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NON-INTERVENTIONAL STUDY STATISTICAL ANALYSIS PLAN		

STATISTICAL ANALYSIS PLAN



Version V2

15/05/2025

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RWE & Data	
Version of SAP and date	V1 – 29/01/2025
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HISTORY OF VERSIONS

Version	Pages or sections concerned	Date	Nature ^(*)	Reasons for changes
1.0	All	29/01/2025	C	Creation of the document
2.0	All	15/05/2025	A	Updated after review of the results by the scientific committee

(*) C: Creation, M: Modification, A: Addition, D: Deletion

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APPROVAL OF THE STATISTICAL ANALYSIS PLAN

PROTOCOL TITLE	A Prospective Non-Interventional Study on STRUctum® in Adult Patients with oSTeoarthritis - TRUST
VERSION	Final version V4.0 – 21/12/2023

DATA REVIEW MEETING 09/01/2025

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1 LIST OF ABBREVIATIONS

<i>ADR</i>	Adverse Drug Reaction
<i>AE</i>	Adverse Event
<i>AR</i>	Adverse Reaction
<i>BMI</i>	Body Mass Index
<i>BONe'S</i>	Burden Osteoarthritis New Scale
<i>CI</i>	Confidence Interval
<i>CS</i>	Chondroitin Sulphate
<i>CSR</i>	Clinical Study Report
<i>eCRF</i>	Electronic Case Report Form
<i>HRQoL</i>	Health-Related Quality of Life
<i>MRI</i>	Magnetic Resonance Imaging
<i>NSAIDs</i>	Non-Steroidal Anti-Inflammatory Drugs
<i>OA</i>	Osteoarthritis
<i>PRO</i>	Patient Reported outcome questionnaire
<i>PT</i>	Preferred Terms
<i>SAP</i>	Statistical Analysis Plan
<i>SAR</i>	Serious Adverse Reaction
<i>SAS</i>	Statistical Analysis System
<i>SF-12</i>	12-Item short Form QoL Survey
<i>SOC</i>	System Organ Class
<i>SYSADOAs</i>	Symptomatic Slow-Acting Drugs for OA

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WOMAC	Western Ontario and McMaster Universities Osteoarthritis Index
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2 INTRODUCTION

This document describes the statistical analysis and reporting plan for data from the study “A Prospective Non-Interventional Study on STRUctum® in Adult Patients with oSTeoarthritis” (TRUST). The TRUST study is an observational, descriptive, national, multicentric, prospective, longitudinal study of patients treated with Structum® for osteoarthritis (OA).

This statistical analysis plan (SAP) is based on protocol version V4, issued December 21st 2023.

As described in the ICH E9 guideline and addendum [1, 2], the purpose of this document is to provide a more technical and detailed elaboration of the principal features of the analysis described in the study protocol, and to include detailed procedures for executing the statistical analysis of the primary and secondary variables and of other data.

Any amendments to the SAP will be made prior to database lock.

Any additional analyses not described in the final SAP or deviations from the final SAP will be documented in the clinical study report (CSR).

ClinSearch will perform the statistical analyses and are responsible for the production and quality control of all tables, listings, and figures.

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3 STUDY OBJECTIVES

3.1 Primary objective

To describe the baseline clinical profile and baseline osteoarthritis (OA) symptom severity (pain, stiffness and function) as assessed by the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) questionnaire, for patients with knee OA and treated with Structum[®], a pharmaceutical grade Chondroitin sulfate (CS).

3.2 Secondary objectives

1. To describe the knee OA symptoms severity (pain, stiffness, and function) as assessed by the WOMAC questionnaire in patients treated with Structum[®] over the 6-month follow-up period.
2. To describe the burden associated with knee OA in daily life (independence, interaction & recreation, psychological, budget, hygiene and beauty) as assessed by the Burden of Osteoarthritis New Scale (BONE'S) questionnaire in patients treated with Structum[®] over the 6-month follow-up period.
3. To describe general health (physical and mental) assessed by the Short Form 12 items (SF-12) questionnaire as a quality-of-life measure in patients treated with Structum[®] over the 6-month follow-up period.
4. To describe treatment persistence in patients treated with Structum[®] over the 6-month follow-up period.
5. To describe the global assessment of the patients treated with Structum[®] over the 6 months follow-up period.

3.3 Exploratory objectives

To assess the correlation between the results of the BONE'S questionnaire and the SF-12 and WOMAC questionnaires, in participating patients over the 6-month follow-up period.

To describe the evolution of the use of Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) and other analgesics over the 6-month follow-up period and compare with the use of NSAIDs and other analgesics during the last 6 months before inclusion.

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4 STUDY METHODS

4.1 Summary of study design

This is an observational, descriptive, national, multicentric, prospective, longitudinal study, which will be conducted over a 6-month follow-up period for each patient. The study will not provide or recommend any specific treatment or procedures. All decisions regarding treatment of included patients will be made by the treating physician in accordance with local best clinical practice and as per local product information of Structum®. All patients will be treated and monitored according to the local clinical practice, and no specific visit dates will be mandated for this study.

The study will take place in Poland and 25 investigations sites are expected to be recruited. All patients affected by OA in the knee, for whom Structum® is prescribed in a participating center, will be screened in a consecutive manner for eligibility. Two additional data collections can be anticipated for these patients as part of their standard of care follow-up visits, which will usually occur around 3 and 6 months after the initial study visit. All available data for each enrolled patient will be collected from study inclusion until the end of their follow-up period at 6 months, or death, study withdrawal or loss to follow-up (whichever comes first). The expected timelines of the study can be found in the Project Management Plan.

Patients are attributed a code for pseudonymisation of their results. This code is made of two components, the number of the investigation site and a number attributed to the patient according to the order in which they are recruited at that center (e.g. 10-1, 10-2...).

4.2 Inclusion/exclusion criteria

Adult patients aged 50 to 85 years at inclusion with a confirmed diagnosis of knee osteoarthritis, with a new prescription for Structum®, as treated by participating centers in Poland.

Patients will be eligible for inclusion if they fulfill ALL of the following criteria:

- Male or female patients aged 50 to 85 years at inclusion.
- Diagnosis of knee OA (either a patient newly diagnosed or with history of knee OA), based on at least the following items 1 and/or 2 (meaning that criteria 3 alone is not enough and that the patient also has to fulfil criteria 1 and/or 2 regardless of whether they fulfil criteria 3):
 1. knee pain lasting for at least 3 months;
 2. patient in the active phase of knee OA disease (knee pain score $\geq$ 40mm at inclusion on the Visual Analog Scale [VAS] 0-100 mm);
 3. knee radiographs showing knee joint narrowing and/or osteophytes.
- Patients who have been prescribed, for the first time or not, Structum®.
- If patient is taking any NSAIDs or other analgesics, patient should be on stable dose at least one week before inclusion to the study.
- Patients able to visit the clinic and attend follow-up visits.
- Patients having signed an informed consent form, according to local regulations.

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Patients will NOT be eligible for inclusion if they fulfil ANY of the following criteria:

- Patients with any ongoing chondroitin sulfate treatment at inclusion or during the last 3 months.
- Patients having received or planning to receive any OA comedication, including SYSADOAs (SYmptomatic Slow-Acting Drugs for OA)¹ (in the last 3 months), and intraarticular injections of corticosteroids, hyaluronic acid, and platelet-rich plasma (in the last 3 months). No glucocorticoids administration in the last 3 months before inclusion. That does not include NSAIDS, paracetamol and other analgesic medications (e.g. tramadol).
- Patients with an artificial knee joint, including unilateral.
- Patients scheduled to undergo knee replacement surgery in the next 6 months.
- Patients with a severe general condition that prevents them from being included in the study as assessed by the investigator.
- Patients participating in interventional trials on investigational drugs at the time of inclusion.

4.3 Data collection schedule

Data will be collected via an electronic Case Report Form (eCRF) completed by the investigator and/or qualified designee (25 sites targeted) for all study patients at three time points in the study: upon study inclusion, and at the 3-month and 6-month follow-up visits (see Table 1). Additionally, patients will be given instructions by site staff on how to complete the patient diary in paper format at each visit.

Table 1. Data collection schedule

<i>Data for:</i>	Inclusion Visit (Baseline)	First follow-up visit (3 months)	Second follow-up visit (6 months)
Patient eligibility criteria and informed consent	X		
Patient demographics and clinical characteristics	X		
Treatment history before index Structum® initiation	X		
Index Structum® treatment details	X	X	X
BONe'S (healthcare professional's form) questions in the	X		

¹ These include cytokine modulators (i.e., diacerein), cartilaginous matrix precursors (i.e., glucosamine, and hyaluronic acid), and other types of drugs such as bisphosphonates.

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<i>Data for:</i>	Inclusion Visit (Baseline)	First follow-up visit (3 months)	Second follow-up visit (6 months)
electronic Case Report Form (eCRF)			
Adverse Event form in the eCRF (if applicable)	X	X	X
Patient Questionnaires			
WOMAC questionnaire	X	X	X
BONe'S questionnaire (patient's form)	X	X	X
SF-12 questionnaire	X	X	X
Structum® treatment satisfaction questionnaire	X*	X	X

*Completion of the questionnaire after the first dose of Structum®

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5 SAMPLE SIZE

Given the descriptive nature of the primary objective and since no predefined clinical assumptions underlie this study, neither a sample size nor a power calculation was conducted. We estimated the number of patients to be included to be approximately 150, to obtain a reasonably representative sample.

In Table 2 below, the precision estimates for a 95% confidence interval (CI) were calculated around proportions ranging from 10% to 50% for the estimated sample size.

Table 2. Precision estimates for a 95% confidence interval

Proportion \ Sample size	10%	20%	30%	40%	50%
150 patients	4.8%	6.4%	7.3%	7.8%	8.0%
140 patients	5.0%	6.6%	7.6%	8.1%	8.3%
130 patients	5.2%	6.9%	7.9%	8.4%	8.6%
120 patients	5.4%	7.2%	8.2%	8.8%	8.9%
110 patients	5.6%	7.5%	8.6%	9.2%	9.3%
100 patients	5.9%	7.8%	9.0%	9.6%	9.8%

In conclusion, a sample size of 150 patients will enable to provide 95% CI of the primary outcomes with a precision not exceeding 8.0%. In other words, a sample size of 150 patients will allow to assess a category of primary objective (clinical profile description of eligible patients) of 50% of patients with a precision of $\pm 8.0\%$ i.e., 50% with 95% CI [42% – 58%]. For secondary objectives, we can expect that some included patients will prematurely exit the study or will be lost to follow-up, therefore the range of 95% CI of estimated outcomes will be larger but should not exceed 10% if no less than 100 patients will complete the study follow-up.

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6 DEFINITIONS OF THE STATISTICAL ELEMENTS

The analyses will be performed in accordance with the ICH E9 guidelines.

6.1 Timing of analysis

No interim analysis is planned for this study.

The final analysis will be performed for all outcomes collectively and once all the following conditions are fulfilled:

- Follow-up visits of all patients included occurred.
- All data has been collected, reviewed, and validated and the database lock has been signed by all involved parties.
- The present version of the SAP has been amended after review of the results during an internal Pierre Fabre presentation and a presentation to the scientific committee, validated and signed by all involved parties. Several additional analyses have been added, as requested by the scientific committee members.

6.2 Versions of documents, software, and databases

6.2.1 Protocol

The statistical analysis plan is based on the final version of the protocol V4.0 – 21/12/2023.

6.2.2 Software

All statistical analyses will be performed by ClinSearch using Statistical software (SAS®), version 9.4 or a later version.

6.2.3 Coding dictionaries

Adverse events will be coded using the MedDRA dictionary version 26.1 into SOC (System Organ Class) and PT (Preferred Term) (cf coding plan).

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6.3 Format, definition and handling of missing data for dates and time intervals

6.3.1 Format

Dates will be formatted using DD/MM/YYYY format.

6.3.2 Definitions

A time period between two dates will be calculated from the difference between the most recent date and the oldest date. Thus, the time period between two events that occurred on the same date is 0 day.

The duration of an event will be calculated from the difference between the most recent date and the oldest date, plus one day. Thus, the duration of an event starting and ending on the same day is 1 day.

Index date: date of first prescription of Structum®.

Baseline period: period before the first prescription of Structum®.

Follow-up period: period comprised between the first prescription of Structum® and the end of the observation period (6 months after the 1st prescription of Structum®, patient's death, patient's study withdrawal, or patient becoming lost to follow-up, whichever comes first).

Follow-up 3-month period: period comprised between the first prescription of Structum® and the 3-month follow-up visit.

Follow-up 3-6-month period: period comprised between the 3-month follow-up visit and the 6-month follow-up visit.

Follow-up 6-month period: period comprised between the first prescription of Structum® and the 6-month follow up.

Temporary discontinuation: discontinuation of Structum® treatment for a minimum of 1 day and a maximum of 6 months.

6.3.3 Missing date

In case of a missing or incomplete date preventing the calculation of the time interval, if not specifically mentioned otherwise, the time period or duration will be considered as a missing data, i.e. if not specifically mentioned otherwise, no dates replacement will be done to allow the calculation of the time interval.

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6.4 Names of Analysis Sets

6.4.1 Enrolled Set

The enrolled set (ENR) will contain all included patients.

6.4.2 Full Analysis Set

The full analysis set (FAS) will contain all enrolled patients who fulfilled the eligibility criteria.

6.4.3 Full Analysis Set at 3-month

The FAS at 3-month (FAS-M3) will contain all enrolled patients who fulfilled the eligibility criteria and who have a 3-month follow-up. Enrolled and eligible patients with documented early exit from the study will be excluded from the set (possible in cases of consent withdrawal, death, or adverse event).

Note 1: Patients with missing data (missed follow-up visit or lost-to-follow-up) will not be excluded from the analysis set (see Section 7.1 for the treatment of patients lost-to-follow-up).

Note 2: Permanent discontinuation of Structum® treatment before the end of the study is not a valid reason for an early exit from the study. However, concerned patients are not required to complete the PROs (Patient Reported outcome questionnaires) for the follow-up visits. This will be clearly reported and explained in the study report to adequately discuss the number of missing data reported.

6.4.4 Full Analysis Set at 6-month

The FAS at 6-month (FAS-M6) will contain all enrolled patients who fulfilled the eligibility criteria and who have a 6-month follow-up. Enrolled and eligible patients with documented early exit from the study will be excluded from the set (possible in cases of consent withdrawal, death, or adverse event).

Note 1: Patients with missing data (missed follow-up visit or lost-to-follow-up) will not be excluded from the analysis set (see Section 7.1 for the treatment of patients lost-to-follow-up).

Note 2: Permanent discontinuation of Structum® treatment before the end of the study is not a valid reason for an early exit from the study. However, concerned patients are not required to complete the PROs for the follow-up visits. This will be clearly reported and explained in the study report to adequately discuss the number of missing data reported.

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6.5 Data management and deliverables

6.5.1 Handling of data after export

The database will be handled accordingly to the TRUST Data Management Plan. Once, the database lock will be performed and the database lock certificate will be completed, the database will be transferred to the Statistical department under SAS format and ready for analysis.

6.5.2 Language of statistical outputs

Source documents are in English and the source databases are in Polish, hence all statistical outputs (tables, figures and listing) will be in English.

6.5.3 Deliverable documents

One final study report will be produced integrating all Tables and figures validated in the present SAP. Individual patient listings will be provided upon relevance for the data presentation.

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7 STATISTICAL METHODOLOGY

7.1 Analysis population

In accordance with the observational design of the study, all patients in the Full Analysis Set (FAS) will be considered for analysis.

Patients declared lost to follow-up at the end of the study follow-up will be considered as missing data but not excluded from the analysis population, as we cannot certify that these data are missing completely at random.

Therefore, for categorical variables, percentages will be calculated using the number of patients with available data in the analysis population (which may vary at each visit timepoint and does not include patients with missing data) as the denominator; and for quantitative variables, only non-missing values can be used for calculations. And in both cases, the number of missing values will be displayed.

7.2 Subgroups analysis

In order to better answer to the first objective (to describe the baseline clinical profile and baseline OA symptom severity), and upon clinical relevance for the analysis, subgroup analyses will be possible for the following sub-group if the number of patients in each subgroup is sufficient ($n \geq 10$ in each modality):

Subgroups:

- Time since diagnosis of knee OA (Newly diagnosed (≤ 12 months before inclusion) / Previously diagnosed (> 12 months before inclusion)).
- Severity of knee OA (Severe / Moderate, as defined with the score of the pain dimension of the WOMAC at baseline with scores $\geq 300/500$ considered as severe and $< 300/500$ as moderate).
- Sex (Male / Female).
- Knee OA location (Unilateral / Bilateral).
- Age (≤ 65 / > 65 years old).
- Patients with a previous NSAID, paracetamol or other analgesic treatment for knee OA in the last 6 months before the inclusion visit (No / Yes).
- Patients with any concomitant treatments during the study (No / Yes).

See Appendix A presenting the details of the specific criteria analysed according to each subgroup.

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7.3 Statistical analysis

The study being single arm (i.e., non-comparative) and for descriptive purposes only, no *a priori* hypothesis will be tested.

7.3.1 Descriptive statistics

Appropriate summary statistics will be used depending on the nature of the variables, and the number of available and missing data will be specified for each variable. Categorical variables will be presented as frequencies and proportions, and continuous data will be expressed as median, mean, standard deviation, min-max, and quartiles (Q1 and Q3). The 95% CI will be presented upon relevance to the analysis (for calculating the differences between 3-month or 6-month with baseline for the PRO scores; See the Appendix for planned table shells).

Primary, secondary, and exploratory outcomes will be analyzed using descriptive statistics.

7.3.2 PROs correlation analysis

For the exploratory outcomes, in addition to descriptive statistics, Spearman correlation coefficients will be used to analyze the correlations between the different questionnaires (see Section 9.4). It will be reported with a P value whose significance will be set at 0.05.

7.3.3 Sensitivity analysis

In case there is a high number of missing total or dimension scores for one questionnaire completed by patients of a particular investigation site, a sensitivity analysis will be performed to assess the robustness of the resulting scores so as to see if the data from this site need to be excluded from the analyses relative to this questionnaire.

7.4 Missing data

Missing data will be considered missing without any imputation performed and described appropriately, with the exception of the PROs for which missing data will be handled as recommended in associated guidelines (see Section **Erreur ! Source du renvoi introuvable.**).

7.5 Quality control

Quality control of the SAS programs will be done by the Statistician in charge of programming them. Quality control of the analysis outputs will be done by the Statistician who generates them, as well as the scientific advisor who reviews them. Double programming will not be performed.

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8 CHANGES IN THE ANALYSIS PLANNED IN THE PROTOCOL

Several additional analyses have been added compared to those outlined in the protocol:

- Treatment compliance calculated for the overall follow-up (between the inclusion and 6-month follow-up) has been added.
- For all score (WOMAC, BONE'S, SF12 questionnaires) changes from baseline, the percentage of differences have been added.
- The correlations between WOMAC score and SF-12 scores (physical and mental summary component scores) at 3 and 6 months have been added.
- The correlations between WOMAC score and the Lequesne algofunctional index score at 3 and 6 months have been added.
- Logistic regression models modelling the responder/non-responder patients at 3 and 6 months have been added.
- Logistic regression models modelling the severity of OA using the pain score of the WOMAC at 3 and 6 months have been added.
- A subgroup analysis describing patients with and without a previous NSAID, paracetamol or other analgesics treatment for knee OA in the 6 months before the study has been added.
- A subgroup analysis describing patients with and without a concomitant treatment during the study has been added.

The following time windows are defined:

- Baseline = M0 (Inclusion visit).
- 1st follow-up visit (3 months): visit performed and PROs completed between 2 – 4 months after M0.
- 2nd follow-up visit (6 months): visit performed and PROs completed between 5 – 7 months after M0.

All patients with follow-up visits with dates outside of these defined acceptable time windows will be reviewed during the data review meeting before database lock to decide on a case-by-case basis if collected data are suitable for analysis purpose or if they should be considered as missing, based on clinical relevance of the actual date of the follow-up visit.

This manual review will be documented and described in the final report. The goal is to limit the impact of potential outliers on the quality of the data, while reducing an unnecessary amount of missing data in the context of a real-life study.

9 STATISTICAL ANALYSIS

9.1 Patient disposition

A flow diagram will be inserted to detail the following variable (number and percentage): patient included as per PIs' declaration, patients enrolled (ENR), patients eligible to analysis (FAS), patients having had

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their 3-month follow-up (FAS-M3), patients having had their 6-month follow-up (FAS-M6; including patients still on Structum® and patients having definitively discontinued Structum® at the 3-month follow-up), and early exit of study at both timepoints.

The safety population will be all patients with at least one dose of Structum® (FAS population).

In addition, the number of sites initiated and of active sites (sites that have included patients), and the number of patients per site will be described.

The different subgroups will be described in a table.

9.2 Primary outcomes

The primary and secondary objectives will be achieved with PROs. Scoring of these validated questionnaires will be applied strictly in accordance with each associated guideline.

The PROs used in the study are:

- The WOMAC (validated questionnaire).
- The BONE'S (validated questionnaire).
- The SF-12 (validated questionnaire).
- The Structum® satisfaction questionnaire (adapted questionnaire).

They will be administered at inclusion / after the first Structum® dose, at 3-month, and at 6-month. They each have their own associated scoring guidelines that will be followed to analyze them. In addition, the validated Lequesne algofunctional index and the Kellgren and Laurence radiologic assessment will be administered by the healthcare practitioners only at inclusion.

9.2.1 WOMAC score at baseline

The primary objective of this study is to collect comprehensive data to describe the clinical profile of knee OA patients for whom Structum® has been prescribed. Hence, the primary outcome cannot be conveyed as a single stand-alone measure but will instead entail a comprehensive description of all source data collected to characterize the clinical profile of included patients as detailed in previous Section 9.2.3 to 9.2.5. The description of symptom severity (pain, stiffness and function) as assessed by the WOMAC at baseline will complete the description of the clinical profiles.

- Knee OA symptom severity description per the WOMAC questionnaire at inclusion
 - WOMAC questionnaire completed (Yes/No).
 - Knee chosen for the WOMAC questionnaire (Left/Right).
 - Total WOMAC score of symptoms' severity, as a continuous variable.
 - Score for the pain dimension, as a continuous variable.
 - Score for the stiffness dimension, as a continuous variable.
 - Score for the physical function dimension, as a continuous variable.

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9.2.1.1. PRO description: WOMAC questionnaire

The WOMAC questionnaire [3] is a questionnaire using visual analogue scales to evaluate OA symptoms' severity. It has 24 questions divided across 3 dimensions: pain (questions 1-5), stiffness (questions 6-7), and physical function (questions 8-24), with each having a 10 cm scale.

All scales in the WOMAC questionnaire have to be exactly 10 cm wide, otherwise a conversion has to be done to the raw measurements using a rule of three. The raw measurements also have to be converted into the appropriate unit before doing the calculations, as data can be collected by the investigation sites either in cm or mm.

Scoring: For each item, the corresponding score of the VAS will be determined according to the questionnaire guideline before entry in the database.

For each dimension, the values scored on each item will be summed to give a dimension score, with pain ranging from 0-500, stiffness 0-200, and physical function 0-1700. A sum of these 3 scores will give a total WOMAC score ranging from 0-2400, with higher scores indicating worse pain, stiffness, and functional limitations.

Missing data: if ≥ 2 items are missing from the pain dimension, or both items are missing from the stiffness dimension or ≥ 4 items are missing from the physical function dimension, that dimension will be considered invalid and will not be used in the analysis. If less items are missing, they will be substituted for the person-specific mean value for that dimension.

Results presentation: The results will be presented as a total score of symptoms' severity and scores for the pain dimension, the stiffness dimension, and the physical function dimension.

9.2.2 Patient socio-demographics characteristics

The following key items will be collected at baseline (during the inclusion visit) for all patients and will be analyzed with descriptive statistics:

- Patient age at inclusion (years): Year of inclusion - Year of birth
- Sex
 - Male
 - Female
- Employment status
 - Full-time employment
 - Part-time employment
 - Retired
 - Full-time student
 - Homemaker
 - Unemployed
 - Incapacity to work
 - Unavailable
 - Other (specify)

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And occupational categories (according to the International Standard Classification of Occupations ISCO-08)

- 1) Managers
 - 2) Professionals
 - 3) Technicians and associate professionals
 - 4) Clerical support workers
 - 5) Service and sales workers
 - 6) Skilled agricultural, forestry and fishery workers
 - 7) Craft related trades workers
 - 8) Plant and machine operators, and assemblers
 - 9) Elementary occupations
 - 10) Armed forces occupations
- Lifestyle – frequency of physical activity
 - More than 2h/day of physical activity
 - Less than 1h/day
 - Twice a week
 - Once a week
 - Occasionally
 - Never
 - Weight (in kgs, as a continuous variable)
 - Height (in m, as a continuous variable)
 - BMI: Weight/Height² (in kg/m², as continuous variable and as categories)
 - Underweight (<18.5)
 - Normal ([18.5 – 25[)
 - Overweight ([25 – 30[)
 - Obese (≥30)

9.2.3 Medical history

The following key items will be collected during the inclusion visit for all patients and will be analyzed with descriptive statistics:

- **Charlson Comorbidity Index at inclusion**
 - Was the test performed (Yes/No)
 - Score as a continuous variable (Score values range from 0 to 37, see point system below for calculation)
 - Patients having at least one comorbidity (Yes/No)
 - Details of the relevant comorbidities (percentages calculated only on patients with at least one comorbidity)
 - Myocardial infection
 - No, 0 point
 - Yes, 1 point
 - Congestive heart failure
 - No, 0 point
 - Yes, 1 point

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- Peripheral vascular disease
 - No, 0 point
 - Yes, 1 point
- Cerebrovascular accident or transient ischemic attack
 - No, 0 point
 - Yes, 1 point
- Dementia
 - No, 0 point
 - Yes, 1 point
- Chronic obstructive pulmonary disease
 - No, 0 point
 - Yes, 1 point
- Connective tissue disease
 - No, 0 point
 - Yes, 1 point
- Peptic ulcer disease
 - No, 0 point
 - Yes, 1 point
- Liver disease
 - None, 0 point
 - Mild, 1 point
 - Moderate to severe, 3 points
- Diabetes mellitus
 - None or diet controlled, 0 point
 - Uncomplicated, 1 point
 - End-organ damage, 2 points)
- Hemiplegia
 - No, 0 point
 - Yes, 2 points
- Moderate to severe chronic kidney disease
 - No, 0 point
 - Yes, 2 points
- Solid tumor
 - None, 0 point
 - Localized, 2 points
 - Metastatic, 6 points
- Leukemia
 - No, 0 point
 - Yes, 2 points
- Lymphoma
 - No, 0 point
 - Yes, 2 points
- Acquired immunodeficiency syndrome
 - No, 0 point

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- Yes, 6 points
 - (The age is not displayed here but used to calculate the score:
 - <50 years, 0 point
 - 50-59 years, 1 point
 - 60-69 years, 2 points
 - 70-79 years, 3 points
 - ≥80 years, 4 points)
- **Metabolic syndrome analysis at inclusion**
 - Was the metabolic syndrome test performed (Yes/No)
 - Presence of a metabolic syndrome confirmed (defined as a patient having central obesity and at least two other factors among patients who performed the test):
 - Presence of metabolic syndrome
 - Confirmed absence of metabolic syndrome
 - Unconfirmed absence of metabolic syndrome (A listing will be presented detailing these patients' results on the metabolic syndrome test).
 - Based on what criteria it has been diagnosed (for patient with presence of metabolic syndrome confirmed)
 - Central obesity
 - BMI above 30kg/m² with assumption of obesity
 - Waist circumference and ethnicity criteria
 - Raised fasting plasma glucose
 - Fasting plasma glucose ≥100 mg/dL (5.6 mmol/L)
 - Previously diagnosed type 2 diabetes
 - Not done
 - Reduced HDL-cholesterol
 - <40 mg/dL (1.03 mmol/L) in men or <50 mg/dL (1.29 mmol/L) in women
 - Specific treatment for this abnormality
 - Not done
 - Raised triglycerides
 - >150 mg/dL (1.7 mmol/L)
 - Specific treatment for this abnormality
 - Not done
 - Arterial pressure
 - Systolic >130 mm Hg
 - Diastolic >85 mm Hg
 - Previously diagnosed and treated hypertension
 - Not done
- **Knee OA clinical characteristics at inclusion (history of knee OA diagnosis):**
 - Time since initial diagnosis of knee OA
 - In months, as a continuous variable: (Date of inclusion – Date of diagnosis + 1)/30.4375, using MM/YYYY for the calculation.
 - As categories

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- Newly diagnosed at inclusion in the TRUST study (≤ 12 months before inclusion)
- Previously diagnosed before the inclusion visit (> 12 months before inclusion)
 - With which criteria was the patient included in the study:
 - a) Knee pain lasting for at least 3 months
 - b) Patient in the active phase of knee OA disease (knee pain score ≥ 40 mm at inclusion on the Visual Analog Scale [VAS] 0-100 mm)
 - c) Knee radiographs showing knee joint narrowing and/or osteophytes)
- **Location and knee severity of knee OA depending on unilateral knee OA – left knee, unilateral knee OA – right knee, bilateral knee OA**
 - Knee OA location (Left / Right / Both knees affected)
 - Lequesne algofunctional index assessment done (Yes/No)
 - Severity of knee OA, as assessed by the investigator using the Kellgren and Laurence radiologic assessment on the most painful knee for unilateral knee OA or on both knees for bilateral knee OA (as categories, grades 0-4 on each knee) and the Lequesne algofunctional index for the most painful knee for both unilateral and bilateral knee OA (as a continuous variable)
 - Whether it is accompanied by an OA of the hip, cervical, lumbar, of the fingers, or other.

9.2.3.1 PRO description: Lequesne algofunctional index

The Lequesne algofunctional index [4] will be used to calculate the severity of knee OA. This questionnaire has 11 questions across 3 dimensions: pain or discomfort in the most painful knee (questions 1-5), maximum distance walked (questions 6-7), and activities of daily living (questions 8-11).

Scoring: Each dimension will be scored out of 8. The results for each dimension will be summed to give a global score out of 24, with a high score indicating a higher handicap. The total score is calculated directly in the EDC (see the Case Report Form of the TRUST study to see the scoring of each question).

Missing data: No imputation will be made if the answer to any item is missing, and in such cases the index is considered invalid.

Results presentation: The results will be presented as the global score.

9.2.3.2 PRO description: Kellgren and Laurence radiologic assessment

The Kellgren and Laurence radiologic assessment [5] will be used to calculate the severity of knee OA on each knee. This assessment has 1 question.

Scoring: The question is scored from 0-4, resulting in a grade for each knee ranging from none (0) to severe (4).

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Missing data: No imputation will be made if the answer to any item is missing, and in such cases the assessment is considered invalid.

Results presentation: The results will be presented as the grade for each knee.

9.2.4 Treatment history

The following key items will be collected at the inclusion visit for all patients and will be analyzed with descriptive statistics:

- Patients with at least one prescription of treatments for knee OA in the last 6-months before the inclusion visit (Yes/No)
- Total number of previous treatments for knee OA in the last 6 months before the inclusion visit.
- Prior treatments for knee OA over the previous 6 months (presented by numbers of patients)
 - SYSADOAs [specify]
 - Oral NSAIDs
 - Topical NSAIDs
 - Paracetamol
 - Analgesics other than paracetamol [specify]
 - Glucocorticoids
 - Intra-articular corticosteroid injection
 - Intra-articular hyaluronic acid injection
 - Forearm crutch
 - Home self-exercising programs
 - Joint overwork reduction advice
 - Other (specify)
- For each treatment, the duration of treatment as a continuous variable in months
 - If the duration of treatment is missing: treatment ongoing (yes/no).
- For each treatment, a listing will present the patients' ID, each previous treatment for knee OA in the past 6 months and their duration (as a continuous variable in months), if ongoing, dose, unit, and frequency.
- *Note: The percentages for each treatment will be calculated on the number of patients who received at least one treatment in the last 6-months before the inclusion visit.*

9.2.5 Structum® treatment patterns

The following key items will be collected during the inclusion visit and at the 3-month and 6-month follow-ups for all patients and will be analyzed with descriptive statistics:

- **Structum® prescription details**
 - Initial index Structum® treatment at inclusion
 - First prescription
 - Prescription renewal
 - Dosage at initiation, 3-month, and 6-month

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- In mg/day as a continuous variable
 - As categories
 - Amount
 - <1000 mg/day
 - 1000 mg/day
 - >1000 mg/day
 - Frequency
 - 1 intake/day
 - >1 intake/day
 - Planned duration at initiation, 3-month, and 6-month
 - In months as a continuous variable
 - As categories
 - <6 months
 - 6 months
 - >6 months
 - *Note: At the 3-month and 6-month visits, the dosage and duration of the Structum® will be presented only for new prescriptions.*
- **Ongoing and concomitant treatments with Structum® for knee OA by type at inclusion, at the 3-month follow-up and at the 6-month follow-up**
 - Patients with a concomitant treatment for knee OA
 - No
 - Yes
 - Missing data
 - Total number of concomitant treatments for knee OA.
 - Type of concomitant treatments for knee OA (presented by numbers of patients, with percentages calculated on the number of patients with at least one concomitant treatment for knee OA during that time period)
 - NSAID (specify)
 - Glucosamine sulfate
 - Paracetamol
 - Analgesics other than paracetamol (specify)
 - Piascledine
 - Hyaluronic acid
 - Hypnotic drugs and/or muscle relaxants
 - Other (specify)
 - For each concomitant treatment for knee OA, a listing will present the patients' ID, each treatment and their duration (as a continuous variable in months), if ongoing, dose, unit, and frequency.
 - *Note: The timing of the treatments is defined as follow:*
 - *Inclusion period: medication started at inclusion*
 - *3-month period: treatment started after inclusion and up to the 3-month visit included*
 - *6-month period: medication started after the 6-month visit*
 - *Note: At 3-month and 6-month visits, only new concomitant treatments will be presented.*

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- **Treatment compliance between the inclusion and the 3-month follow-up, between the 3-month and 6-month follow-ups, and for the overall follow-up (between the inclusion and 6-month follow-up) for all patients and depending on Structum® dosage (<1g/day, 1g/day, >1g/day)**
 - No missed tablets
 - < 18 missed tablets of 500mg
 - 18 – 36 missed tablets of 500mg
 - > 36 missed tablets of 500mg
 - I don't know
 - *Note: The patients who stopped Structum® treatment before or at the 3-month visit will be excluded from the 6-month analysis.*
 - *Note: The patients who changed their dosage of Structum® during the time period analyzed will be categorized into the groups <1g/day, 1g/day, or >1g/day depending on the dosage taken for the longest time during that period.*
- **Any change to Structum® treatment at the 3-month and 6-month follow-ups**
 - Treatment dosage modification
 - Introduction of new concomitant treatment
 - Temporary treatment discontinuation
 - Definitive treatment discontinuation
 - Treatment not changed (no dosage modification, temporary discontinuation, or definitive discontinuation)
 - *Note: The patients who stopped Structum® treatment before or at the 3-month visit will be excluded from the 6-month analysis.*
- **Details of the dosage modifications of Structum® treatment between the inclusion and the 3-month follow-up and between the 3-month and 6-month follow-ups**
 - Patients with at least one modification
 - No
 - Yes
 - Number of treatment modifications per patient as a continuous variable and as categories
 - 1 modification
 - 2 modifications
 - >2 modifications
 - Duration of treatment before treatment modification since the inclusion visit for the first modification only, in months as a continuous variable
 - $(\text{Date of first treatment modification} - \text{Date of inclusion} + 1)/30.4375$, using MM/YYYY for the calculation
 - Duration of treatment before treatment modification since the 3-month follow-up for the first modification only, in months as a continuous variable
 - $(\text{Date of first treatment modification} - \text{Date of 3-month follow-up} + 1)/30.4375$, using MM/YYYY for the calculation
 - New daily dosage for the first modification only
 - Increased dosage

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- Decreased dosage
 - Reasons for treatment modification for the first modification only
 - Worsening condition
 - Adverse event
 - Physician's decision
 - Patient's decision
 - Other (specify)
 - Reasons for treatment modification for all modifications
 - Worsening condition
 - Adverse event
 - Physician's decision
 - Patient's decision
 - Other (specify)
- **Details of the temporary discontinuations of Structum® treatment between the inclusion and the 3-month follow-up and between the 3-month and 6-month follow-ups**
 - Patients with at least one temporary discontinuation
 - No
 - Yes
 - Number of temporary discontinuations per patient as a continuous variable and as categories
 - 1 temporary discontinuation
 - 2 temporary discontinuations
 - >2 temporary discontinuations
 - Duration of treatment before temporary discontinuation since the inclusion visit / the 3-month follow-up for the first discontinuation, in months as a continuous variable:
 - (Date of first treatment temporary discontinuation – Date of inclusion or Date of 3-month follow-up + 1)/30.4375, using MM/YYYY for the calculation
 - Duration of treatment temporary discontinuation for the first discontinuation, in days as a continuous variable:
 - (Date of treatment resuming – Date of treatment temporary discontinuation + 1)
 - Daily dosage after temporary discontinuation for the first discontinuation
 - Increased dosage
 - No modification of dosage
 - Decreased dosage
 - Reasons for treatment modification for the first temporary discontinuation only
 - Worsening condition
 - Adverse event
 - Physician's decision
 - Patient's decision
 - Other (specify)
 - Reasons for treatment modification for all temporary discontinuations
 - Worsening condition
 - Adverse event
 - Physician's decision

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- Patient's decision
 - Other (specify)
- Switch to another treatment following the temporary Structum® discontinuation for the first discontinuation
 - Patient switched onto another treatment (Yes/No)
 - Treatments switched towards:
 - SYSADOAs [specify]
 - Oral NSAIDs
 - Topical NSAIDs
 - Paracetamol
 - Analgesics other than paracetamol [specify]
 - Glucocorticoids
 - Intra-articular corticosteroid injection
 - Intra-articular hyaluronic acid injection
 - Forearm crutch
 - Home self-exercising programs
 - Joint overwork reduction advice
 - Other (specify)
 - For each treatment, patients' ID, date of initiation, dose, unit, and frequency will be presented in a listing.
- **Details of the definitive discontinuations of Structum® treatment between the inclusion and the 3-month follow-up and between the 3-month and 6-month follow-ups**
 - Patients with a definitive discontinuation
 - No
 - Yes
 - Duration of treatment before permanent discontinuation since the inclusion visit / the 3-month follow-up, in months as a continuous variable
 - (Date of treatment permanent discontinuation – Date of inclusion or Date of 3-month visit + 1)/30.4375, using MM/YYYY for the calculation
 - Reasons for definitive discontinuation
 - Worsening condition
 - Adverse event
 - Physician's decision
 - Patient's decision
 - Other (specify)
 - Switch to another treatment following the definitive Structum® discontinuation
 - Patient switched onto another treatment (Yes/No)
 - Treatments switched towards:
 - SYSADOAs [specify]
 - Oral NSAIDs
 - Topical NSAIDs
 - Paracetamol
 - Analgesics other than paracetamol [specify]

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- Glucocorticoids
- Intra-articular corticosteroid injection
- Intra-articular hyaluronic acid injection
- Forearm crutch
- Home self-exercising programs
- Joint overwork reduction advice
- Other (Specify)
- For each treatment, patients' ID, date of initiation, dose, unit, and frequency will be presented in a listing.

9.3 Secondary outcomes

Note: For patients who definitively discontinued Structum®, the questionnaires will be excluded from the analyses at subsequent visits (if questionnaire completion date > date of definitive discontinuation).

The following secondary outcomes will be described:

1) Secondary WOMAC outcomes at 3-month and 6-month follow-up

- WOMAC questionnaire completed (Yes/No)
- Total WOMAC score of symptoms' severity, as a continuous variable
- Score for the pain dimension, as a continuous variable
- Score for the stiffness dimension, as a continuous variable
- Score for the physical function dimension, as a continuous variable
- Absolute and percentage of differences in total WOMAC scores at 3 and 6 months (compared to baseline), as continuous variables
- Absolute and percentage of differences in pain dimension score, stiffness dimension score, and physical function dimension, at 3 and 6 months (compared to baseline), as continuous variables
- *Note: Missing data will be presented for each dimension.*

2) BONE'S outcomes at baseline, 3-month and 6-month follow-up (from the patient questionnaire)

- BONE's questionnaire completed (Yes/No)
- Global score of the OA burden, as a continuous variable
- Score for the independence dimension, as a continuous variable
- Score for the interaction & recreation dimension, as a continuous variable
- Score for the psychological dimension, as a continuous variable
- Score for the budget dimension, as a continuous variable
- Score for the hygiene & beauty dimension, as a continuous variable
- Absolute and percentage of differences in global OA burden scores at 3 and 6 months (compared to baseline), as continuous variables
- Estimation of pain on a 0 – 10 scale, as a continuous variable
- Estimations of personal expenses for OA during the last month that were not refunded, as a continuous variable (in €)

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- Estimations of personal expenses for OA during the last month that were not refunded in category (quartile), presenting the limits of each quartile and the percentages of patients in each quartile
- Changes in health state between the inclusion and 3-month visit and between the 3-month and 6-month visits
 - Much improved
 - Moderately improved
 - Slightly improved
 - Same
 - Slightly worsened
 - Moderately worsened
 - Much worsened
- Proportions of patients at 3-month and at 6-month that:
 - Sometimes forget their treatment
 - Sometimes have troubles remembering to take their treatment
 - Stop taking their treatment when they feel better
 - Stop taking their treatment when they feel worse after taking it
- *Note: Missing data will be presented for each dimension.*

3) SF-12 outcomes at baseline, 3-month and 6-month follow-up

- SF-12 questionnaire completed (Yes/No)
- Score of the physical component summary, as a continuous variable
- Score of the mental component summary, as a continuous variable
- Absolute and percentage of differences in the score of the physical component summary at 3 and 6 months (compared to baseline), as continuous variables
- Absolute and percentage of differences in the score of the mental component summary at 3 and 6 months (compared to baseline), as continuous variables
- *Note: Missing data will be presented for each dimension.*

4) Persistence outcomes at 3-month and 6-month follow-up

- Proportion of patients with ongoing Structum® at 3 months
- Proportion of patients with ongoing Structum® at 6 months

5) Personal global assessment, after first dose of Structum®, at 3-month and at 6-month follow-up:

- Patient satisfaction questionnaire completed (Yes/No)
- Proportion of patients with a positive assessment of Structum®, as assessed by Structum® treatment satisfaction questionnaire, with a positive assessment defined as a patient have a score ≥ 50 in their Structum® satisfaction questionnaire.
- Global satisfaction score, as a continuous variable
- Score for the convenience dimension, as a continuous variable
- Score for the effectiveness dimension, as a continuous variable
- Score for the overall satisfaction dimension, as a continuous variable
- *Note: Missing data will be presented for each dimension.*

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9.3.1 PRO description: BONE'S questionnaire

The BONE'S questionnaire is a questionnaire used to measure OA burden on patients' daily life [6]. It has 19 questions across 5 dimensions: independence (7 questions; questions 2, 3, 7-10, 19), interaction & recreation (4 questions; questions 11-14), psychological (3 questions; questions 15, 18, 20), budget (2 questions; questions 16, 17), and hygiene & beauty (3 questions; questions 4-6). It also has extra questions that are not included in the calculation of the BONE'S score (question 21-26).

Scoring: The questionnaire uses 6-point Likert scales ranging from “never” to “constantly” (with an additional response of “not applicable”), with each attributed a numerical value from 0 to 5 (and “not applicable” considered as “never”). The score of each dimension will be calculated by adding up the score of each item in that dimension, and the global score will be the sum of all individual item scores that is then transformed onto a 0-100 scale. Higher scores represent a heavier burden.

Missing data: A way to handle missing data has not yet been included in the methodology of the BONE'S questionnaire. In the TRUST study, if an item score is missing and at least half of the items in the domain are complete (*i.e. ≥ 2 items completed for all dimensions except ≥ 4 items completed for independence dimension*), domain scores will be imputed from the person-specific mean score of completed items. If more than half items are missing, that dimension will be considered invalid and will not be used in the analysis.

Results presentation: The results will be presented as a global score of OA burden and scores for the independence dimension, the interaction & recreation dimension, the psychological dimension, the budget dimension, and the hygiene & beauty dimension. In addition, the answers to questions 22-26 will be described as category variables and question 21 will also be presented as a continuous variable as well as quartiles.

9.3.2 PRO description: SF-12 questionnaire

The SF-12 questionnaire [7] is a general health questionnaire with 12 questions across 8 subscales (physical functioning, role - physical, bodily pain, general health, vitality, social functioning, role - emotional, mental health).

Scoring: A special scoring program, accessible via the license purchase of the questionnaire, will be used to analyze this questionnaire by giving a ponderation to each item to result in two different dimension scores. Scores range from 0 to 100, with higher scores indicating a better physical and mental health functioning.

Missing data: No imputation will be made if the answer to any item is missing, and in such cases the index is considered invalid.

Results presentation: The results will be presented as a score for the physical health dimension, and a score the mental health dimension.

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9.3.3 PRO description: Structum[®] satisfaction questionnaire

The Structum[®] satisfaction questionnaire is a questionnaire adapted from the Treatment Satisfaction Questionnaire for Medication [8], a questionnaire used to assess patients' satisfaction with pharmacological treatment. It examines different aspects of treatment satisfaction and has 5 items divided across 3 dimensions: the convenience of use (questions 1-2), the effectiveness (questions 3-4), and the overall satisfaction (question 5), with the version of the questionnaire administered "after the first dose" having only the 2 questions from the convenience of use dimension.

Scoring: Each item will be scored from 1 (very inconvenient/very dissatisfied/very difficult) to 5 (very convenient/very satisfied/very easy). The scores for each item of one dimension will be summed and transformed onto a 0-100 scale to give a dimension score with the following formula:

$$\frac{\text{Sum of the score of each item in a dimension} - \text{Number of item in that dimension}}{\text{Maximum score of that dimension} - \text{Minimum score of that dimension}} \times 100$$

The mean of the three dimensions scores will be used to obtain the global score.

Missing data: If an item score is missing in the dimension, that dimension will be considered invalid and will not be used in the analysis.

Results presentation: The results will be presented as a global score of satisfaction and scores for the convenience dimension, the effectiveness dimension, and the overall satisfaction dimension.

9.4 Exploratory outcomes

9.4.1 Correlation between questionnaires and description of the NSAIDs changes

- **Calculation of the Spearman correlation coefficients at inclusion, 3, and 6 months for the correlations between:**
 - The BONE'S questionnaire (the independence + interaction & recreation + hygiene & beauty scores) and the SF-12 questionnaire (physical component summary dimension).
 - The BONE'S questionnaire (psychological score) and the SF-12 questionnaire (mental component summary dimension).
 - The global score of the BONE'S questionnaire and the total WOMAC score.
 - The Total WOMAC score and the SF-12 questionnaire (physical component summary score).
 - The Total WOMAC score and the SF-12 questionnaire (mental component summary score).
 - The Total WOMAC score and the Lequesne algofunctional index score.
- **Description of the proportions of patients with a change in their prescription of NSAIDs and other analgesics for knee OA 6 months before inclusion, at inclusion, and at 3 and 6 months, with a change being defined as any change of the daily dose of NSAIDs (calculated from the frequency of intake and the dose of each intake)**

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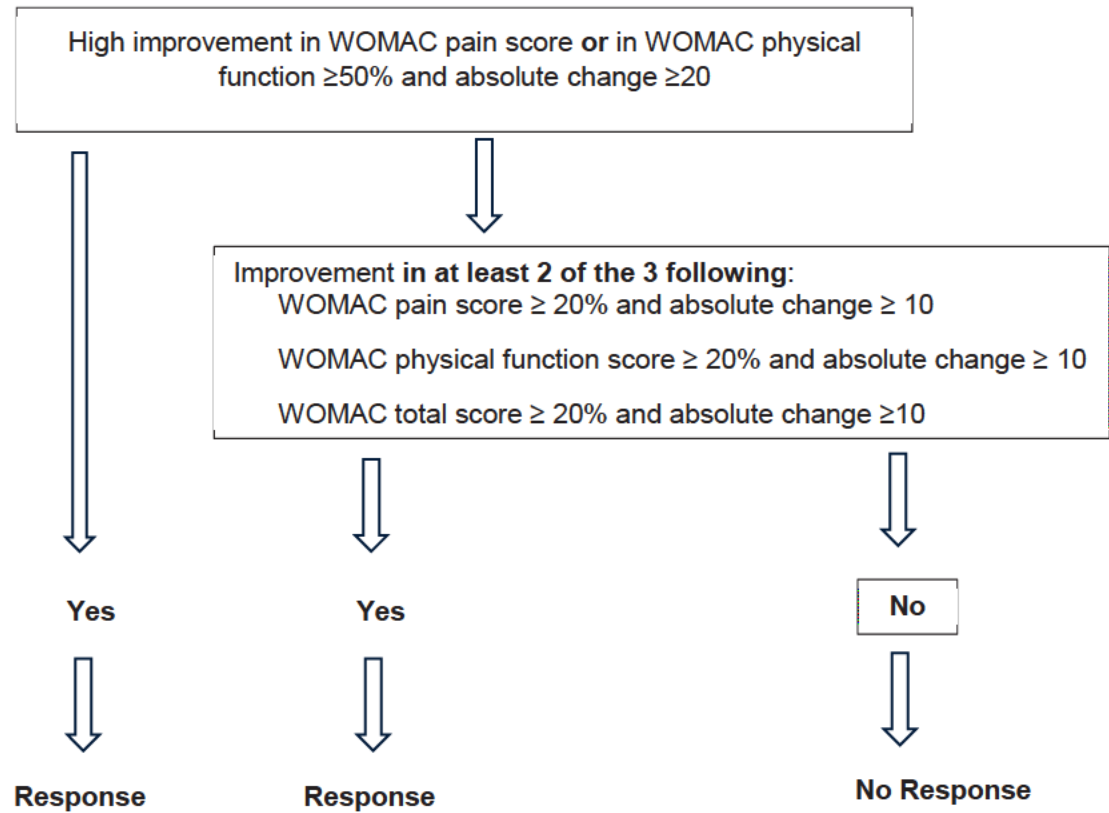
- No treatment taken between either of the two periods being compared
- Treatment stopped
- Reduced dosage
- Treatment stable
- Increased dosage
- New treatment

Note: For this table, will be considered: NSAIDs (topical and oral), Paracetamol, and Analgesics other than paracetamol.

9.4.2 Factors associated with Structum® response and the severity of OA

9.2.1.2. Definition of Structum® response

The definition of the response will be based on the OMERACT-OARSI set of responder criteria described below [9]. The responder patients will be defined at the 3-month and 6-month visits.



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9.2.1.3. Definition of the severity of OA

The severity of OA has been defined using the WOMAC pain score:

- Moderate: WOMAC pain score <300/500
- Severe: WOMAC pain score $\geq$ 300/500.

9.2.1.4. Modelling of the response and severity of OA

An analysis on the FAS-3 and FAS-6 populations will be performed to identify factors associated with response (and severity of OA). A logistic regression, with odds ratio, confidence interval and p-values associated will be used to estimate these factors.

Each factor will be tested in a univariate logistic regression model. If the factor is associated with the response (or severity of OA) at a significance level of $p=0.20$ or if the factor is known to be associated with response (and severity of OA) in the literature, this factor will be included in the multivariate model. The final multivariate model will be built using an automatic stepwise selection of factors with a significance level of $p=0.05$.

The following variables will be tested:

- Sex (Male* vs Female)
- Age in categories (≤ 65 years old* vs > 65 years)
- BMI in categories (Normal ($[18.5 \text{ kg/m}^2 - 25 \text{ kg/m}^2]$) vs Overweight ($[25 \text{ kg/m}^2 - 30 \text{ kg/m}^2]$) vs Obese ($\geq 30 \text{ kg/m}^2$))
- Knee OA location (Unilateral (Left/Right)* vs Both knees affected)
- Patients with a previous NSAID, paracetamol or analgesic treatment for knee OA in the last 6 months before the inclusion visit (No* vs Yes)^a
- Duration of prescription of Structum® (≤ 6 months (< 6 months/6 months)* vs > 6 months)
- Time since initial diagnosis of knee OA (≤ 12 months before inclusion* vs > 12 months before inclusion)
- Patients having at least one comorbidity (No* vs Yes)
- Lequesne algofunctional index score (< 12 * vs ≥ 12 ; see [10])^a
- Kellgren and Laurence grade (< 3 * vs ≥ 3 ; for patients with several assessments, only the maximum grade will be considered)^b

**This modality will be used as reference in the models.*

^aThe Lequesne algofunctional index will be tested for the response model only.

^bThe Kellgren Laurence grade will only be kept after checking that the correlation with the Lequesne algofunctional index score is < 0.80 .

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9.5 Safety evaluation

Safety analysis will be performed throughout the study and it will include all eligible patients included in the study and who will have received at least one dose of Structum®.

Definitions (for full definitions, see protocol):

- An adverse event (AE) is any untoward medical occurrence in a patient to whom a medicinal product is administered, and which does not necessarily have a causal relationship with this treatment.
- An adverse reaction (AR) is defined as a response to a medicinal product which is noxious and unintended. An AR is any AE judged as having a reasonable suspected causal relationship to product.
- A serious AR (SAR) is an adverse reaction which results in death, is life-threatening, requires in-patient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability or incapacity, or is a congenital anomaly/birth defect.

The occurrence of adverse events will be summarized globally for all patients:

- Reporting at least one AE
- Reporting at least one AR
- Reporting at least one SAE
- Reporting at least one SAR
- Number of AEs per patients, as a continuous variable
- Number of SAEs per patients, as a continuous variable

Will also be presented **the details of the adverse events by numbers of patients and by numbers of events** (with percentages calculated out of the total number of patients in the safety population):

- AE outcomes
 - Recovered without sequelae
 - Recovered with sequelae
 - Recovering
 - Not recovered
 - Death
 - Unknown
- Actions taken because of the AEs
 - Did not require corrective treatment
 - Required a corrective treatment (details of the corrective treatments will be presented in a listing that will include: patients' ID, the AE, its seriousness, the details of the corrective treatments, and the outcomes of the AE)
 - Structum® dosage modification
 - Decreased
 - Increased
 - Not changed
 - Temporary discontinued
 - AE reoccurred
 - AE did not reoccur

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- Missing data
 - Permanent discontinuation
- Seriousness of the AEs
 - Not serious
 - Other serious medical situation
 - Situation 1
 - Situation 2
 - Hospitalization or prolongation of hospitalization
 - Incapacity of permanent disability
 - Congenital anomaly or malformation present at birth
 - Life threatening
 - Death

Summary MedDRA tables for the overall length of the study will present the frequency of AEs by numbers of patients and by number of events (with patient percentages calculated out of the total number of patients in the safety population) presented by SOC and PT according to:

- Seriousness
- Relationship to Structum® (ARs / SARs)

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9.6 Summary of outcomes and corresponding results tables

Objectives	Outcomes	Tables
Patient disposition		
/	Patient disposition	1. Subgroups of interest
		Figure 1. Flow chart
Primary		
To describe the baseline clinical profile and baseline OA symptom severity (pain, stiffness and function) as assessed by the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) questionnaire, for patients with knee OA and treated with Structum®, a pharmaceutical grade chondroitin sulfate	The description of symptom severity (pain, stiffness, and function) as assessed by the WOMAC questionnaire at baseline	2. WOMAC scores at inclusion
		3. Baseline socio-demographic characteristics of the study population
	Comprehensive description of all source data collected to characterize the clinical profile of included patients treated with Structum®	4. Charlson Comorbidity Index Score and details of relevant comorbidities at inclusion
		5. Metabolic syndrome at inclusion
		6. Knee OA clinical characteristics at inclusion
		7. Location and severity of knee OA at inclusion
	Additional outcome: Treatment characteristics outcomes	8. Prior treatment for knee OA received over the 6 months before the inclusion
		9. Details of Structum® prescription*
		10. Concomitant treatment for knee OA (n=XX patients)
		11. Structum® treatment compliance throughout the follow-up

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		12. Modification of Structum® treatment at the 3-month and 6-month follow-ups
		13. Details of the dosage modifications of Structum® treatment at the 3-month follow-up and the 6-month follow-up
		14. Details of the temporary discontinuations of Structum® at the 3-month follow-up and the 6-month follow-up
		15. Details of the definitive discontinuations of Structum® treatment at the 3-month follow-up and the 6-month follow-up
Secondary		
To describe the knee OA symptoms severity (pain, stiffness, and function) as assessed by the WOMAC questionnaire in patients treated with Structum® over the 6-month follow-up period	Secondary WOMAC outcomes: mean global score of symptoms' severity, mean score of each dimension, and mean differences in symptoms' severity scores at 3 and 6 months (compared to baseline)	16. Description of WOMAC scores at the 3-month and 6-month follow-ups and evolution of total WOMAC score
To describe the burden associated with knee OA in daily life (independence, interaction & recreation, psychological, budget, hygiene and beauty) as assessed by the Burden of Osteoarthritis New Scale (BONe'S) questionnaire in patients treated with Structum® over the 6-month follow-up period	BONe'S outcomes: mean global score of symptoms' severity, mean score of each dimension, and mean differences in symptoms' severity scores at 3 and 6 months (compared to baseline)	17. Description of BONe'S questionnaire at inclusion and at the 3-month and 6-month follow-ups and evolution of global OA burden score
To describe general health (physical and mental) assessed by the Short Form 12 items (SF-12) questionnaire as a quality-of-life measure in patients treated with Structum® over the 6-month follow-up period	SF-12 outcomes: mean global score of general health, mean score of each dimension (physical and mental), and mean differences in general health scores at 3 and 6 months (compared to baseline)	18. Description of SF-12 score at inclusion and at the 3-month and 6-month follow-ups and evolution of the physical and mental scores
To describe treatment persistence in patients treated with Structum® over the 6-month follow-up period	Persistence outcomes: proportion of patients with ongoing Structum® treatment at 3 months and 6 months	19. Patients' persistence with Structum® at the 3-month and 6-month follow-ups

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To describe the global assessment of the patients treated with Structum® over the 6 months follow-up period	Personal global assessment: proportion of patients with a positive assessment of Structum®, as assessed by Structum® treatment satisfaction questionnaire at 3 and 6 months	20. Description of patient satisfaction with the treatment
Exploratory		
To assess the correlation between the results of the BONE'S questionnaire and the SF-12 and WOMAC questionnaires, in participating patients over the 6-month follow-up period	Spearman correlation coefficient and P value for the correlation between the BONE'S questionnaire and the SF-12 questionnaire and between the BONE'S questionnaire and the WOMAC questionnaire at inclusion, 3 and 6 months	21. Correlations between the BONE'S questionnaire and the SF-12 questionnaire and between the BONE'S questionnaire and the WOMAC questionnaire
To describe the evolution of the use of Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) and other analgesics over the 6-month follow-up period and compare with the use of NSAIDs and other analgesics during the last 6 months before inclusion	Proportion of patients with changes in the prescription of NSAIDs and other analgesics	22. Changes in the prescription of NSAIDs and other analgesics
Safety		
/	Additional outcome: Safety outcomes	23. Summary of the reportable safety events and their relationship to Structum®
		24. Summary of the outcomes of the reportable safety events
		25. Reportable safety events according to MedDRA classification and their seriousness and relationship to Structum®

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10 APPENDIX A: SUB-GROUP TABLE

	Time since diagnosis of knee OA (≤12/ >12 months)	Severity of knee OA (Severe /Moderate)	Gender (Male/ Female)	Knee OA location (Unilateral/ Bilateral)	Age (≤65/ >65 years old)	Previous NSAID/ analgesics treatment for knee OA (No/Yes)	Concomitant treatment during the study (No/Yes)
WOMAC scores at inclusion	X		X	X	X	X	X
Baseline socio-demographic characteristics of the study population	X	X	X	X		X	
Charlson Comorbidity Index Score and details of relevant comorbidities at inclusion	X	X	X	X	X	X	
Metabolic syndrome at inclusion		X					
Knee OA clinical characteristics at inclusion	X	X	X	X	X	X	
Location and severity of knee OA at inclusion	X	X	X		X	X	
Prior treatment for knee OA received over the 6 months before the inclusion	X	X	X	X	X		
Details of Structum® prescription	X	X			X		
Concomitant treatment for knee OA	X	X	X	X	X	X	
Structum® treatment compliance throughout the follow-up	X	X					
Modification of Structum® treatment at the 3-month and 6-month follow-ups	X	X	X	X	X		
WOMAC scores at the 3-month and 6-month follow-ups	X		X	X	X	X	X
BONe'S questionnaire at inclusion and at the 3-month and 6-month follow-ups	X	X	X	X	X	X	
SF-12 score at inclusion and at the 3-month and 6-month follow-ups	X	X	X	X	X	X	
Correlations BONe'S questionnaire vs SF-12 questionnaire and BONe'S questionnaire vs WOMAC questionnaire		X					
Changes in the prescription of NSAIDs and other analgesics	X	X	X	X	X		

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