed and up to the End of Study visit (including those happening prior, during, and immediately post-injection) must be recorded in the eCRF. Patients experiencing pain and swelling at the target joint or any other AE will be instructed to contact the study staff.

All procedures were documented carefully in the patient notes and appropriate eCRF pages.

8.2 NON-INVESTIGATIONAL MEDICINAL PRODUCT(S)

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).

Patients will be allowed to take a maximum total daily dose of 3000 mg acetaminophen (6 tablets of 500 mg each) as rescue medication in case of unbearable pain during the study period. The Investigator should consider the use of rescue medication other than acetaminophen on a case-by-case basis, ie. in case of unbearable pain and based on the risk of acetaminophen overdose; rescue medication will be considered on an as-needed:

- Acetaminophen as first line (up to 3000 mg/day);
- If ineffective, after stopping acetaminophen, acetaminophen 325 mg combined with tramadol hydrochloride 37.5 mg, up to 1 tablet 6 times daily; Or,
- If ineffective, after stopping acetaminophen, acetaminophen 325 mg combined with oxycodone 5 mg, up to 1 tablet 4 times daily.

Note: If patients are taking stable doses of selective serotonin re-uptake inhibitors (SSRIs), the rescue medication tramadol should not be prescribed, regarding the risk of serotonin syndrome.

The usage of any rescue medicine whenever during the study must be recorded.

8.3 BLINDING PROCEDURES

8.3.1 Methods of blinding

The patient and evaluator will be blinded to the IMP or placebo received.

Refer to Section 10.5 for suspected unexpected adverse drug reaction unblinding by the Sponsor.

8.3.2 Randomization code breaking during the study

In case of an AE, the code should only be broken in circumstances when knowledge of the IMP is required for treating the patient.

Code breaking can be performed at any time by using the proper module of the IVRS provided by the Sponsor. If the blind is broken, the Investigator should document the date, time of day and reason for code breaking.

8.4 METHOD OF ASSIGNING PATIENTS TO TREATMENT GROUP

Randomization occurred only after patients provided written informed consent, completed all screening visit procedures, and met the requirements of designated inclusion and exclusion criteria. The randomized treatment kit number list is generated centrally by Sanofi. The IMPs or placebo are packaged in accordance with this list. The randomization and treatment allocation are performed centrally by an IVRS. The IVRS generates the patient randomization list and allocates the treatment number and the corresponding treatment kits to the patients according to it. The randomization ratio of hylan G-F 20: placebo is 1:1. Randomization was determined from a centralized list in the custody of the randomization service. All study sites received their randomization assignments from the same list. Patient study numbers were allocated by the central randomization service following the system specified by the Sponsor. Any patient

enrolled but not randomized into the study was assigned a screening number but not a randomization number. All consenting patients were documented in the patient-screening log.

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 Day1. A new patient number will be allocated.

8.5 PACKAGING AND LABELING

The Sponsor will coordinate the packaging and labeling of the investigational products (Synvisc-One and placebo control [PBS]). The Sponsor is preparing clinical study material kits solely for the convenience of the Unblinded Injector (see Table 1).

Synvisc-One and the placebo control (PBS) syringes will be labeled with a single panel label and the panel text will minimally include the protocol number, product name, lot number and expiry date in accordance with the local regulatory specifications and requirements. The syringes will be packaged into kits that appear identical.

Each kit will contain a labeled Pre-filled syringe. The kit will be labeled with a single panel label and tamper sealed. The panel text will minimally include the protocol number, product name, storage conditions, kit code and the Sponsor's name and address.

Detailed Investigational Product handling instructions will be provided in the Investigational Product Handling Manual.

The Sponsor will keep a record of all Synvisc-One and placebo control (PBS) lot numbers and associated kit numbers shipped to each study site. This information will be maintained in the Sponsor's clinical inventory management system as well as IVRS. This information can be available in the event that certain lot numbers must be identified and located during the course of the study.

Synvisc-One and placebo kits being supplied by the Sponsor will include, but are not limited to those listed in Table 1.

Table 1 - Synvisc-One and Placebo Kit

Synvisc-One Kit	Placebo Kit
Day 1	**Day 1**
Synvisc-One	**Placebo**
One (1) pre-filled Synvisc-One syringe	One (1) pre-filled phosphate buffered saline syringe

NOTE: Synvisc-One and placebo are to be administered only by qualified personnel. Under no circumstance will the clinical study material be used other than as directed by the protocol. All clinical supplies must be kept in a secure place with limited access.

8.6 STORAGE CONDITIONS AND SHELF LIFE

Patient Kits with study product must be stored at room temperature below 30°C (86°F) in a location with limited access in the original packaging protected from light. The study product must not be frozen. Do not use any product if its package is opened or damaged.

The seal of the kit should not be broken until the treatment is prepared by unblinded study personnel.

8.7 RESPONSIBILITIES

The Investigator, the hospital pharmacist, or other personnel allowed to store and dispense the IMP will be responsible for ensuring that the IMP used in the clinical trial is securely maintained as specified by the Sponsor and in accordance with applicable regulatory requirements.

All IMP will be dispensed in accordance with the Investigator's prescription and it is the Investigator's responsibility to ensure that an accurate record of IMP issued and returned is maintained.

Any quality issue noticed with the receipt or use of an IMP (deficiency in condition, appearance, pertaining documentation, labeling, expiration date and etc.) should be promptly notified to the Sponsor. Some deficiencies may be recorded through a complaint procedure.

A potential defect in the quality of IMP may be subject to initiation of a recall procedure by the Sponsor. In this case, the Investigator will be responsible for promptly addressing any request made by the Sponsor, in order to recall IMP and eliminate potential hazards.

Under no circumstances will the Investigator supply IMP to a third party, allows the IMP to be used other than as directed by this clinical trial protocol, or dispose of IMP in any other manner.

8.7.1 Treatment accountability and compliance

The Investigator will maintain accurate records of clinical study material that is received, dispensed, and destroyed at the clinical site. Refer to the Investigational Product Handling Manual for details.

The monitor in charge of the study then checks the eCRF data by comparing them with the IMP which he/she has retrieved and treatment log forms. Once the treatment was given, the empty kit was stored in a location with limited access until monitor in charge of the study performed the accountability check.

8.7.2 Return and/or destruction of treatments

Disposition of Used and Unused Clinical Supplies:

Following treatment administration, all used needles and syringes will be disposed of per institutional procedures. All resealed Synvisc-One and placebo boxes must not be thrown away

until the Sponsor or designee has performed accountability at the site. Until accounted for, resealed boxes must be maintained in a limited access area.

Unused kits must be maintained under adequate storage conditions in a limited access area. If any unused material is remaining at the clinical site at study completion the material will be destroyed only after the following:

- Accountability has been performed by the Sponsor or designee
- The Sponsor or designee completes documentation of disposition with the Investigator or designee. A copy of the documentation of disposition must be returned to the Sponsor or designee. The original must be maintained in the clinical site study files

For IMP provided by the Sponsor:

All partially-used or unused treatments will be retrieved by the Sponsor. A detailed treatment log of the returned IMP will be established with the Investigator (or the pharmacist) and countersigned by the Investigator and the monitoring team.

For non-investigational medicinal product (NIMP) not provided by the Sponsor, acetaminophen (as the active ingredient) will be supplied by the patient. The Sponsor recommends each patient follow the approved dosing information in the package insert. Acetaminophen is a clinically proven analgesic that produces analgesia by elevation of the pain threshold.

8.8 CONCOMITANT MEDICATION

A concomitant medication is any treatment received by the patient concomitantly to any IMP(s). All concomitant medications must be documented in the patient diary and the eCRF including the name of the medication, dose, start and stop dates, and the associated indication.

8.8.1 Medication Washout Requirements before Study Visits

Acetaminophen (rescue medication) are permitted for causes other than target knee OA pain (eg, flu, headache, non- target joint pain) during the study (see Section 8.8.3), but must not be taken within 48 hours prior to a study visit, so as to not interfere with any patient-rated assessments. If acetaminophen or analgesics are taken within this 48-hour period, then the study visit must be rescheduled within the time window specified in Section 1.

Acetaminophen will be self-provided by the patient. Information on acetaminophen will be captured in the eCRF and should include the date, medication strength, dose (e.g. number of tablets per day), dosage form, and whether or not it was taken for target knee OA pain.

Please refer to Appendix C for details of the medication average plasma half-life and washout requirements.

8.8.2 Prohibited Treatment

Following are the list of forbidden concomitant medications:

- Acetaminophen/oxycodone or Acetaminophen/tramadol within 48 hours of each site visit.
- NSAID use (including topical preparation) is not allowed during the 26 weeks of the study.
- Antidepressants (except for stable [>30 days] regimens of SSRIs for treatment of anxiety or depression), anti-epileptic or mexiletine for the treatment of pain.
- Opioids (with the exception of those permitted as rescue medication as mentioned in the present section) or morphino-mimetics.
- Acetyl salicylic acid (ASA) except up to 325 mg/day, as platelet aggregation inhibitor, for myocardial infarction or transient ischemic attack prophylaxis.
- Benzodiazepines other than indicated at low doses for sleep disorders.
- Systemic corticosteroid(s), either oral or injection
- Any topical analgesic on the target joint containing NSAIDs, salicylates, capsaicin or counter-irritants
- Local corticosteroid injection into any joint viscosupplementation injected into any joint other than as required by the protocol
- Heparin or anti-vitamin K (eg, crystalline warfarin) anticoagulant therapy, either orally or parentally
- Any investigational drug or biologic used during the study (other than as required by the protocol)
- Physical therapy at outpatient department (OPD) or clinic for OA treatment in the lower extremities
- Any medications claim to have pain control effect, such as traditional Chinese medicine (TCM), except what are specified on the protocol.

Other platelet aggregation inhibitors (eg, clopidogrel) are allowed.

Patients may continue glucosamine, chondroitin sulfate, diacerhein, oravocado/soya extracts, provided it has been started at least 2 months prior to enrollment; it should not be initiated or substantially altered during the study.

Patients may continue a regimen of therapeutic exercise, provided it has been stable for at least 8 weeks prior to enrollment. No new therapeutic exercise regimens should be implemented during the study. Physical therapy or therapeutic massage should not be initiated during the study. Heat or ice therapy can be used during the study, except within 48 hours prior to a visit on clinical site. Electrical stimulation devices and acupuncture are not allowed during the study and should be discontinued 2 weeks prior to enrollment.

8.8.3 Permitted Treatments

Table 2 - Permitted Treatments and/or Medications

Treatments Allowed	Restriction
Rescue medication: acetaminophen, acetaminophen/oxycodone, or Acetaminophen/tramadol	Rescue medication only, but not to exceed max doses please refer to Section 8.2.
	Not within 48 hours prior to study evaluation.
	Patients will be instructed not to take medications (other than rescue medications) for target knee OA pain relief.
Low-dose ASA, or other platelet aggregation inhibitors (eg, clopidogrel)	Not to exceed 325 mg/day
Topical corticosteroids for skin irritations	Allowed at any site other than the target knee
Inhaled corticosteroids for pulmonary disease	None
Non pharmacologic therapy (except physical therapy at OPD or clinic for OA treatment) for the lower extremities	Allowable if started ≥ 4 weeks before Screening visit, not to be initiated or substantially altered during the study except for discontinuation
Non pharmacologic therapy (eg, physical therapy) for joints other than in the lower extremities, or other conditions	Allowed without restriction at any site other than the lower extremities (see line above)
Assistive devices	Allowable if used ≥ 4 weeks before Screening visit and will continue to be used throughout the study
Glucosamine, chondroitin sulfate	Allowable if started at least 2 months before Screening visit, not to be initiated or substantially altered during the study

Abbreviations: OA: osteoarthritis; ASA: acetyl salicylic acid; OPD: outpatient department

9 ASSESSMENT OF INVESTIGATIONAL MEDICINAL PRODUCT

9.1 PRIMARY ENDPOINT

9.1.1 Primary efficacy endpoint

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

9.2 SECONDARY ENDPOINTS

9.2.1 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), WOMAC A, 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.

9.2.2 Safety endpoints

Safety will be assessed by evaluation of the incidence of treatment-emergent AEs and changes in standard safety parameters (eg, vital signs) from screening visit through the last follow-up visit.

9.2.2.1 Adverse events

Adverse events, serious adverse event (SAE) (including deaths) and AEs leading to treatment discontinuation from the screening visit through the last follow-up visit must be documented in the eCRF.

9.2.2.2 Laboratory safety variables

Not applicable.

9.2.2.3 Vital signs

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

9.3 TERTIARY EFFICACY ENDPOINTS AND OTHER ENDPOINTS

9.3.1 Tertiary efficacy endpoints

Tertiary efficacy endpoints include the differences between treatment groups in:

- Changes from baseline at Week 4, 8, 12, 16, and 20, and 26 in 7-day average walking pain score (measured by daily 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.

9.3.2 Quality of life/health economic variables

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

10 STUDY PROCEDURES

10.1 VISIT SCHEDULE

This study was conducted as outlined in the following sections. Study flow chart (in Section 1.2) summarizes the schedule of study events at each visit for patients enrolled in the study. Study visits were based on calendar days from baseline (Day 1). If the first injection did not occur on the same day as the Day 1 study visit, subsequent study visits were based on calendar days from the date of the first study intervention (injection) as shown in study flow chart. Re-screens and rescheduled visits were required to occur within the time windows specified in study flow chart (details for re-screens please refer to Section 8.4).

10.1.1 Visit 1 (Screening)

Patients will attend a Screening visit where the Investigator will discuss all aspects of the study with the patient; allowed sufficient time for the patient to consider participation in the study; and obtain written informed consent from the patient before proceeding further.

After the patient provides written informed consent, and the Investigator documents this in the patient notes, the following assessments will be performed:

- Eligibility of the patient (according to inclusion/exclusion criteria);
- Demographics;
- Height and weight;
- Vital signs;
- Relevant medical history;
- Physical examination (including X-ray; previously taken X-rays of the target knee joint that are no older than 3 months at Screening visit may be used to provide the Modified Kellgren-Lawrence Numerical Grading System of OA);
- Liver function tests;
- WOMAC (NRS);
- AE/SAE recording;
- Concomitant Medications;
- Agreed on the next visit.

A paper patient diary is dispensed. Instruction on how to complete the patient diary on a daily basis will be done by site staff. The details of the diary are provided in Appendix E.

A medical history will be obtained at screening visit (up to 21 days prior to Day 1). Specific information will be 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.

10.1.2 Visit 2 (Treatment Day 1)

Visit 2 will be scheduled (at any time in that period) to randomize and administer the injection of Synvisc-One or placebo. At this visit the following assessments will be performed:

- Confirmed eligibility of the patient;
- Vital signs;
- If female and of childbearing potential: pregnancy test (urine) to confirm non pregnancy;
- WOMAC (NRS);
- PTGA;
- COGA;
- EQ-5D;
- Patient diary;
- Withhold intake of permitted pain medications for 48 hours;
- Randomization and administration of IMP/placebo;
- Rescue Medication Monitoring;
- Documentation of AE(s);
- Prior and concomitant treatment.

Once all these assessments are performed and the eligibility criteria are confirmed, the Investigator telephones the central randomization service to receive the patient study number. Adverse events that may have occurred between the signature of the informed consent and Day 1 are to be reported in the eCRF by the investigator. The Investigator then immediately administered the injection of IMP as randomized. AEs occurring during visit 2 are recorded in the patient notes and the eCRF. A date for the next visit 1 week later is scheduled and AEs occurring during this visit are recorded in the patient notes and the eCRF. The Investigator must ensure that the patient has properly completed all questionnaires before leaving the Investigator's clinic.

10.1.3 Visit 3 – Week 1 follow-up (Week 1 ± 4 days)

One week after the first injection, the patient will be seen by the Investigator. The following assessments will be performed:

- Patient diary;
- Withhold intake of permitted pain medications for 48 hours;
- Rescue Medication Monitoring;
- Documentation of AE(s);

- Assessment of concomitant medication;
- Agreement on the next visit.

AEs that have occurred between the previous visit and the present visit are to be recorded in the eCRF and in the patient's notes.

10.1.4 Visit 4 to 8– Week 4, Week 8, Week 12, Week 16 and Week 20 follow-up (Week 4 ± 4 days, Week 8 ± 7 days, Week 12 ± 7 days, Week 16 ± 7 days and Week 20 ± 7 days)

Four (4), 8, 12, 16, and 20weeks after the first injection, the patient will be seen by the Investigator. The following assessments will be performed:

- WOMAC (NRS);
- PTGA;
- COGA;
- EQ-5D;
- Patient diary;
- Withhold intake of permitted pain medications for 48 hours;
- Rescue Medication Monitoring;
- Documentation of AE(s);
- Assessment of concomitant medication;
- Agreement on the next visit.

AEs that have occurred between the previous visit and the present visit are to be recorded in the eCRF and in the patient's notes.

10.1.5 Visit 9 – Week 26 Follow up (Week 26 ± 7 days)

The following assessments will be performed at the final study visit (Week 26):

- Vital signs;
- Physical examination;
- If female and of childbearing potential: pregnancy test (urine) to confirm nonpregnancy;
- WOMAC (NRS);
- PTGA;
- COGA;
- EQ-5D;
- Patient diary;
- Withhold intake of permitted pain medications for 48 hours;
- Rescue Medication Monitoring;
- Documentation of AE(s);
- Assessment of concomitant medication;
- Study Termination.

AEs that have occurred between the previous visit and the present visit are to be recorded in the eCRF and in the patient's notes.

10.1.6 Physical examination

A physical examination will be conducted at Screening visit (up to 21 days prior to Day 1) and the final study visit (Week 26). Any abnormal findings must be recorded on the eCRF.

10.1.7 Western Ontario and McMaster Universities Osteoarthritis Index Numerical Rating Scale

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. The questionnaire consists of 24 questions (4) 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.

All questionnaires provided to the patient will be in local language and must be completed only by the patient. As determined during the baseline visit, only one knee will be included in the efficacy assessment and will be considered the Target Knee. All follow-up efficacy assessments (that are knee specific) should be collected relative to the Target Knee.

WOMAC A1

The WOMAC A1 is a single question assessing target knee pain while walking on a flat surface.

WOMAC A

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

10.1.8 Patient Global Assessment

The patient will be given a global self-assessment (PTGA) of target knee OA condition at the specified timepoints. The patient will be asked to respond to the following 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." An 11-point NRS ranging from 0 (best possible) to 10 (worst possible) will be used to capture the patient's response to each of the questions. The patient's response will be recorded directly on the PQ, and the PQ will serve as the source documentation.

10.1.9 Clinical Observer Global Assessment

The physician will perform a global assessment (COGA) of the patient's target knee OA using the 11-point NRS pain intensity rating scale ranging from 0 (best possible) to 10 (worst possible) at the specified timepoints. The physician will be asked to respond to the following question: "Considering all the ways that the arthritis of the patient's target knee affects him/her, select one response 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. All COGAs must be completed after the patient completes self-assessments. The physician will record their global assessment of the patient's disease status in the eCRF and this will serve as the source documentation.

10.1.10 EuroQol Five Dimensions

EQ-5D is a general, preference-weighted health status instrument that asks patient questions about their overall health status and Health-Related Quality of Life (HRQOL). EQ-5D measures health status using the following 5 dimensions: mobility, self-care, usual activity, pain/discomfort, and anxiety/depression. EQ-5D has 3L and 5L versions, and 5L could increase reliability and sensitivity (discriminatory power) while maintaining feasibility and potentially reducing ceiling effects, compared with 3L. EQ-5D-5L includes 5 levels of severity in each of the five dimensions: no problems, slight problems, moderate problems, severe problems, and extreme problems.

The patient's response will be recorded directly on the PQ, and the PQ will serve as the source documentation.

10.1.11 Pregnancy Test

Females of childbearing potential must undergo a urine pregnancy test at baseline (Day 1) prior to administration of IMP and last study visit (Week 26). Patients are carefully screened to ensure that all women of childbearing potential will use a medically acceptable form of contraception for at least 1 month prior to Screening visit and will continue use for the duration of the study period. Women who could not comply must not enroll in the study.

Women of non-childbearing potential due to surgical sterility must confirm that they are surgically sterile. Menopause in this setting will be defined by at least one year's absence of menstruation in women over the age of 50. This information must be recorded on the Medical History page of the eCRF.

10.2 DEFINITION OF SOURCE DATA

Original documents, data, and records include hospital records, clinical and office charts, laboratory notes/reports, memoranda, patients' evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies of transcriptions certified after verification as being accurate copies, source document worksheets (ie, for study visits, including the interim phone call worksheets), and X-rays are considered source documents. Medical

histories and narrative statements relating to the subject's progress (ie, source documents) will be maintained during the trial and for a period of 15 years after completion of the study. The investigator must provide direct access to the source documents to Sanofi or its representative.

All data captured for this study are to be recorded in the patient's notes first and then entered in the eCRF, except for the items listed below. These are considered source documents, and will be completed by the patient and recorded directly into a PQ:

- Total WOMAC 3.1
- PTGA
- EQ-5D
- PainDETECT
- PHQ-9
- GAD-7
- ISI.

10.3 COMPLETION OF A PATIENT'S PARTICIPATION IN THE STUDY AND OVERALL STUDY COMPLETION

10.3.1 Completion of a Patient's Participation in the Study

The length of a patient's participation will be from the time the informed consent form is signed until last planned assessment/visit at Week 26 and will be approximately 29 weeks in duration, inclusive of the Screening visit period (21 calendar days) through the Week 26 visit (±7 calendar days). A patient will be considered "completed" when the patient receives study treatment and remains in the study through to the day of his/her last scheduled study visit (Week 26).

10.3.2 Overall Study Completion

The study will be considered to be complete when the last patient completes the last study visit.

10.3.3 Patient withdrawal

Patients are free to withdraw consent and/or discontinue participation from the study at any time and without prejudice to further treatment. Withdrawal of consent for treatment should be distinguished from withdrawal of consent for follow-up visits and from withdrawal of consent for non-patient contact follow-up, eg, medical records check. Patients requesting withdrawal should be informed that withdrawal of consent for follow-up may jeopardize the public health value of the study.

Patients who withdraw should be explicitly asked about the contribution of possible AEs to their decision to withdraw consent, and any AE information elicited should be documented. Preferably the patient should withdraw consent in writing and, if the patient or the patient's representative refuses or is physically unavailable, the site should document and sign the reason for the patient's failure to withdraw consent in writing.

- In addition, a patient's participation in the study may be discontinued at the discretion of the Investigator at any time. Justifiable reasons for the Investigator to remove a patient from the study may include but are not limited to the following:
  - The patient is uncooperative, including failure to appear at 1 or more study visits
  - The patient develops a concurrent disease or condition that disqualifies him/her based on eligibility criteria
  - The patient suffers an intolerable AE
  - The Sponsor terminates the study
- Patients may be discontinued from the study if the study is terminated by the Sponsor.

All study withdrawals should be recorded by the Investigator in the appropriate screens of the CRF or e-CRF and in the patient's medical records when considered as confirmed. In the medical record, at least the date of the withdrawal and the reason should be documented.

10.3.4 Procedure and consequence for patient withdrawal from study

Patients will be followed-up according to the study procedures specified in this protocol up to the scheduled date of study completion, or up to recovery or stabilization of any AE to be followed-up as specified in this protocol, whichever comes last.

If possible, and after the permanent discontinuation of treatment, the patients will be assessed using the procedure normally planned for the last dosing day with the IMP.

A patient will be considered early terminated if a patient does not complete the study at any time after enrollment. A patient will be considered discontinued due to an AE if the patient received treatment, but did not complete the study due to an AE, regardless of whether that AE was assessed by the Investigator as related to the study treatment. At the end of the patient's participation in the study the Investigator will complete the discontinuation eCRF, documenting the reason(s) for study discontinuation.

For patients who fail to return to the site, the Investigator should make the best effort to recontact the patient (eg, contacting patient's family or private physician, reviewing available registries or health care databases), and to determine his/her health status, including at least his/her vital status. Attempts to contact such patients must be documented in the patient's records (eg, times and dates of attempted telephone contact, receipt for sending a registered letter).

Patients who have withdrawn from the study cannot be re-randomized (treated) in the study. Their inclusion and treatment numbers must not be re-used.

10.3.5 Permanent treatment discontinuation

Permanent treatment discontinuation is not appropriate in this study and please refer to Section 10.3.4.

10.4 OBLIGATION OF THE INVESTIGATOR REGARDING SAFETY REPORTING

10.4.1 Definitions of adverse events

10.4.1.1 Adverse event

An **adverse event** (AE) is any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.

An AE can, therefore, be any unfavorable and unintended symptom, sign, disease or condition, or test abnormality whether or not considered related to the investigational product.

Adverse events include:

- Symptoms described by the patient or signs observed by the Investigator or medical staff.
- Test abnormalities (laboratory tests**,** electrocardiogram, X-rays, etc.) that result in an alteration in medical care (diagnostic or therapeutic).

Abnormalities present at baseline are considered AEs only if they reoccur after resolution or they worsen during the study.

10.4.1.2 Serious adverse event

A SAE is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening

  Note: The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity: An AE that results in a substantial disruption of a person's ability to conduct normal life functions
- Intervention Required: An AE requiring medical or surgical intervention to preclude permanent impairment of a body function or prevent permanent damage to a body structure.
- Is a congenital anomaly/birth defect
- Is a medically important event

  Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention (ie, specific measures or corrective treatment) to prevent one of the other outcomes listed in the definition above.

Note: The following list of medically important events is intended to serve as a guideline for determining which condition has to be considered as a medically important event. The list is not intended to be exhaustive:

- Intensive treatment in an emergency room or at home for:

1. Allergic bronchospasm
2. Blood dyscrasias (ie, agranulocytosis, aplastic anemia, bone marrow aplasia, myelodysplasia, pancytopenia and etc.)
3. Convulsions (seizures, epilepsy, epileptic fit, absence and etc.).

- Development of drug dependency or drug abuse
- ALT >3 x ULN + total bilirubin >2 x ULN or asymptomatic ALT increase >10 x ULN
- Suicide attempt or any event suggestive of suicidality
- Syncope, loss of consciousness (except if documented as a consequence of blood sampling)
- Bullous cutaneous eruptions
- Cancers diagnosed during the study or aggravated during the study (only if judged unusual/significant by the Investigators in oncology studies)
- Chronic neurodegenerative diseases (newly diagnosed) or aggravated during the study (only if judged unusual/significant by the Investigators in studies assessing specifically the effect of a study drug on these diseases).

10.4.1.3 Adverse event of special interest (AESI)

An adverse event of special interest (AESI) is an AE (serious or non-serious) of scientific and medical concern specific to the Sponsor's product or program, for which ongoing monitoring and rapid communication by the Investigator to the Sponsor may be appropriate. Such events may require further investigation in order to characterize and understand them. Adverse events of special interest may be added or removed during a study by protocol amendment. For Synvisc-One, the following events will be collected as AESI:

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

10.4.2 Serious adverse events waived from expedited regulatory reporting to health authorities

Not applicable.

10.4.3 General guidelines for reporting adverse events

- All AEs, regardless of seriousness or relationship to IMP/NIMP, spanning from the signature of the informed consent form until the end of the study as defined by the protocol for that patient, are to be recorded on the corresponding page(s) or screen(s) of the eCRF.
- When a safety event is categorized as a primary outcome, the event will be reported as an AE but will be waived from reporting to health authorities providing an agreement has been reached with them (see Section 10.4.2).
- Whenever possible, diagnosis or single syndrome should be reported instead of symptoms. The Investigator should specify the date of onset, intensity, action taken with respect to IMP, corrective treatment/therapy given, additional investigations performed, outcome, and his/her opinion as to whether there is a reasonable possibility that the AE was caused by the IMP. In studies that require the use of combined/multiple IMPs/NIMPs, Chief Medical Evaluators (CME) with input from other appropriate study team members must determine if the causal relationship will either be assessed for the combined product as a regimen or as distinct entities. Chief Medical Evaluators must communicate this decision to the study team for inclusion in the protocol and AE eCRF.
- The Investigator should take appropriate measures to follow all AEs until clinical recovery is complete and laboratory results have returned to normal, or until progression has been stabilized, or until death, in order to ensure the safety of the patients. This may imply that observations will continue beyond the last planned visit per protocol, and that additional investigations may be requested by the monitoring team up to as noticed by the Sponsor. Patients with a SAE should be followed until resolution, stabilization, or death.
- When treatment is prematurely discontinued, the patient's observations will continue until the end of the study as defined by the protocol for that patient.
- Laboratory and vital signs abnormalities are to be recorded as AEs only if:
  - Symptomatic and/or
  - Requiring either corrective treatment or consultation, and/or
  - Leading to IMP discontinuation or modification of dosing, and/or
  - Fulfilling a seriousness criterion, and/or
  - Defined as AESI.
- The following AEs may occur at the injection site following IA injection of Synvisc-One: pain, swelling, redness, itching, tenderness, warmth, bruising, bleeding and rash.

10.4.4 Adverse Device Effect (Expectedness)

Anticipated: An adverse device experience is considered anticipated if it is listed in the current product label, IB, or defined in the protocol for the investigational device.

Unanticipated: Any serious adverse effect on health or safety, or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including supplementary plan or application), or any other serious unanticipated problem associated with a device that relates to the rights, safety, or welfare, of patients. All reports of

death are unexpected, unless the possibility of a fatal outcome from the AE is stated in the IB, protocol, or labeling.

10.4.5 Evaluation of Adverse Events/Serious Adverse Events

10.4.5.1 Relationship to Study Treatment

Assessment of the association between the AE and study exposure is important for regulatory reporting. This assessment is to be made in blinded studies and also for known comparators. For each AE/SAE the Investigator determines whether there is a reasonable possibility that the AE may have been caused by the study treatment according to the categories below:

- Not Related: There is no suspicion of a causal relationship between exposure and the AE.
- Unlikely Related: There is no evidence for a causal relationship between exposure and the AE; however, such a relationship cannot be ruled out.
- Possibly Related: There is some evidence supporting the possibility of a causal relationship between exposure and the AE.
- Related: There is strong evidence that there is a causal relationship between exposure and the AE.

A relationship to the investigational product must be given for each AE/SAE recorded, even if there is only limited information at the time.

The Investigator may change his/her opinion of causality in light of follow-up information, amending the AE/SAE report accordingly.

10.4.5.2 Grading of Adverse Event Scoring

Note that this is not the same as "seriousness," which is defined in Section 10.4.1.2. Seriousness serves as a guide for defining regulatory reporting obligations.

The Investigator will assess the severity of all AEs/SAEs as Mild, Moderate, or Severe, based on the following definitions (developed from Clinical Data Interchange Standards Consortium CDISC Study Data Tabulation Model standard terminology v3.1.1).

Definitions:

Mild: A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.

Moderate: A type of AE that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort, but poses no significant or permanent risk of harm to the research participant.

Severe: A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

10.4.5.3 Outcome

Outcome describes the status of the AE. The Investigator will provide information regarding the patient outcome of each AE.

Definitions for possible results of an AE outcome:

- Fatal: The termination of life as a result of an AE.
- Not recovered/not resolved: The patient has not recuperated or the AE has not improved.
- Recovering/resolving: The patient is recuperating or the AE is improving.
- Recovered/resolved: The patient has recuperated or the AE has resolved.
- Recovered with sequelae/resolved with sequelae: The AE has resolved, but the patient has been left with symptoms or pathology.
- Unknown: Not known, not observed, not recorded, or refused.

10.4.6 Instructions for reporting serious adverse events

In the case of occurrence of a SAE, the Investigator must immediately:

- ENTER (within 24 hours) the information related to the SAE in the appropriate screens of the eCRF; the system will automatically send a notification to the monitoring team after approval of the Investigator within the eCRF or after a standard delay.
- SEND (preferably by fax or e-mail) a photocopy of all examinations carried out and the dates on which these examinations were performed, to the representative of the monitoring team whose name, fax number, and email address appear on the clinical trial protocol. Care should be taken to ensure that the patient's identity is protected and the patient's identifiers in the clinical trial are properly mentioned on any copy of a source document provided to the Sponsor. For laboratory results, include the laboratory normal ranges.
- All SAEs that occur from signing the ICF through the last study evaluation must be reported to the Sponsor within 24 hours of the Investigator’s first knowledge of the event regardless of relationship to study procedures or treatment. The Investigator is requested to supply detailed information regarding the event at the time of the initial report.
- All expedited safety data should be transmitted to Global Pharmacovigilance & Epidemiology (GPE) within 1 working day of receipt from the Investigator or identification by the Monitoring Team. In case safety information is received from sites during a weekend or holiday or the office is closed for more than 2 consecutive days, it will be transmitted by the Clinical Safety Officer to GPE immediately but in a maximum of 3 calendar days.
- All further data updates should be recorded in the eCRF as appropriate, and further documentation as well as additional information (for laboratory data, concomitant medications, patient status and etc.) should be sent (by fax or e-mail) to the monitoring team within 24 hours of knowledge. In addition, every effort should be made to further document any SAE that is fatal or life threatening within a week (7 days) of the initial notification.

A back-up plan (using a paper CRF process) is available and should be used when the eCRF system does not work. If there is a malfunction with eCRF SAE reporting system, in order to maintain compliance with regulatory requirements, SAE reports can be submitted by fax or email to the following local contact˜

Fax: [redacted]

E-mail: [redacted]

Any SAE brought to the attention of the Investigator at any time after the end of the study for the patient and considered by him/her to be caused by the IMP with a reasonable possibility, should be reported to the monitoring team.

For patients who prematurely discontinue study treatment but who are not withdrawn from the study, AEs will continue to be recorded until the patient completes the study.

If, at any time after the patient has completed participation in the study the Investigator or study staff becomes aware of a SAE that they believe is possibly related or related to the investigational product then the event and any known details should be reported promptly to the Sponsor.

10.4.7 Guidelines for reporting adverse events of special interest

The needs for specific monitoring, documentation, and management of AESIs are described in this section.

Adverse event of special interest will be collected after the patient signed the written consent form until completion of study.

For AESIs, the Sponsor will be informed immediately (ie, within 24 hours), as per the SAE notification instructions described in Section 10.4.6, even if not fulfilling a seriousness criterion, using the corresponding pages in the eCRF.

- Anaphylaxis
- Foreign Body Reaction
- Pseudosepsis
- SAIR
- Joint infection
- Injection site allergy
- Drug allergy
- Pregnancy
  - Pregnancy occurring in a female patient included in the clinical trial. Pregnancy will be recorded as an AESI with immediate notification in all cases. It will be qualified as a SAE only if it fulfills the SAE criteria.
  - Follow-up of the pregnancy is mandatory until the outcome has been determined.

- Female patients will be instructed to notify the Investigator immediately if they discover they are pregnant. Male patients will be instructed to notify the Investigator immediately if they discover that their sexual partner is pregnant.
- If the Investigator learns of a report of pregnancy at any time after signing the informed consent, the Investigator should follow the instructions to contact Sponsor within 24 hours; however, the Investigator will be asked to complete the Pregnancy forms rather than SAE forms, because healthy pregnancy is not an AE. The patient will be followed until the outcome of the pregnancy is known (eg, live birth or stillbirth).
- If not otherwise established, the Investigator will inform the patient that the Sponsor is required to gather information regarding the course and outcome of the pregnancy after exposure to a study product. The progress of the pregnancy must be followed until the outcome of the pregnancy is known (ie, delivery, elective termination, or spontaneous abortion). If the pregnancy results in the birth of a child, additional follow-up information may be requested.
- The Investigator will be asked to obtain follow-up information no later than 2 months after the gestational period to obtain maternal/fetal/neonatal outcome and any other relevant information.
- Follow-up information may be requested at additional timepoints. All study related visits involving a known pregnancy should include pregnancy status assessment until pregnancy outcome is known.
- Please note that pregnancy in and of itself is not an AE or a SAE. Pregnancy should not be entered into the eCRF as an AE unless the Investigator suspects an interaction between the study treatment and the contraceptive method. Additionally all information received will be assessed for any AEs and SAEs and processed per study guidelines. If the patient is discontinued because of pregnancy, pregnancy will be documented as the reason for study discontinuation. Spontaneous abortions and stillbirths are reported as SAEs.

10.4.7.1 Follow up of adverse event of special interest

All AESI documented at a previous visit/contact that are designated as ongoing will be reviewed by the Investigator at subsequent visits. The Investigator will provide follow-up information for any AESI to the Sponsor, as soon as it is available. The Sponsor or regulatory authorities may request additional information regarding an AESI. Should an event which has been reported as an AESI (ie, non-serious) meet serious criteria at any point, it must be reported as a SAE. Adverse events of special interest will be followed until resolution, the condition stabilizes, or the Investigator and Sponsor agree that follow up is no longer necessary. Rules for AESI follow up apply to all patients, including those withdrawn prematurely to the extent allowed by the patient's consent. The Investigator will ensure that follow up includes further investigations consistent with appropriate for medical management and patient consent to elucidate the nature and/or causality of the AESI.

10.4.8 Product handling and complaints reporting

Investigators will promptly notify a Sponsor representative of any complaint concerning the clinical study material. A complaint for a clinical product is defined as the following: dissatisfaction regarding the identity, quality, durability, reliability, or performance of the product.

10.4.9 Guidelines for management of specific laboratory abnormalities

Decision trees for the management of certain laboratory abnormalities by Sanofi are provided in Appendix A. The following laboratory abnormalities should be monitored, documented, and managed according to the related flow chart in protocol appendices, if laboratory tests were performed for any AE, SAE, AESI or TEAE.

- Neutropenia
- Thrombocytopenia
- Acute renal insufficiency
- Suspicion of rhabdomyolysis

10.5 OBLIGATIONS OF THE SPONSOR

During the course of the study, the Sponsor will report in an expedited manner:

- All SAEs that is both unexpected and at least reasonably related to the IMP (SUSAR), to the health authorities, IECs/IRBs as appropriate and to the Investigators.
- All SAEs that is expected and at least reasonably related to the IMPs to the health authorities, according to local regulations.

In this study, some AEs are considered related to the underlying condition and thus will not be considered unexpected (please refer to the IB).

Any other AE not listed as an expected event in the IB or in this protocol will be considered unexpected.

For safety reason, the treatment code will be unblinded for reporting to the health authorities of any suspected unexpected serious adverse reaction (SUSAR), ie, any SAE that is both unexpected (per the IB) and reasonably associated with the use of the IMP according to either the judgment of the Investigator and/or the Sponsor.

The Sponsor will report all safety observations made during the conduct of the trial in the clinical study report (CSR).

10.6 SAFETY INSTRUCTIONS

No specific safety instructions required in relation to the clinical trial.

10.7 ADVERSE EVENTS MONITORING

All events will be managed and reported in compliance with all applicable regulations, and included in the final CSR.

11 STATISTICAL CONSIDERATIONS

The material of Section 11 of the clinical trial protocol is the basis for the Statistical Analysis Plan (SAP) for the study. This plan may be revised during the study to accommodate clinical trial protocol amendments and to make changes to adapt to unexpected issues in study execution and data that affect planned analyses. These revisions will be based on blinded review of the study and data, and a final plan will be issued at the latest 6 to 8 weeks before final database lock.

11.1 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.

11.2 DISPOSITION OF PATIENTS

The total number of patients for each of the following categories will be presented in the CSR.

- Screened patients are defined as any patient who met the inclusion criteria and signed the informed consent.
- Randomized patients consist of all patients with a treatment kit number allocated and recorded in IVRS/IWRS database, and regardless of whether the treatment kit was used or not.
- The safety population (as defined in Section 11.3.2)
- The mITT population (as defined in Section 11.3.1.1)
- Patients who discontinued from the study, and the reasons for study discontinuation

11.3 ANALYSIS POPULATIONS

11.3.1 Efficacy populations

11.3.1.1 Modified intent-to-treat population

Modified intent-to-treat population: mITT population contains all randomized and treated patients who have at least a baseline measurement of WOMAC A1, as randomized and treated patients who have at least a baseline measurement.

For any patient randomized more than once, only the data associated with the first randomization will be used in any analysis population.

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

11.3.2 Safety population

All-Treated (AT) population: defined as randomized population who did actually receive 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, but their safety data will be presented separately.
- Randomized patients for whom it is unclear whether they took the study medication will be included in the safety population as randomized.
- For any patient randomized more than once, the safety experience associated with any later randomization will be assessed separately

For any patient randomized more than once, 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.

11.3.3 Other analysis population

None.

11.4 STATISTICAL METHODS

Continuous data will be summarized for each treatment group using the number of observations available (N), means, SD, minimums, medians, and maximums.

Categorical data will be summarized for each treatment group using counts and percentages. Missing data will not be categorized in the summaries.

In general, descriptive statistics of quantitative efficacy and safety parameters (result and change from baseline) by visit will be provided on observed cases (OC), ie, the inclusion of only patients having non-missing assessments at a specific visit.

11.4.1 Extent of study treatment exposure and compliance

Study treatment exposure will be listed by actual treatment received within the safety population.

11.4.1.1 Extent of investigational medicinal product exposure

As there is only one immediate injection of study drug in this study, duration of IMP exposure will not be defined. Compliance

No compliance analysis will be done for this study.

11.4.2 Analyses of efficacy endpoints

11.4.2.1 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 ANCOVA model will include terms for treatment, site, visit and visit-by-treatment interaction, as well as the baseline WOMAC A1 score as a covariate.

For the primary efficacy analysis, the baseline is defined as the last available value prior to the injection of IMP after or on randomization.

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.

In addition, subgroup analysis of primary endpoint could be performed for age (<=60/ >60) or other baseline characteristics using the same approach as above and will be considered as exploratory.

The statistical analysis plan will be finalized and submitted to regulatory authorities prior to database lock and analysis.

11.4.2.2 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 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 secondary efficacy analysis, the baseline is defined as the last available value prior to the injection of IMP after or on the randomization day, same as the primary efficacy analysis.

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.

11.4.2.3 Multiplicity considerations

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 Procedure (18) 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 for synv
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

Statistical comparisons of tertiary endpoints will be presented with unadjusted p-values and considered exploratory.

11.4.3 Analyses of safety data

The descriptive summaries of AEs and vital signs will be provided by treatment group for the AT population. Further details will be presented in the SAP.

All safety analyses will be performed on the safety population, as defined in Section 11.3.2. The safety analysis will be based on the reported AEs and other safety information (vital signs).

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

The observation period will be divided into two segments:

- 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 for safety variables is defined as the time from the injection of IMP up to week 26 follow up visit.

The following definitions will be applied to laboratory parameters and vital signs.

- 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 one PCSA during the on-treatment period, taking into account all evaluations performed during the on-treatment period, including non-scheduled or repeated evaluations. The number of all such patients will be the numerator for the on-treatment PCSA percentage.

Thresholds for PCSA in laboratory parameters and vital signs will be those defined by the Sponsor's pharmacovigilance department and in effect at the time of the database lock. Potentially clinically significant abnormality criteria for parameters not cited in the protocol as safety parameters will not be analyzed.

11.4.3.1 Analysis of Adverse Events

The AE will be divided as follows:

- Pre-treatment AEs are defined as AEs that developed or worsened or became serious during the pre-treatment period.

- Treatment-emergent AEs (TEAEs) are defined as AEs that developed or worsened (according to the Investigator's opinion) or became serious during the on-treatment period.

The focus of AE reporting in the CSR will be on TEAEs.

All adverse events

Adverse event incidence tables will present by system-organ-class (SOC) (sorted by internationally agreed order), high level group term (HLGT), high level term (HLT),preferred term (PT) and low level term (LLT) sorted in alphabetical order for each treatment group, the number (n) and percentage (%) of patients experiencing an AE. 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.

Each AE will be coded to a LLT, PT, HLGT, HLT, and associated SOC according to the MedDRA dictionary using the most current version before the database lock.

Summaries of all TEAEs in each treatment group will include the following:

- The overview of AEs, summarizing number (%) of patients with any
  - TEAE
  - serious TEAE
  - AESI
  - TEAE leading to death
  - TEAE leading to permanent study discontinuation
- The number (n) and percentage (%) of patients with at least one TEAE by SOC, HLGT, HLT and PT
- Summary of TEAEs by intensity (severe, moderate, mild), presented by SOC and PT
- Summary of TEAEs by relationship to IMP, presented by SOC and PT

A detailed listing of TEAE summaries will be provided in the SAP.

Adverse events of special interest

AESIs listed in Section 10.4.1.3 will be summarized and presented as number and percent of patients in each treatment group if appropriate.

Death and serious adverse events

SAEs will be summarized and presented as number and percent of patients in each treatment group if appropriate.

The following deaths summaries will be generated:

- Number (%) of patients who died by study period (TEAE, on-study) and reasons for death summarized on the safety population by treatment received
- Death in non-randomized patients or randomized and not treated patients

- All AEs leading to death (death as an outcome on the AE eCRF page as reported by the Investigator), by primary SOC, HLGT, HLT and PT, showing number (%) of patients sorted by internationally agreed order of SOC and alphabetic order of HLGT, HLT, and PT
- TEAE leading to death (death as an outcome on the AE eCRF page as reported by the Investigator) by primary SOC, HLGT, HLT and PT showing number (%) of patients sorted by internationally agreed order of SOC and alphabetic order of HLGT, HLT, and PT.

Adverse events leading to study discontinuation

TEAEs leading to permanent study discontinuation will be summarized and presented as number and percent of patients in each treatment group.

11.4.3.2 Analysis of laboratory variables

Not applicable.

11.4.3.3 Analysis of vital sign variables

Patients with PCSA for each vital sign variable will be identified. Number and percentage of patients with PCSA at any post-randomization time point during the on-treatment period will be summarized for each vital sign parameter within each treatment group. The summaries will include patients in the safety population who have at least one parameter to be analyzed during the on-treatment period. When the PCSA definition involves the change from the baseline value, patients need also to have a baseline value to be included in the summaries. The baseline value is defined as the last available measure before the injection of IMP.

Descriptive statistics will also be used to summarize the results and changes from baseline for each treatment group.

Other tabular and graphical methods may be used to present the results for parameters of interest.

Listings will be provided with flags indicating the PCSA values.

11.4.4 Analyses of pharmacokinetic and pharmacodynamic variables

Not applicable.

11.4.5 Analyses of quality of life/health economics variables

Not applicable.

11.5 INTERIM ANALYSIS

No interim analysis is planned for this study.

12 ETHICAL AND REGULATORY STANDARDS

12.1 ETHICAL PRINCIPLES

This clinical trial will be conducted in accordance with the principles laid down by the 18th World Medical Assembly (Helsinki, 1964) and all applicable amendments laid down by the World Medical Assemblies, and the ICH guidelines for good clinical practice (GCP).

In compliance with Sanofi public disclosure commitments, this clinical trial will be recorded in the public registry website clinicaltrials.gov before the enrollment of the first patient. The registry will contain basic information about the trial sufficient to inform interested patients (and their healthcare practitioners) how to enroll in the trial.

12.2 LAWS AND REGULATIONS

This clinical trial will be conducted in compliance with all international guidelines, and national laws and regulations of the country(ies) in which the clinical trial is performed, as well as any applicable guidelines.

12.3 INFORMED CONSENT

The Investigator (according to applicable regulatory requirements), or a person designated by the Investigator, and under the Investigator's responsibility, should fully inform the patient of all pertinent aspects of the clinical trial including the written information giving approval/favorable opinion by the Ethics Committee (IRB/IEC). All participants should be informed to the fullest extent possible about the study, in language and terms they are able to understand.

Prior to a patient’s participation in the clinical trial, the written informed consent form should be signed, name filled in and personally dated by the patient or by the patient’s legally acceptable representative, and by the person who conducted the informed consent discussion. A copy of the signed and dated written informed consent form will be provided to the patient.

The informed consent form used by the Investigator for obtaining the patient's informed consent must be reviewed and approved by the Sponsor prior to submission to the appropriate Ethics Committee (IRB/IEC) for approval/favorable opinion.

12.4 INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE (IRB/IEC)

As required by local regulation, the Investigator or the Sponsor must submit this clinical trial protocol to the appropriate Ethics Committee (IRB/IEC), and is required to forward to the respective other party a copy of the written and dated approval/favorable opinion signed by the Chairman with Ethics Committee (IRB/IEC) composition.

The clinical trial (study number, clinical trial protocol title and version number), the documents reviewed (clinical trial protocol, informed consent form, IB, Investigator's curriculum vitae [CV] and etc.) and the date of the review should be clearly stated on the written (IRB/IEC) approval/favorable opinion.

Investigational medicinal product will not be released at the study site and the Investigator will not start the study before the written and dated approval/favorable opinion is received by the Investigator and the Sponsor.

During the clinical trial, any amendment or modification to the clinical trial protocol should be submitted to the Ethics Committee (IRB/IEC) before implementation, unless the change is necessary to eliminate an immediate hazard to the patients, in which case the IRB/IEC should be informed as soon as possible. It should also be informed of any event likely to affect the safety of patients or the continued conduct of the clinical trial, in particular any change in safety. All updates to the IB will be sent to the Ethics Committee (IRB/IEC).

A progress report is sent to the Ethics Committee (IRB/IEC) at least annually and a summary of the clinical trial's outcome at the end of the clinical trial.

13 STUDY MONITORING

13.1 RESPONSIBILITIES OF THE INVESTIGATOR(S)

The Investigator(s) and delegated Investigator staff undertake(s) to perform the clinical trial in accordance with this clinical trial protocol, ICH guidelines for GCP and the applicable regulatory requirements.

The Investigator is required to ensure compliance with all procedures required by the clinical trial protocol and with all study procedures provided by the Sponsor (including security rules). The Investigator agrees to provide reliable data and all information requested by the clinical trial protocol (with the help of the eCRF, Discrepancy Resolution Form [DRF] or other appropriate instrument) in an accurate and legible manner according to the instructions provided and to ensure direct access to source documents by Sponsor representatives.

If any circuit includes transfer of data particular attention should be paid to the confidentiality of the patient's data to be transferred.

The Investigator may appoint such other individuals as he/she may deem appropriate as Sub-investigators to assist in the conduct of the clinical trial in accordance with the clinical trial protocol. All Sub-investigators shall be appointed and listed in a timely manner. The Sub-investigators will be supervised by and work under the responsibility of the Investigator. The Investigator will provide them with a copy of the clinical trial protocol and all necessary information.

13.2 RESPONSIBILITIES OF THE SPONSOR

The Sponsor of this clinical trial is responsible to health authorities for taking all reasonable steps to ensure the proper conduct of the clinical trial protocol as regards ethics, clinical trial protocol compliance, and integrity and validity of the data recorded on the eCRF. Thus, the main duty of the monitoring team is to help the Investigator and the Sponsor maintain a high level of ethical, scientific, technical and regulatory quality in all aspects of the clinical trial.

At regular intervals during the clinical trial, the site will be contacted, through monitoring visits, letters or telephone calls, by a representative of the monitoring team to review study progress, Investigator and patient compliance with clinical trial protocol requirements and any emergent problems. These monitoring visits will include but not be limited to review of the following aspects: patient informed consent, patient recruitment and follow-up, SAE documentation and reporting, AE documentation, IMP allocation, patient compliance with the IMP regimen, IMP accountability, concomitant therapy use and quality of data.

13.3 SOURCE DOCUMENT REQUIREMENTS

According to the ICH guidelines for GCP, the monitoring team must check the eCRF entries against the source documents, except for the pre-identified source data directly recorded in the eCRF. The informed consent form will include a statement by which the patient allows the Sponsor's duly authorized personnel, the Ethics Committee (IRB/IEC), and the regulatory authorities to have direct access to original medical records which support the data on the eCRF (eg, patient's medical file, appointment books, original laboratory records). These personnel, bound by professional secrecy, must maintain the confidentiality of all personal identity or personal medical information (according to confidentiality and personal data protection rules).

13.4 USE AND COMPLETION OF ELECTRONIC CASE REPORT FORMS AND ADDITIONAL REQUEST

It is the responsibility of the Investigator to maintain adequate and accurate eCRFs designed by the Sponsor to record (according to Sponsor instructions) all observations and other data pertinent to the clinical investigation in a timely manner. All eCRFs should be completed in their entirety in a neat, legible manner to ensure accurate interpretation of data.

Should a correction be made, the corrected information will be entered in the eCRF overwriting the initial information. An audit trail allows identifying the modification.

Data are available within the system to the Sponsor as soon as they are entered in the eCRF.

The computerized handling of the data by the Sponsor when available in the eCRF may generate additional requests (DRF) to which the Investigator is obliged to respond by confirming or modifying the data questioned. The requests with their responses will be managed through the eCRF.

13.5 USE OF COMPUTERIZED SYSTEMS

Computerized systems used during the different steps of the study are:

- For data management activities, ORACLE
- For statistical activities, SAS
- For pharmacovigilance activities, AWARE
- For monitoring activities, IMPACT
- For medical writing activities, DOMASYS.

14 ADMINISTRATIVE EXPECTATIONS

14.1 CURRICULUM VITAE

A current copy of the CV describing the experience, qualification and training of each Investigator and Sub-investigator will be signed, dated and provided to the Sponsor prior to the beginning of the clinical trial.

14.2 RECORD RETENTION IN STUDY SITES

The Investigator must maintain confidential all study documentation, and take measures to prevent accidental or premature destruction of these documents.

The Investigator should retain the study documents at least 15 years after the completion or discontinuation of the clinical trial.

However, applicable regulatory requirements should be taken into account in the event that a longer period is required.

The Investigator must notify the Sponsor prior to destroying any study essential documents following the clinical trial completion or discontinuation.

If the Investigator's personal situation is such that archiving can no longer be ensured by him/her, the Investigator shall inform the Sponsor and the relevant records shall be transferred to a mutually agreed upon designee.

14.3 CONFIDENTIALITY

All information disclosed or provided by the Sponsor (or any company/institution acting on their behalf), or produced during the clinical trial, including, but not limited to, the clinical trial protocol, the eCRFs, the IB and the results obtained during the course of the clinical trial, is confidential, prior to the publication of results. The Investigator and any person under his/her authority agree to undertake to keep confidential and not to disclose the information to any third party without the prior written approval of the Sponsor.

However, the submission of this clinical trial protocol and other necessary documentation to the Ethics committee (IRB/IEC) is expressly permitted, the IRB/IEC members having the same obligation of confidentiality.

The Sub-investigators shall be bound by the same obligation as the Investigator. The Investigator shall inform the Sub-investigators of the confidential nature of the clinical trial.

The Investigator and the Sub-investigators shall use the information solely for the purposes of the clinical trial, to the exclusion of any use for their own or for a third party's account.

Furthermore, the Investigator and the Sponsor agree to adhere to the principles of personal data confidentiality in relation to the patients, Investigator and its collaborators involved in the study.

14.4 PROPERTY RIGHTS

All information, documents and IMP provided by the Sponsor or its designee are and remain the sole property of the Sponsor.

The Investigator shall not mention any information or the Product in any application for a patent or for any other intellectual property rights.

All the results, data, documents and inventions, which arise directly or indirectly from the clinical trial in any form, shall be the immediate and exclusive property of the Sponsor.

The Sponsor may use or exploit all the results at its own discretion, without any limitation to its property right (territory, field, continuance). The Sponsor shall be under no obligation to patent, develop, market or otherwise use the results of the clinical trial.

As the case may be, the Investigator and/or the Sub-investigators shall provide all assistance required by the Sponsor, at the Sponsor's expense, for obtaining and defending any patent, including signature of legal documents.

14.5 DATA PROTECTION

- The patient's personal data, which are included in the Sponsor database shall be treated in compliance with all applicable laws and regulations;
- When archiving or processing personal data pertaining to the Investigator and/or to the patients, the Sponsor shall take all appropriate measures to safeguard and prevent access to this data by any unauthorized third party.
- The Sponsor also collects specific data regarding Investigator as well as personal data from any person involved in the study which may be included in the Sponsor’s databases, shall be treated by both the Sponsor and the Investigator in compliance with all applicable laws and regulations.

Subject race or ethnicity eg, ‘Asian/Oriental, others’ be collected in this study because these data are required by health authorities (eg, on Asian population for the PMDA in Japan or SFDA in China).

The data collected in this study will only be used for the purpose(s) of the study and to document the evaluation of the benefit/risk ratio, efficacy and safety of the product(s). They may be further processed if they have been anonymized.

14.6 INSURANCE COMPENSATION

The Sponsor certifies that it has taken out a liability insurance policy covering all clinical trials under its sponsorship. This insurance policy is in accordance with local laws and requirements. The insurance of the Sponsor does not relieve the Investigator and the collaborators from maintaining their own liability insurance policy. An insurance certificate will be provided to the Ethics Committees (IECs/IRBs) or health authorities in countries requiring this document.

14.7 SPONSOR AUDITS AND INSPECTIONS BY REGULATORY AGENCIES

For the purpose of ensuring compliance with the clinical trial protocol, GCP and applicable regulatory requirements, the Investigator should permit auditing by or on the behalf of the Sponsor and inspection by regulatory authorities.

The Investigator agrees to allow the auditors/inspectors to have direct access to his/her study records for review, being understood that these personnel is bound by professional secrecy, and as such will not disclose any personal identity or personal medical information.

The Investigator will make every effort to help with the performance of the audits and inspections, giving access to all necessary facilities, data, and documents.

As soon as the Investigator is notified of a planned inspection by the authorities, he will inform the Sponsor and authorize the Sponsor to participate in this inspection.

The confidentiality of the data verified and the protection of the patients should be respected during these inspections.

Any result and information arising from the inspections by the regulatory authorities will be immediately communicated by the Investigator to the Sponsor.

The Investigator shall take appropriate measures required by the Sponsor to take corrective actions for all problems found during the audit or inspections.

14.8 PREMATURE DISCONTINUATION OF THE STUDY OR PREMATURE CLOSE-OUT OF A SITE

14.8.1 Decided by the Sponsor

Decided by the Sponsor in the following cases:

- If the information on the product leads to doubt as to the benefit/risk ratio;
- If the Investigator has received from the Sponsor all IMP, means and information necessary to perform the clinical trial and has not included any patient after a reasonable period of time mutually agreed upon;
- In the event of breach by the Investigator of a fundamental obligation under this agreement, including but not limited to breach of the clinical trial protocol, breach of the applicable laws and regulations or breach of the ICH guidelines on GCP;
- If the total number of patients are included earlier than expected;

In any case the Sponsor will notify the Investigator of its decision by written notice.

14.8.2 Decided by the Investigator

The Investigator must notify (30 days' prior notice) the Sponsor of his/her decision and give the reason in writing.

In all cases (decided by the Sponsor or by the Investigator), the appropriate Ethics Committee(s) (IRB/IEC) and Health Authorities should be informed according to applicable regulatory requirements.

14.9 CLINICAL TRIAL RESULTS

The Sponsor will be responsible for preparing a CSR and to provide a summary of study results to the Investigator.

14.10 PUBLICATIONS AND COMMUNICATIONS

The Investigator undertakes not to make any publication or release pertaining to the study and/or results of the study prior to the Sponsor's written consent, being understood that the Sponsor will not unreasonably withhold its approval.

As the study is being conducted at multiple sites, the Sponsor agrees that, consistent with scientific standards, first presentation or publication of the results of the study shall be made only as part of a publication of the results obtained by all sites performing the protocol. However, if no multicenter publication has occurred within twelve (12) months of the completion of this study at all sites, the Investigator shall have the right to publish or present independently the results of this study to the review procedure set forth herein. The Investigator shall provide the Sponsor with a copy of any such presentation or publication derived from the study for review and comment at least 30 days in advance of any presentation or submission for publication. In addition, if requested by the Sponsor, any presentation or submission for publication shall be delayed for a limited time, not to exceed 90 days, to allow for filing of a patent application or such other measures as the Sponsor deems appropriate to establish and preserve its proprietary rights.

The Investigator shall not use the name(s) of the Sponsor and/or its employees in advertising or promotional material or publication without the prior written consent of the Sponsor. The Sponsor shall not use the name(s) of the Investigator and/or the collaborators in advertising or promotional material or publication without having received his/her and/or their prior written consent(s).

The Sponsor has the right at any time to publish the results of the study.

15 CLINICAL TRIAL PROTOCOL AMENDMENTS

All appendices attached hereto and referred to herein are made part of this clinical trial protocol.

The Investigator should not implement any deviation from, or changes of the clinical trial protocol without agreement by the Sponsor and prior review and documented approval/favorable opinion from the IRB/IEC of an amendment, except where necessary to eliminate an immediate hazard(s) to clinical trial Patients, or when the change(s) involves only logistical or administrative aspects of the trial. Any change agreed upon will be recorded in writing, the written amendment will be signed by the Investigator and by the Sponsor and the signed amendment will be filed with this clinical trial protocol.

Any amendment to the clinical trial protocol requires written approval/favorable opinion by the Ethics Committee (IRB/IEC) prior to its implementation, unless there are overriding safety reasons.

In some instances, an amendment may require a change to the informed consent form. The Investigator must receive an IRB/IEC approval/favorable opinion concerning the revised informed consent form prior to implementation of the change and patient signature should be re-collected if necessary.

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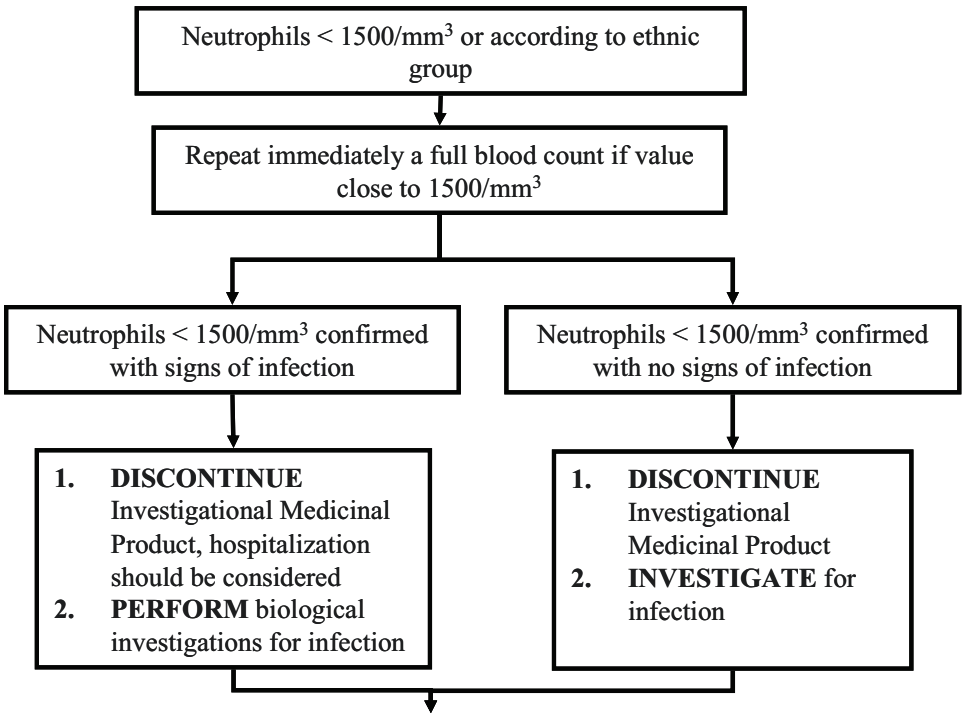
17 APPENDICES

Appendix A General Guidance for the follow-up of laboratory abnormalities by Sanofi

NEUTROPENIA



3. **INFORM** the local monitor
4. **INVESTIGATE** previous treatments particularly long-term, even a long time ago, exposure to toxic agents, e.g., benzene, X-rays, etc.
5. **PERFORM** and collect the following investigations (results):
   - RBC and platelet counts
   - Serology: EBV, (HIV), mumps, measles, rubella
6. **DECISION** for bone marrow aspiration: to be taken in specialized unit
7. **FREEZE** serum (5 mL x 2) on Day 1 (cessation of investigational medicinal product) and Day 5 (for further investigations)
8. **MONITOR** the leukocyte count 3 times per week for at least one week, then twice a month until it returns to normal

Note:

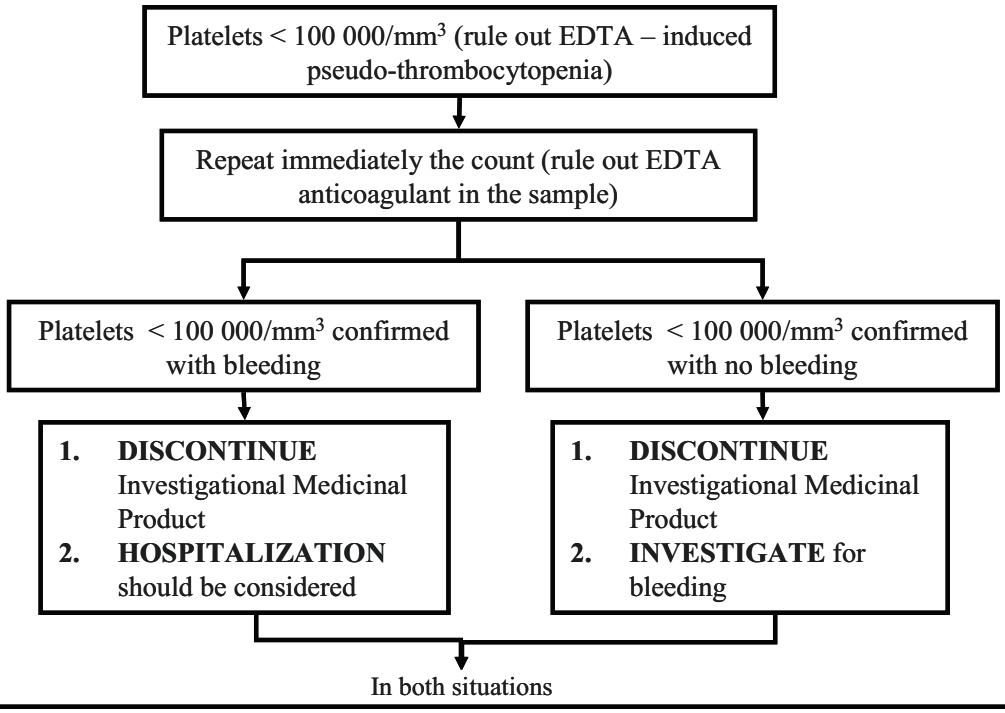
•The procedures described in the above flowchart are to be discussed with the patient only in case the event occurs. If applicable (according to local regulations), an additional consent (e.g., for HIV testing) will only be obtained in the case the event actually occurs.

•For individuals of African descent, the relevant value of concern is <1000/mm3

Neutropenia are to be recorded as AE only if they are :

- Symptomatic, and/or
- Requiring either corrective treatment or consultation, and/or
- Leading to IMP discontinuation or modification of dosing, and/or
- Fulfilling a seriousness criterion [in that case, the event (SAE) should be notified within 1 working day to the MT], and/or
- Defined as an Adverse Event of Special Interest (AESI) with immediate notification

THROMBOCYTOPENIA

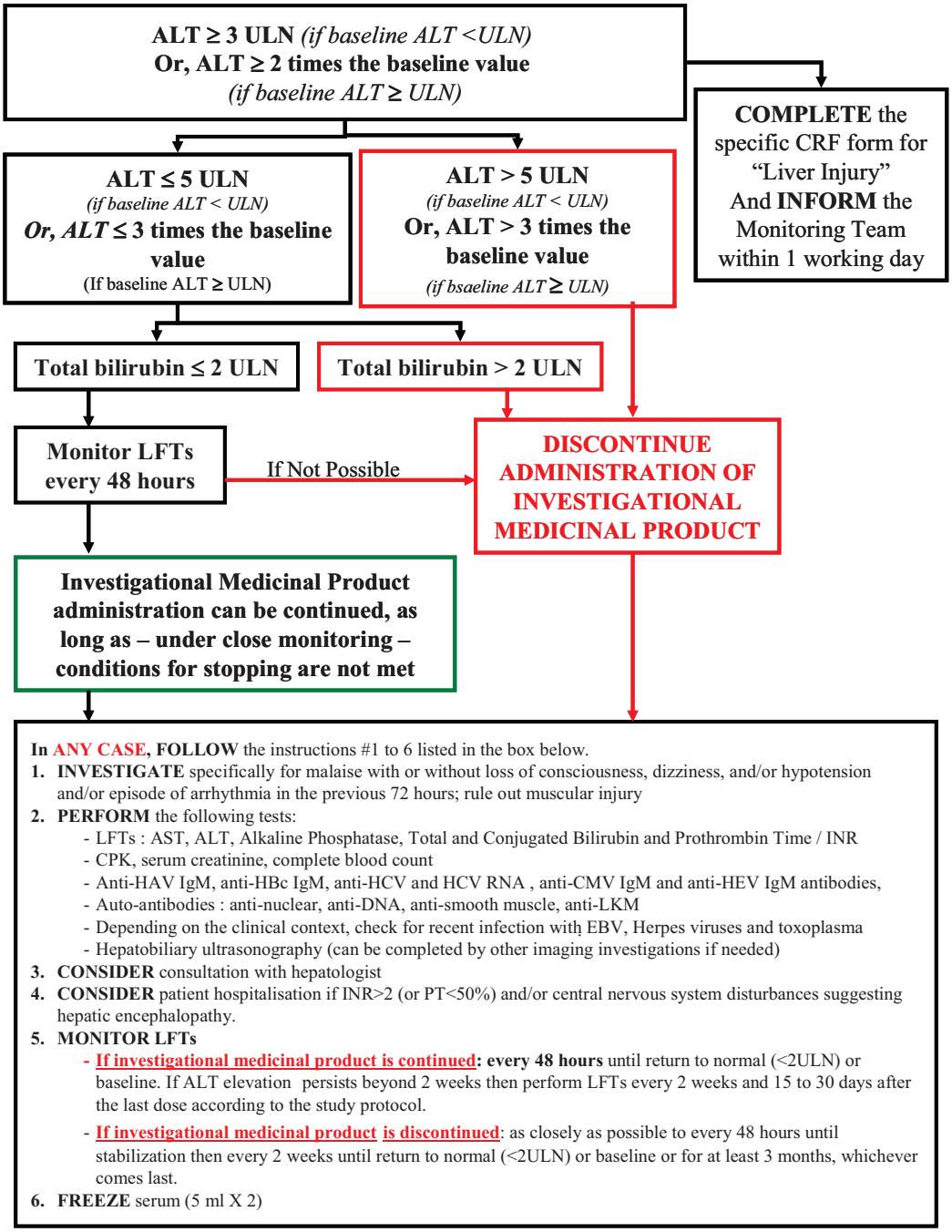


3. **INFORM** the local Monitor
4. **QUESTION** about last intake of quinine (drinks), alcoholism, heparin administration
5. **PERFORM** or collect the following investigations:
   - Complete blood count, schizocytes, creatinine
   - Bleeding time and coagulation test (fibrinogen, PT, aPTT), Fibrin Degradation Product
   - Viral serology: EBV, HIV, mumps, measles, rubella
6. **FREEZE** serum (5 mL x 2) on Day 1 (end of treatment) and Day 5 to test for drug-induced antiplatelets antibodies
7. **DECISION** for bone marrow aspiration: to be taken in specialized unit
   - On Day 1 in the case of associated anemia and/or leukopenia
   - On Day 8 if the Platelets remain < 50 000/mm^3
8. **MONITOR** the platelet count every day for at least one week and then regularly until it returns to normal

Note:
the procedures described in the above flowchart are to be discussed with the patient only in case the event occurs. If applicable (according to local regulations), an additional consent (e.g., for HIV testing) will only be obtained in the case the event actually occurs.

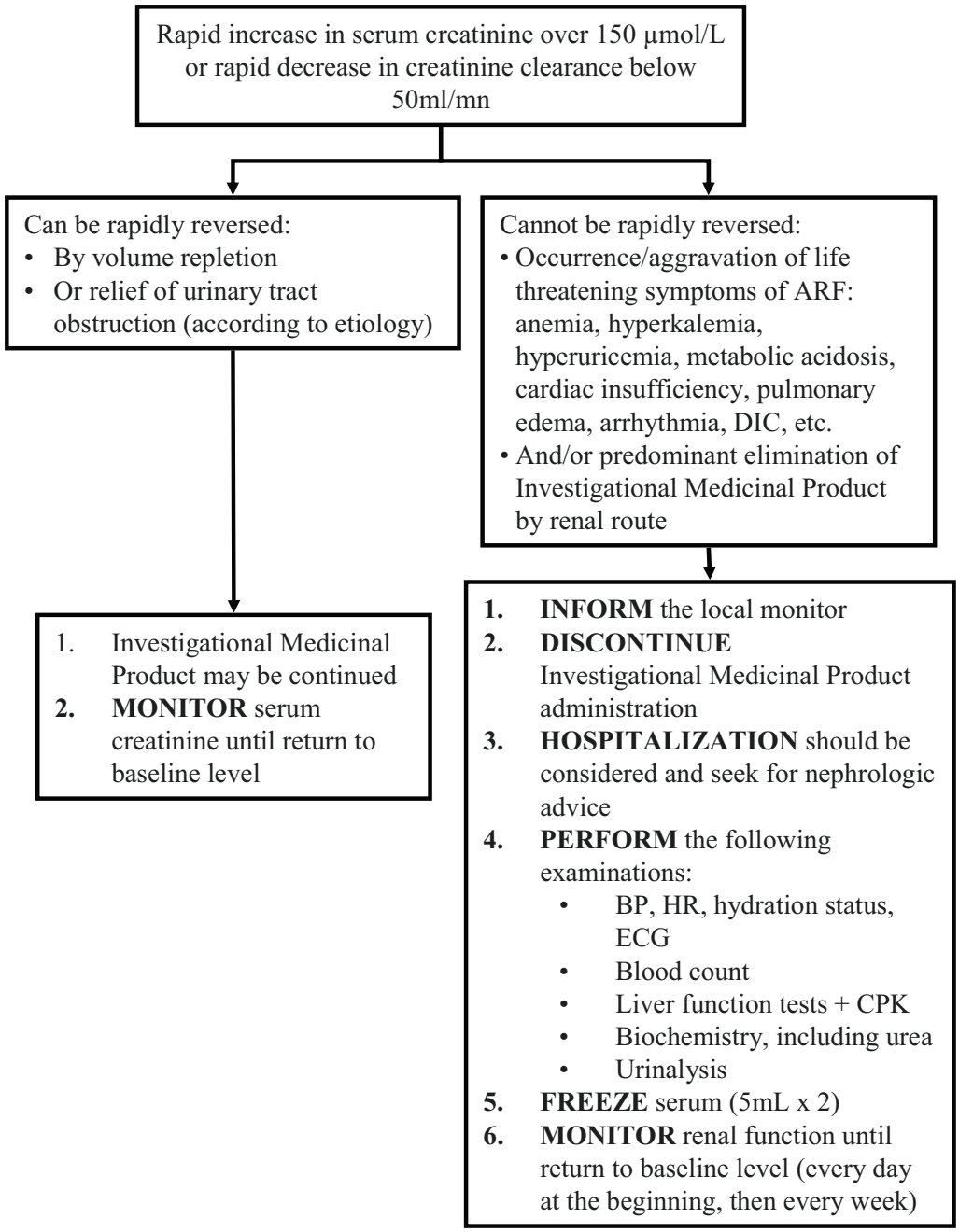
Thrombocytopenia are to be recorded as AE only if they are:
- Symptomatic, and/or
- Requiring either corrective treatment or consultation, and/or
- Leading to IMP discontinuation or modification of dosing, and/or
- Fulfilling a seriousness criterion [in that case, the event (SAE) should be notified within 1 working day to the MT], and/or
- Defined as an Adverse Event of Special Interest (AESI) with immediate notification

INCREASE IN ALT



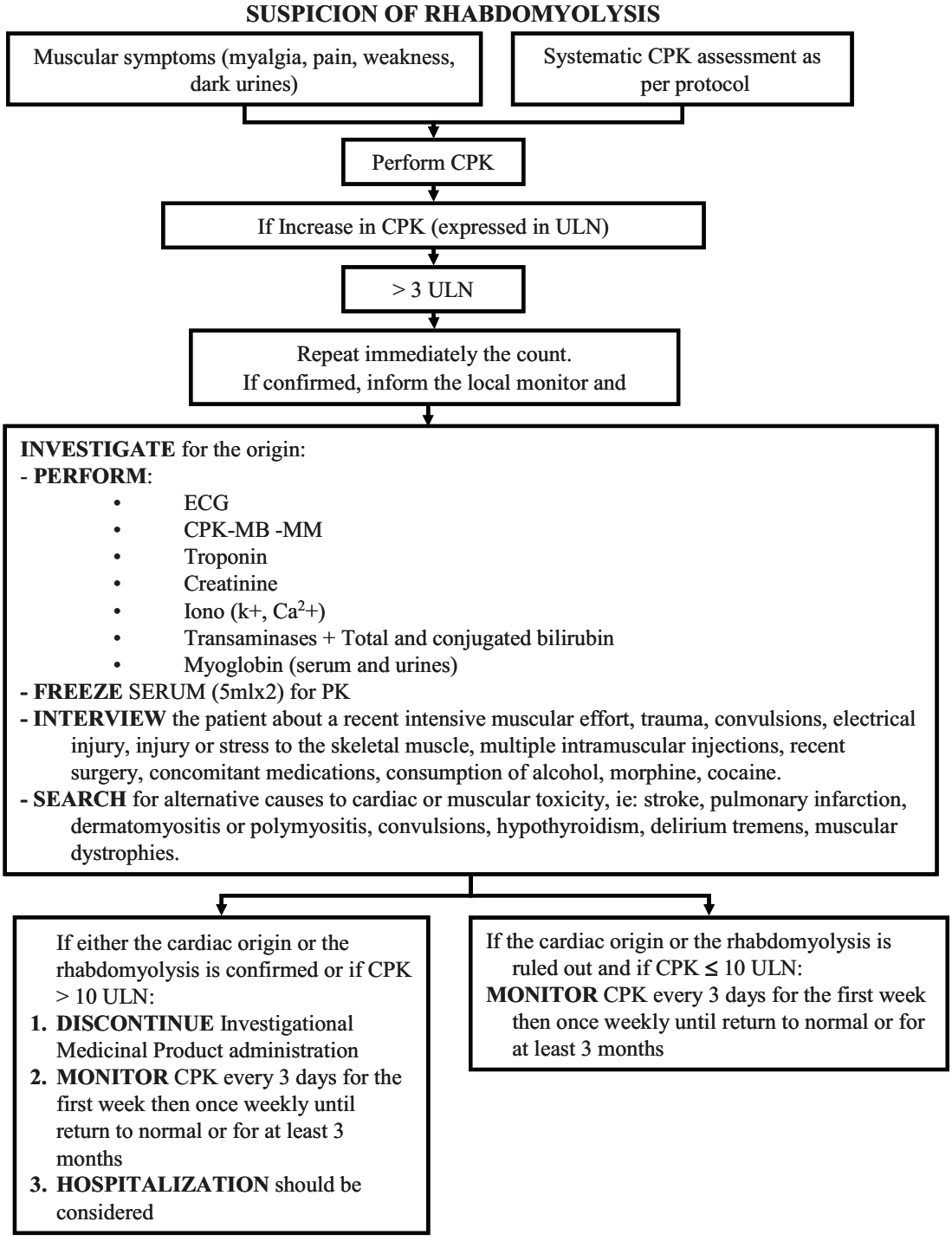
NOTE: IN ADDITION, AS SOON AS A SERIOUSNESS CRITERION IS MET, THE EVENT SHOULD BE NOTIFIED WITHIN 1 WORKING DAY TO THE MONITORING TEAM.

ACUTE RENAL FAILURE



Acute renal failure is to be recorded as AE only if it is :

- Symptomatic, and/or
- Requiring either corrective treatment or consultation, and/or
- Leading to IMP discontinuation or modification of dosing, and/or
- Fulfilling a seriousness criterion [in that case, the event (SAE) should be notified within 1 working day to the MT], and/or
- Defined as an Adverse Event of Special Interest (AESI) with immediate notification



Suspicion of rhabdomyolysis is to be recorded as AE only if it is:

- Symptomatic, and/or
- Requiring either corrective treatment or consultation, and/or
- Leading to IMP discontinuation or modification of dosing, and/or
- Fulfilling a seriousness criterion [in that case, the event (SAE) should be notified within 1 working day to the MT], and/or
- Defined as an Adverse Event of Special Interest (AESI) with immediate notification

Appendix B American College of Rheumatology Criteria for Classification of Idiopathic Osteoarthritis of the Knee

Appendix C Common Pain and OA Medications

Common pain and OA medications are summarised in below table.

Generic Name	Average Plasma Half-Life (hours)	Wash-Out (days)
Aceclofenac	3	1
Acetaminophen/paracetamol	2	1
Aspirin Enteric-coated Aspirin	Parent – 15 to 30 min	1
	Dose dependent	
	Low (300 to 600 mg) = 3	Low – 1
Choline Magnesium Trisalicylate	Dose dependent Low = 2 to 3	Low - 1
Choline Salicylate	Dose dependent Low = 2 to 3	Low - 1
Dexketoprofen	0.35 to 1.6	12 hours
Diclofenac Sodium	2	1
Fenoprofen Calcium	2.5 to 3	1
Ibuprofen	2	1
Indomethacin	4.5	1
Ketoprofen	1 to 4	1
Sodium Meclofenamate	2 to 3.3	1
Mefenamic Acid	3.5	1
Tiaprofenic Acid	1.5 to 2.5	12 hours
Tolmetin Sodium	2	1
Aspirin Enteric-coated Aspirin	Mid dose (after 1 g) = 5 to 6 High dose = 10 hours	Mid/High - 2
Celecoxib	11	2
Choline Magnesium Trisalicylate	Dose dependent High = 30	High - 6
Choline Salicylate	Dose dependent High = 30	High - 6
Difnisal	8 to 12	3
Etodolac	7	2
Etodolac ER	8	3
Fenbufen	10	3
Flurbiprofen	5 to 6	2
Ketoprofen SR	5.4	2
Ketorolac Tromethamine	2 to 8	2
Meloxicam	20	5
Nabumetone	24	5
Naproxen	12 to 15	3

Generic Name	Average Plasma Half-Life (hours)	Wash-Out (days)
Oxaprozin	40 to 50	9
Piroxicam	45 to 50	9
Rofecoxib	17	4
Salsalate	7 to 8 hours	2
Sulindac	8 Parent 17 Metabolite	4
Tenoxicam	70	17

Appendix D Questionnaire Description and Instructions

Subject questionnaires are to be completed by the subject and the answers to the questions on the questionnaires should come from the subjects directly, not from family, friends, or the study support personnel. The questionnaires should be given to subjects to complete in as quiet an area as possible. The subject questionnaires for a specific study visit should only be completed at that specific study visit. Therefore, if the subject refuses to complete any of the subject questionnaires at a particular visit, or the study site personnel inadvertently forget to administer any of the questionnaires at a particular visit, no attempt should be made at any subsequent visit to administer the missed questionnaires. The study site personnel should also not attempt to correct any omissions, errors, or discrepancies on questionnaires completed at previous study visits. A subject must not have access to previously completed questionnaires.

1. Screening Questionnaires

PainDETECT Questionnaire (PD-Q)

The painDETECT is a self-administered questionnaire designed to detect neuropathic pain components to differentiate nociceptive pain from neuropathic pain. Completion takes around 5 minutes and the recall period is current moment and the past 4 weeks[2].

Patient Health Questionnaire (PHQ-9)

The PHQ-9 is a self-administered questionnaire designed to screen, diagnose, monitor, and measure the severity of depression[3].

General Anxiety Disorder 7-item (GAD-7)

The GAD-7 is a self-administered 7-item questionnaire used as a screening tool to measure the severity of general anxiety disorder[4].

Insomnia Severity Index (ISI)

The ISI is a self-administered questionnaire designed to assess the nature, severity, and impact of insomnia and monitor treatment response in adults. It has seven questions. The seven answers are added up to get a total score[5].

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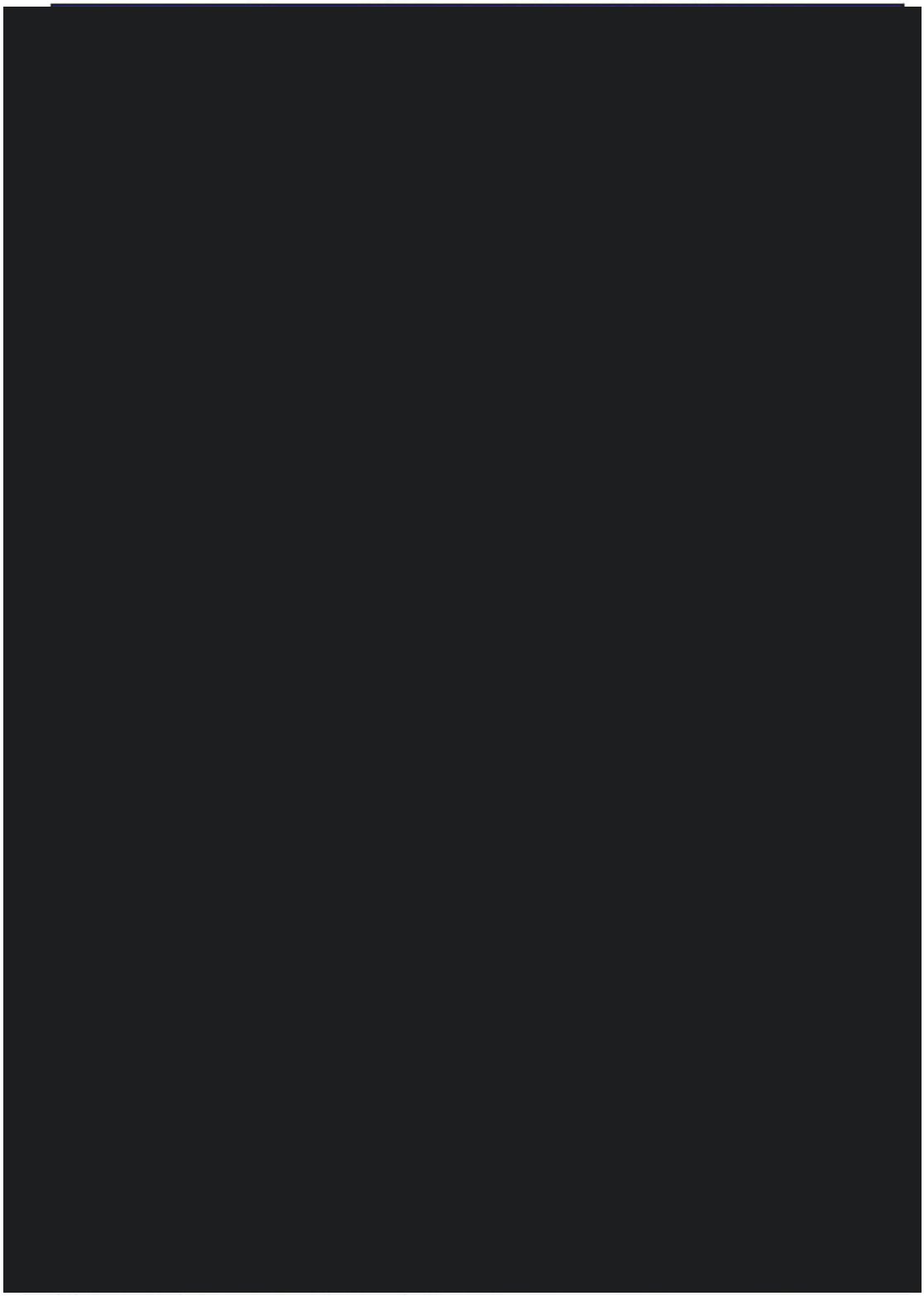
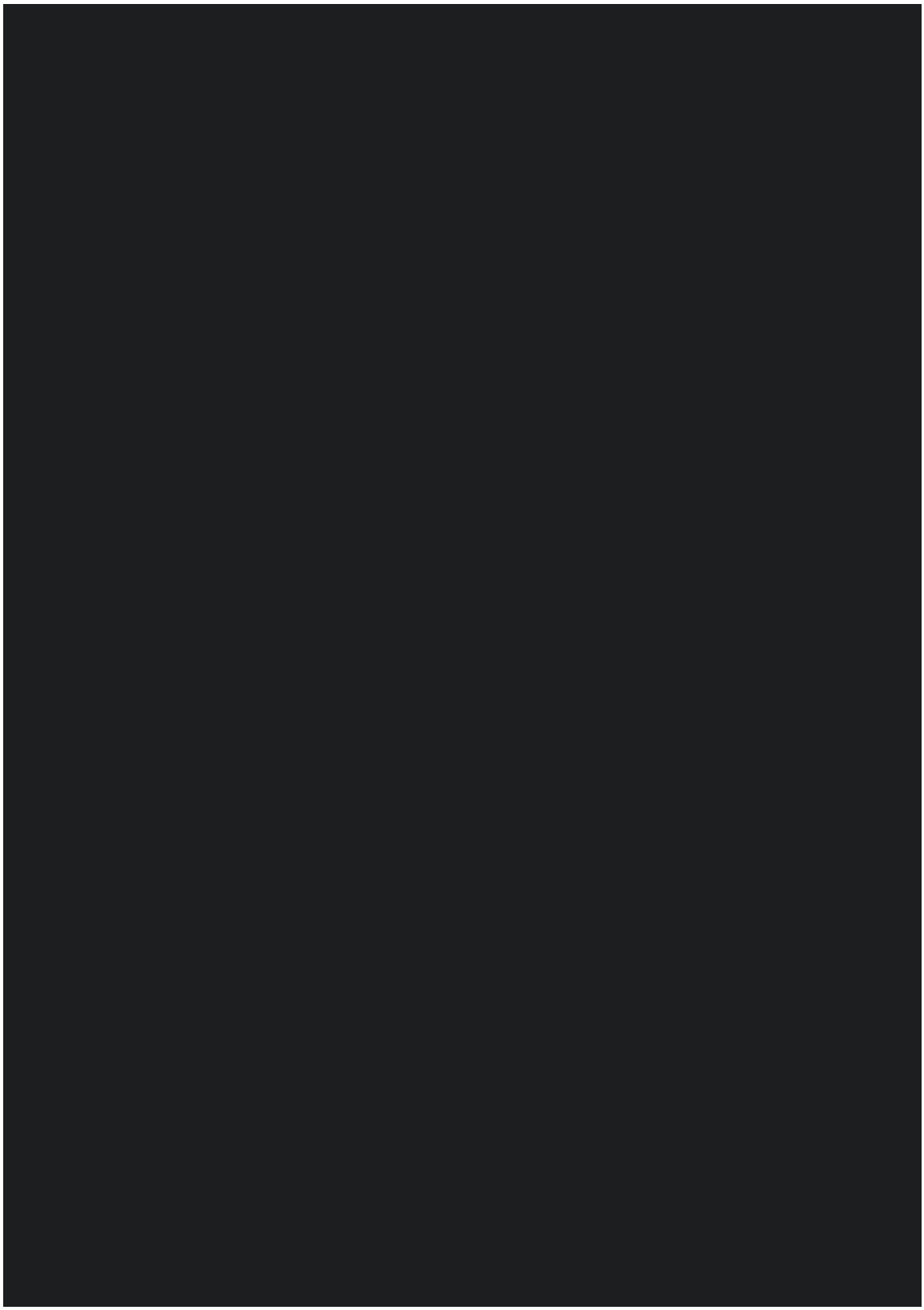
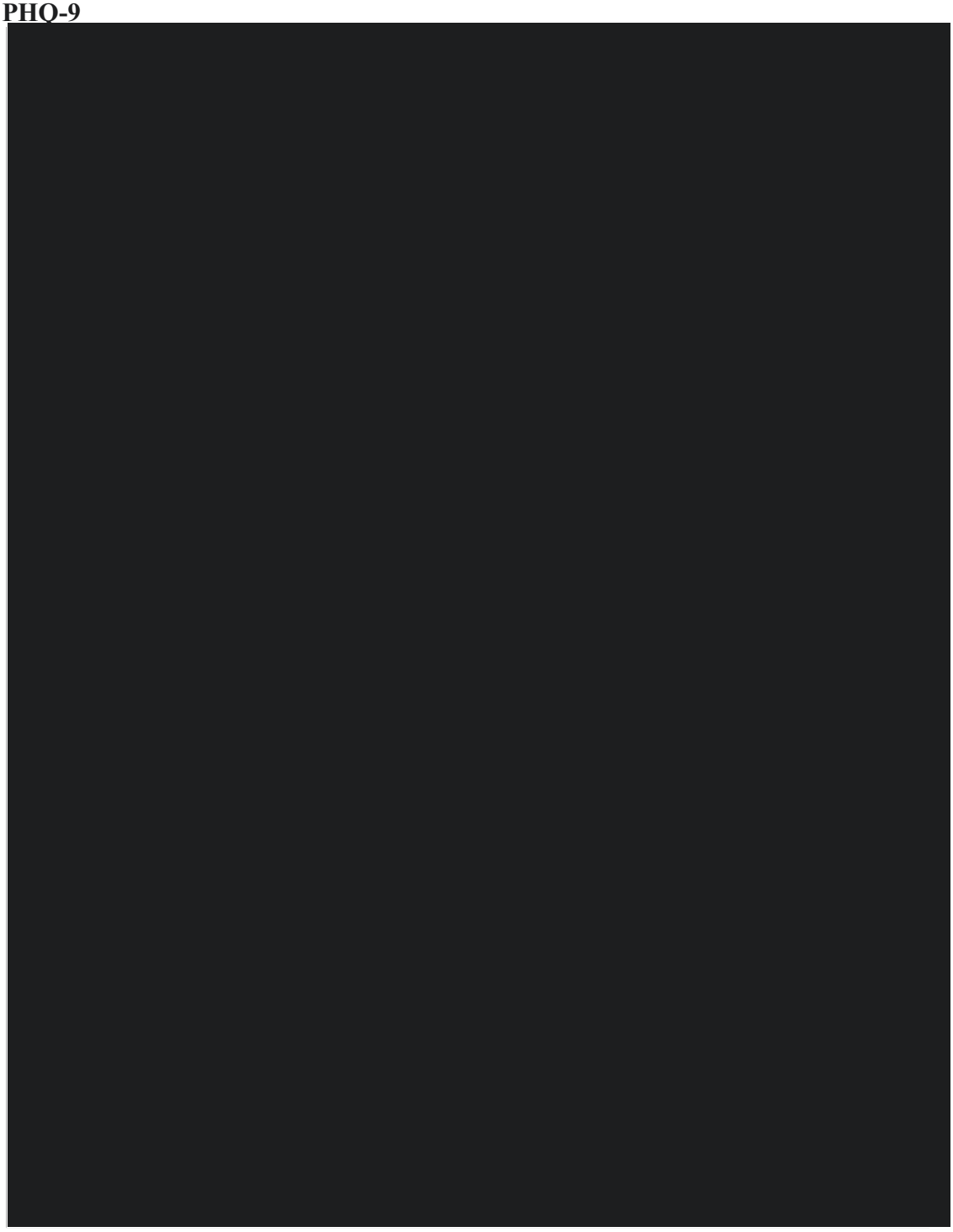
2. Sample questionnaires

PD-Q



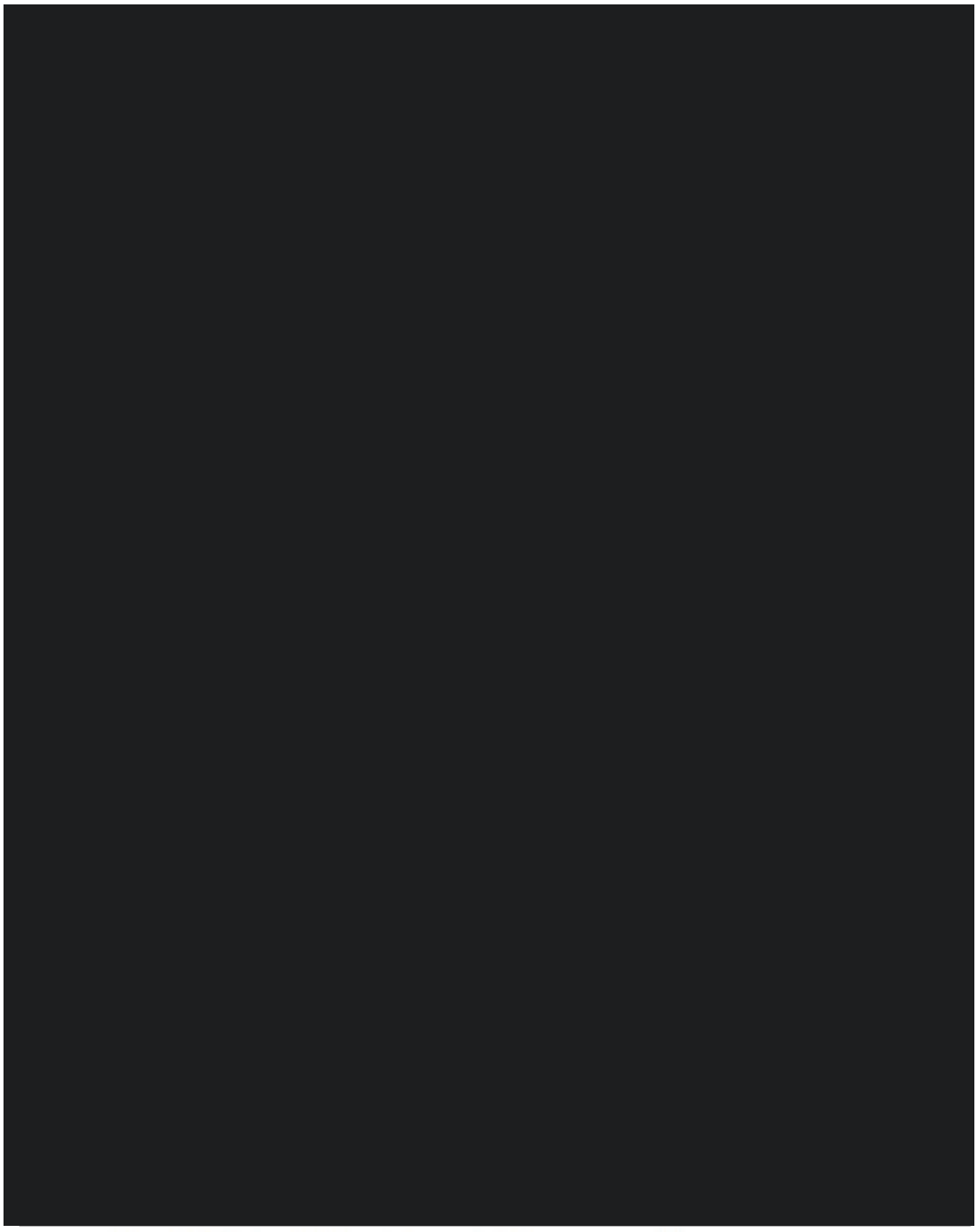


PHQ-9



GAD-7

ISI



Appendix E Sample Diary Questions

The following questions will be completed directly by the subjects on a daily basis using a paper diary. All data are to be recorded once daily, preferably approximately the same time in the evening. The paper diary will ask questions regarding daily pain and use of rescue medication (acetaminophen). The use of rescue medicine will be captured throughout the study; however, the daily pain will only be recorded 7 days prior to every visit.

Question 1: "How much pain have you had when walking on a flat surface during the last 24 hours?"

The subject needs to record a single whole number using an 11-point NRS ranging from 0 (no pain) to 10 (worst pain possible).

Question 2: In the last 24 hours, how many pills of acetaminophen or other rescue medicines did you take for your knee osteoarthritis pain?

The subject need to record the number of pills taken in whole numbers only (0, 1, 2, 3, etc.). Any portion of a pill taken will be recorded as 1 pill (eg, 1 ¼ or 1 ½ pills would be recorded as 2 pills). If none taken, he or she will record "0".

EFC12723 Amended Protocol 01 - China

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm)
[redacted]	Regulatory Approval	20-Mar-2017 10:42 GMT+0100
[redacted]	Clinical Approval	20-Mar-2017 11:12 GMT+0100
[redacted]	Clinical Approval	20-Mar-2017 14:13 GMT+0100