Document Type:	Study Protocol
Official Title:	Prospective multicenter non-interventional study in patients with knee or hip osteoarthritis having a Theraflex treatment to evaluate changes in pain, functions in daily living, and quality of life for an observation period up to 64 weeks.
NCT Number:	NCT03330288
Document Date:	04 Jul 2018

BAYER

NON-INTERVENTIONAL STUDY PROTOCOL

Title:	Prospective multicenter non-interventional study in patients with knee or hip osteoarthritis having a Theraflex® treatment to evaluate changes in pain, functions in daily living, and quality of life for an observation period up to 64 weeks.
Drug:	Theraflex® (Glucosamine hydrochloride 500 mg and Chondroitin sodium sulfate 400 mg)
Sponsor's name and address:	A/O BAYER 3rd Rybinskaya str., 18, bld. 2 107113, Moscow, Russian Federation
Study Identifier	IMPACT number 19649
Version /Date:	3.0 / 4 Jul 2018
Development Phase:	Phase IV, Non-interventional study

By signing this document, these persons agree to conduct the study in accordance to this Protocol

Responsibility for study conducting:	Signature:
PPD Clinical Research Study Manager	Date:
Responsibility for medical aspects:	Signature:
PPD Medical Affairs Consumer Health Team Leader	Date:
Responsibility for product safety:	Signature:
PPD Pharmacovigilance Country Head	Date:
Responsible study statistician:	Signature:
PPD, Statistics, Bayer US, LLC	Date:

1. Table of contents

Оглавление

2. List of abbreviations

AE	Adverse Event
ATC	Anatomical Therapeutic Chemical (Classification System)
CFR	Code of Federal Regulations
Ch	Chondroitin Sulfate
CRF	Case Report Form
CRO	Contract Research Organization
DMP	Data Management Plan
EC	European Commission
EDC	Electronic Data Capture
EFPIA	European Federation of Pharmaceutical Industries and Associations
EMA	European Medicine Agency
ENCePP	European Network of Centers in Pharmacoepidemiology and Pharmacovigilance
EU	European Union
EULAR	European League Against Rheumatism
FDA	Food and Drug Administration
GCP	Good Clinical Practice
Gl	Glucosamine
GPP	Good Publication Practice
GVP	Good Pharmacovigilance Practice
HEOR	Health Economics and Outcomes Research
HOOS	Hip injury and Osteoarthritis Outcome Score
HOOS-PS	HOOS-physical short form
ICD	International Classification of Diseases
ICH	International Conference of Harmonization
IEC	Independent Ethics Committee
INN	International Nonproprietary Name
IRB	Institutional Review Board
IT	Information Technology
KOOS	Knee injury and Osteoarthritis Outcome Score
KOOS-PS	KOOS- physical short form
MAH	Marketing Authorization Holder
MedDRA	Medical Dictionary for Regulatory Activities
MRP	Medical Review Plan
N/A	Not Applicable
NIS	Non-interventional Study
NNH	Number Needed to Harm
OA	Osteoarthritis
OS	Observational Study
PAS	Post-Authorization Study
PASS	Post-Authorization Safety Study

PBRER	Periodic benefit-risk evaluation report
PRO	Patient Reported Outcome
PSUR	Periodic Safety Update Report
QPPV	Qualified Person Responsible For Pharmacovigilance
QRP	Quality Review Plan
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
WHO DD	World Health Organization Drug Dictionary

3. Responsible parties

3.1 Study initiator and funder/MAH

Role:	Author
Name:	PPD, Clinical Research Manager, Medical Affairs Consumer Health
E-mail:	PPD
Role:	Study Initiator
Name:	PPD, Category manager HCP, PPD, Russia
E-mail:	PPD
Role:	Study conduct responsible
Name:	PPD, Clinical Research Manager
E-mail:	PPD
Role:	Study safety lead
Name:	PPD, PV Country Head
E-mail:	PPD
Role:	Study medical expert
Name:	PPD, Medical Affairs Consumer Health Team Leader
E-mail:	PPD
Role:	Study statistician
Name:	PPD, Statistics, Bayer US, LLC
E-mail:	PPD

Contact details of the responsible parties A/O Bayer are available upon request.

4. Synopsis

Acronym/Title	Prospective multicenter non-interventional study in patients with knee or hip osteoarthritis having a Theraflex® treatment to evaluate changes in pain, functions in daily living, and quality of life for an observation period up to 64 weeks
Protocol version identifier	3.0
Date of last version of protocol	4-Jul-2018
IMPACT study number	19649
Drug	Theraflex® (BAY 874017)
Study type/Study phase	Phase IV, non-interventional study
Author	PPD , Clinical Research Manager Medical Affairs Consumer Health
Rationale and background	This long-term prospective observational study in subjects with knee or hip OA, who receive Theraflex®, will allow to obtain valuable information in respect of dynamics of pain syndrome, functions of living, quality of life and satisfaction of patient as well as of actual drug utilization by patients with OA for an observation period up to 64 weeks. Since in Russia at the present time there are no approved standards of Regulatory Authorities for the management of patients with OA, we expect that this study will help to evaluate the approach of doctors to the treatment of OA and to understand the role of Theraflex® in their recommendations.
Research question and objectives	The primary objective of the study is: • To evaluate changes in pain, functions in daily living, and OA related quality of life for an observation period up to 64 weeks The secondary objectives in this study are: • To assess drug utilization with Theraflex® for an observation period up to 64 weeks period • To assess patients satisfaction with Theraflex® treatment for an observation period up to 64 weeks • Description of the use of analgesics for OA for an observation period up to 64 weeks

	• Description of patient characteristics (Age, BMI, Weight, Analgesics intake)
Study design	Open-label, multicenter, single country, non-interventional prospective study in a cohort of patients with Hip or Knee OA stage I to III who started a treatment with Theraflex® with evaluation of health status by physical examination and validated patient and physician's questionnaires for an observation period up to 64 weeks
Population	Male and female patients from 45 to 75 years of age with hip or knee osteoarthritis stage I to III. Approximately 1100 subjects are planned to enrolled in the study in about 60 study centers in Russia.
Variables	Variables to determine the primary endpoint(s) • Changes in pain, other symptoms, functions and knee related quality of life assessed by KOOS in patients with knee OA • Changes in pain, others symptoms, functions and hip related quality of life assessed by HOOS in patients with hip OA Variables to determine the secondary endpoint(s): • Drug utilization of Theraflex® therapy as reported by the patient to their physician • Patient satisfaction measured with a Likert response scale (from 5 – very satisfied to 1-very dissatisfied) • Type, frequency and length of painkiller for the symptomatic treatment of hip OR knee OA for an observation period up to 64 weeks • Other medication/physical therapy for OA related pain (drugs, duration of use, dose, frequency)
Data sources	The investigator collects historic data (demographic and clinical characteristics) from medical records if available. Likewise, the investigator collects treatment related data during visits that take place in routine practice. Each patient is identified by a unique central patient identification code, which is only used for study purposes. For the duration of the study and afterwards, only the patient's treating physician or authorized site personnel is able to identify the patient based on the patient identification code.

Study size	It is planned to enroll approximately 1100 patients into the study.
Data analysis	All variables will be analyzed in an exploratory manner with appropriate descriptive statistical methods: categorical variables by frequency tables (absolute and relative frequencies) and continuous variables by sample statistics (i.e. mean, standard deviation, minimum, median, quartiles and maximum). Statistical analyses will be performed using validated statistical software (e.g. SAS, SAS Institute Inc.).
Milestones	Planned start of data collection – Oct, 2017 FPFV –Oct 2017; LPLV –Feb 2020; end of study –May 2020

5. Amendments

Table 1: Amendments

Amendment Number	Reason for Amendment	New version number	Effective Date
1	Correction of exclusion criteria was conducted, since it became obvious that with initial exclusion criteria slow patient recruitment is predictable The approach for completing the questionnaire was clarified in case the patient has multiple joint OA or bilateral Knee/Hip OA. Requirements for collection of vital signs and data of physical examination were clarified. Information about the Independent Ethics Committee responsible for protocol related documentation review and approval was updated The number of patients is reduced from 1500 patients to 1100 patients.	2,0	17-Nov-2017
2	Originally planned to conduct an observational study of the Theraflex product in 80 study centers of Moscow, St. Petersburg and Yaroslavl regions. In connection with the additional administrative barrier on the part of the Moscow Health Care Department, instead of 40 centers planned for opening in the Moscow region, the number of study centers in Moscow has dropped to 20. Thus, the total number of study centers will not exceed 60, which is 75% of the planned number of clinical centers. In proportion with reduced number of study centers, the number of patients in the study is also reduced by 25%, which in numerical terms approximately corresponds to 1100 patients. In order to calculate the indicator of "patients lost to follow-up subjects", was made a simple analysis of the V2 frequency on the group of the first 10% of subjects included into the study. The analysis was carried out after 3-6 months from the date of patients recruitment, which corresponds to allowable time-window for the second visit. As a result of this analyses, "patients lost to follow-up" index is about 7%, which is significantly lower than initially assumed figure for this indicator (In the Study Risk Register this risk factor was registered as 20% and above). This additionally makes possible to reduce the study population to	3.0	4-Jul-2018

	1100 subjects without negative effect on the result of the whole study. Since the analysis of all variables in the study will be carried out using appropriate methods of descriptive statistics, a decrease in the number of patients cannot have a negative impact on the representativeness. Initially It was planned to have interim analysis after all subjects have completed V2. With this amendment the starting point is changing – Interim analysis will be conducted after 50% of subjects (first 550 enrolled) have completed V2 in order to assess the changes after the first course at the half of the study population..		

6. Milestones

Definitions:

- Start of study: FPFV
- Start of data collection: date of first data entry in database
- End of data collection: date of last data entry in database
- End of study: date of clean database
- Observation period: time-window for data collection
- Final report: final report of study results 12 months after clean database

7. Rationale and background

In the recommendations of The Osteoarthritis Research Society International (OARSI) and The European League Against Rheumatism (EULAR), all therapeutic agents for Osteoarthritis (OA) treatment are classified to non-pharmacological, pharmacological and invasive treatments, which can have not only symptom-modifying, but also structure-modifying effects on the basis of their ability to positively influence disease progression (Zhang W. et al., 2008). Structure-modifying medications for OA treatment are those whose actions are based on anabolic processes activation in cartilage matrix, suppression of lysosomal enzymes and stimulation of chondrocyte functions (Jerosch J., 2011). Slow-acting drugs (glucosamine, chondroitin, hyaluronic acid, diacerein, unsaponifiable matters of avocado and soya) exert a delayed effect that lasts beyond discontinuation. These therapeutic agents possess not only symptomatic effects, but also, probably, may retard the OA progression, having an influence on several pathogenesis links of the disease (Zhang W. et al., 2008).

The demonstrated efficacy of glucosamine (Gl) and chondroitin sulfate (Ch) in form of mono-medication in several studies created the necessary prerequisites for combined therapy (Qiu GX.,et al., 2005, Zegels B., 2013). It was shown in an experimental model, that combination of chondroitin sulfate and glucosamine increased chondrocyte production of glycosaminoglycans by 96,9% versus 32% in case of an administration of chondroitin sulfate or glucosamine alone (Lippielo L. et al., 1999). The GAIT trial studying the impact of glucosamine (500 mg 3 times daily) and chondroitin sulfate (400 mg 3 times daily) on the joint space narrowing progression

in gonarthrosis have shown higher potential of clinical effect predominantly in the II radiological stage (Kellgren/Lawrence) in comparison with the III one in the subgroup of patients with moderate-to-severe knee pain (Clegg DO. et al., 2006). Moreover, the authors focused attention on good safety profile of the therapy that was comparable with placebo administration (Sawitzke, 2010). According to Lapane KL. et al., about a half (47%) of patients over 49 years with radiographic knee OA use additional medicines and about a quarter (24%) combined additional and conventional (predominantly NSAIDs) medications. The most popular additional medicines were glucosamine and chondroitin: more than 55% used these products alone or in combination (Lapane KL. et al., 2012). Investigators of the University of Queensland (Australia), have found out while questioning of patient of 27-95 years old with knee and hip joints OA, that for the purpose of pain relief and joint function improvement most frequently used medications are those containing GL and Ch (51% of males and 60% of females) (Ng NT. et al., 2012).

Up to 30% of OA patients over 55 years in UK don't receive an adequate therapy of chronic pain syndrome (McAlindon TE. et al., 1992). Chronic pain in OA leads to shortening of patient life duration by an average of 10 – 12 years (Nuesch, Dieppe, & Reichembach, 2011..) Chronic disability in OA leads to an 2.4 times increase in mortality (hazard ratio 3.91) but in association with multi-morbidity in 4 times (hazard ratio 3.91) compared with general population (Landi F. et al., 2010).

Russian Ministry of Health recommends to use only NSAIDs ("The Standard of Primary Health Care in Gonarthrosis and Similar Clinical Conditions", 2012). However, in Russia a variety of medicinal products from chondroprotectors category are widely recommended by physicians and the majority of leading scientific experts consider this treatment as effective as a part of the complex therapy. This fact was reflected in the recently published "Recommendations for the Treatment of Patients with Osteoarthrosis with Comorbidity in Clinical Practice of GPs", 2015. This document, prepared by Russian Scientific Society of GPs and Association of Russian Rheumatologist, compiled by 100 main Russian experts from different regions, affirms, that a complex OA therapy should include symptomatic slow acting drugs and the best clinical results would be obtained with the combination of Gl and Ch.

Thus, the long-term prospective observational study in subjects with knee or hip OA, who receive Theraflex®, will allow to obtain valuable information in respect of dynamics of pain syndrome, functions of living, quality of life and satisfaction of patient as well as of actual drug utilization by patients with OA for an observation period up to 64 weeks.

Use of Gl and Ch is widespread among OA patients worldwide, however since in Russia at the present time there are no standards approved by Regulatory Authorities for the management of patients with OA, we expect that this study will help to evaluate the approach of doctors to the treatment of OA and to understand the role of Theraflex® within the therapeutic algorithm in the context of routine clinical practice.

8. Research questions and objectives

8.1 Primary objective

The primary objective of the study is:

- To evaluate changes in pain, functions in daily living, and OA related quality of life for an observation period up to 64 weeks

8.2 Secondary objectives

The secondary objectives in this study are:

- To assess drug utilization with Theraflex® for an observation period up to 64 weeks
- To assess patients satisfaction with Theraflex® treatment for an observation period up to 64 weeks
- Description of the use of analgesics for OA for an observation period up to 64 weeks
- Description of patient characteristics (Age, BMI, Weight, Analgesics intake at baseline)

9. Research methods

9.1 Study design

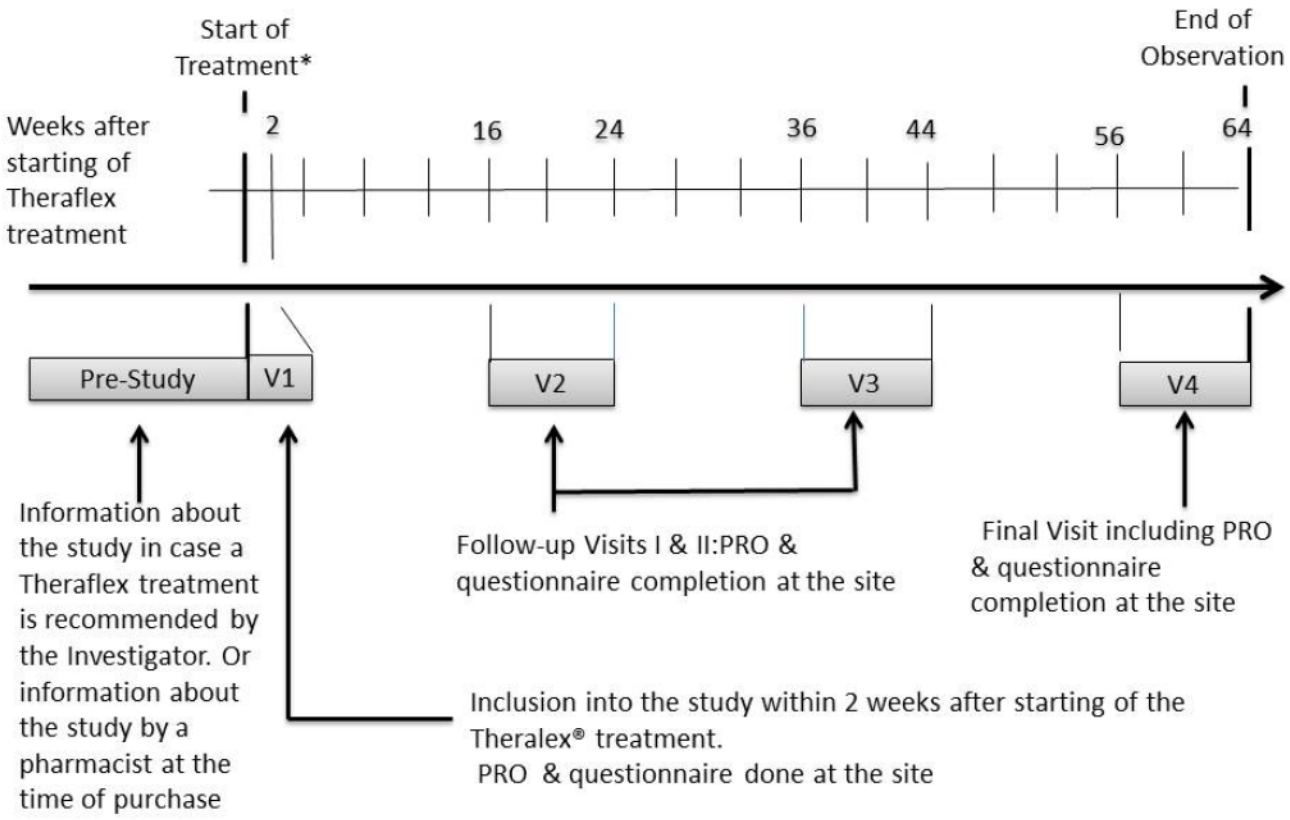
This is a company sponsored, single country, open-label multicenter non-interventional prospective study in a cohort of patients with Hip or Knee OA stage I to III who started a treatment with Theraflex® with evaluation of health status by physical examination and validated patient and physician's questionnaires for an observation period up to 64 weeks.

There are up to 4 study visits planned: within two weeks after starting the Theraflex® treatment subjects will be included into the study in the initial study visit if they meet all inclusion criteria and none of the exclusion criteria. The initial visit is followed by two follow-up visits and final end of observation visit for an observation period up to 64 weeks. If patient switches to another Gl and Ch brand the observation of the patient is terminated.

During all visits data generated during the normal clinical practice will be collected by the investigator. In addition the patient reported outcome assessing Knee or Hip osteoarthritis outcome will be collected at the time of the visit as well as a simple patient satisfaction questionnaire.

For Knee OA the Knee injury and Osteoarthritis Outcome Score (KOOS) will be used. For Hip OA the Hip Osteoarthritis Outcome Score (HOOS) will be used (See section 9.3.3.8)).To reduce the number of questions and the burden of the patient, the physical short form of both patient reported outcomes (PRO) (KOOS-PS, HOOS-PS) containing reduced number of questions replaces the two subscales functions "daily living" and "functions, sports and recreational activities"

Figure 1: Study Overview



*start of treatment occurs after purchase of the product at the pharmacy (self-selection)

9.1.1 Primary endpoint(s)

The Primary endpoints are:

- Changes in pain, other symptoms, functions and knee related quality of life assessed by KOOS in patients with knee OA from the first assessment throughout the observation period
- Changes in pain, others symptoms, functions and hip related quality of life assessed by HOOS in patients with hip OA from the first assessment throughout the observation period

9.1.2 Secondary endpoint(s)

The secondary endpoint(s) is/are:

- Drug utilization of Theraflex® therapy as reported by the patient to their physician
- Patient satisfaction measured with a Likert response scale (from 1-very dissatisfied to 5 – very satisfied)
- Type, frequency and length of painkiller for the symptomatic treatment of hip OR knee OA for an observation period up to 64 weeks
- Other medical/physical therapy for OA related pain (drugs/type of therapy, duration of use, dose, frequency)

9.1.3 Strengths of study design

The non-interventional study design was chosen to allow evaluation (or assessment) of current clinical practices. In contrast to clinical studies, the design of non-interventional studies (NIS) does not include randomization and "blinding", and selection of patients does not depend on the strict criteria of inclusion/exclusion. There are also limitations to this design (e.g. no possibility for comparison), but for the purpose of the objectives in this study this methodology shall provide sufficient data.

Non-interventional studies are a valuable instrument as they allow analysis samples of patients without special selection during routine clinical practice.

A prospective non-interventional study, in contrast to a retrospective one, makes it possible to plan in advance the design, procedure of gathering and processing of data, which considerably increases validity of the results.

9.2 Setting

9.2.1 Eligibility

Male and female patients from 45 to 75 of age with hip or knee osteoarthritis stage I to III. Approximately 1100 subjects are planned to be included in the study in about 60 study centers in Russia.

9.2.2 Inclusion criteria

Inclusion criteria:

- Patients 45 to 75 years with Hip or Knee OA stage I to III
- Patient started current treatment with Theraflex® not more than 2 weeks prior to inclusion into the study
- Personally signed and dated informed consent.

9.2.3 Exclusion criteria

Exclusion criteria:

- Patients participating in an investigational program with interventions outside of routine clinical practice
- Patients with Hip or Knee OA stage 0 or stage IV
- Contraindications for use of Theraflex® in accordance with approved label(known hypersensitivity, severe chronic renal failure)
- Females who are pregnant or breastfeeding
- Patients who completed a treatment with Theraflex® or the other Symptomatic Slow-Acting drug in Osteoarthritis (SYSADOA) less than 5 months before start of the current treatment
- Patients who completed intra-articular corticosteroids treatment in the last 3 months before enrollment .
- Patients who completed hyaluronic injections and/or platelet-rich plasma (PRP) therapy of the lower limbs in the last 6 months.

9.2.4 Withdrawal

In this observational study, withdrawal from the study is independent of the underlying therapy and will not affect the patient's medical care. Each patient can refuse to further participate or may withdraw from the study at any time and without giving a reason. If a patient wants to terminate the study participation, no further data will be collected. However, the patient will be asked whether she/he agrees that the data collected so far can be used. In case the patient does not agree, these data will not be used for any patient level analysis of study data. This includes safety data with the exception that data already captured in the company's safety database will be kept. However, data which are relevant for primary outcomes might be displayed on an aggregated level to assess a potential bias. In case a patient would like to withdraw the consent given earlier, s/he should inform his/her doctor and the site should document the withdrawal in the Case Report Form as well as in the patient medical records.

9.2.5 Replacement

Patients will not be replaced after drop out.

9.2.6 Representativeness

The patients included in the study should be selected only based on eligibility according to inclusion criteria. No further selection should be applied. Investigators will be asked to sample consecutive patients whenever possible to reduce selection bias.

9.2.7 Visits

The investigator documents an initial visit, follow-up visits and the end of observation/final visit for each patient in the case report form (CRF). Follow-up visits occur during routine practice, the study protocol does not define exact referral dates for those visits. The end of

observation/final visit is to be documented for a period up to 64 weeks after start of the initial treatment.

The observation period for each patient is up to 64 weeks. If patient switches to another Gl and Ch brand the observation of the patient is terminated.

9.2.7.1 Prior to inclusion

A subject can only be included in the study after he/she has purchased the product in a pharmacy. However potential patient who like to participate in the study should be included as early as possible but not later than 2 weeks after they started the treatment into the study to gain data in the beginning of the Theraflex® treatment.

Patient can be made aware about the study either by the treating physician OR by a pharmacist when a patient is purchasing Theraflex®.

Physician

At the time the physician decides to give a recommendation for Gl+Ch treatment to a patient diagnosed with hip OR knee OA and once a patient is found to be potentially eligible for inclusion, the investigator will inform the patient about the study together with the recommendation of the treatment.

The investigator must explain to the patients that he/she will make the final choice on the Gl+Ch product available on the market.

Pharmacy

Pharmacy may also be approached for the recruitment of potential study participants. At the time point a subject is purchasing Theraflex® the pharmacist may inform the subject about the potential study and if there is interest by the patient, the pharmacist would make a referral to an investigator nearby participating in the study.

9.2.7.2 Visit 1: Enrollment/Initial visit

Visit 1 is the first Visit at the physician after the subject bought the product in a pharmacy and started treatment with Theraflex®. Visit 1 must be within the first 2 weeks after start of treatment with Theraflex®.

A patient who has not been informed about the study prior to the recommendation of Gl+Ch but is currently on Theraflex® treatment within no more than for 2 weeks and meets all inclusion and none of the exclusion criteria can also be included in the study.

During the visit the investigator gives the necessary explanations about the NIS, asks the patient to read the information for the study patients and the informed consent form. If the patient gives the consent to participate in the study, the informed consent is signed both by the patient and the investigator.

During the visit the investigator conducts all examinations according to the local routine clinical practice. In addition the investigator provides to the subject the PRO questionnaire and the overall satisfaction question for completion for Visit 1. If the patient has multiple joint OA or double-sided (bilateral) Knee/Hip OA, only one «target» joint to be selected for the evaluation, where the patient experiences the most severe pain at the time of enrollment. Filling in a questionnaire, the patient needs to associate his/her responses with the "target" joint only during the entire follow-up period.

Following information will be captured in the CRF:

- Date of visit
    - day, month, year
- Date of informed consent
- Radiological Diagnosis of OA of Hip or Knee according to the Kellgren and Lawrence Criteria *
- Patient demographic data
- Gender
- Date of birth
- Race / ethnicity
- Physical Examination
- Weight (kg)
- Height (cm) (V1 only)
- Vital Signs
    - Blood Pressure
    - Body Temperature (axillary temperature)
    - Heart rate
- Lifestyle
- Alcohol and tobacco use
- Review of Theraflex® drug utilization
    - Start / End of treatment
    - Dose/frequency of treatment
- KOOS or HOOS Questionnaire (PRO)
- Patient satisfaction with Theraflex®
- Medical history
- Concomitant disease(s)
- Concomitant medication
- Concomitant non-medication therapies (e.g. physiotherapy, surgery)
- Adverse events

All examinations are performed according to the local routine institutional practice as indicated by the attending physician. PRO should be completed at the time of the visit at the physician by the patient.

9.2.7.3 Follow-up Visits I & II

Follow-up visit will be the first visit at the physician during the time frame week 16-24 (Follow-up I), week 36-44 (Follow-up II), after start of treatment with Theraflex®. If patient switches to another Symptomatic Slow-Acting drug in Osteoarthritis (SYSADOA), the observation of the patient is terminated.

During the follow-up visit the investigator conducts all examinations according to the local routine clinical practice. In addition the investigator provides to the subject the PRO

questionnaire and the overall satisfaction question for completion. The patient needs to assess the outcome of joint treatment, which was selected as the "target" at the first visit.

Following information will be captured in the CRF:

- Date of visit
    - day, month, year
- Physical Examination
- Weight (kg)
- Vital Signs
    - Blood Pressure
    - Body Temperature (axillary temperature)
    - Heart rate
- Review of Theraflex® drug utilization
    - Start / End of treatment
    - Dose/frequency of treatment
- KOOS or HOOS Questionnaire (PRO)
- Patient satisfaction with Theraflex®
- Concomitant medication
- Concomitant disease(s)
- Concomitant non- medication therapies (e.g. physiotherapy, surgery)
- Adverse events

All examinations are performed according to the local routine institutional practice as indicated by the attending physician. PRO should be completed at the time of the visit at the physician by the patient.

9.2.7.4 Final Visit / End of Observation

Final Visit / End of Observation will be the first visit at the physician's office after an observation period up to 64 weeks after start of treatment with Theraflex®. Final visit should be performed during the time frame week 56-64

During the visit the investigator conducts all examinations according to the local routine clinical practice. In addition the investigator provides to the subject the PRO questionnaire and the overall satisfaction question for completion.The patient needs to assess the outcome of joint treatment, which was selected as the target at the first visit.

Following information will be captured in the CRF:

- Date of visit
    - day, month, year
- Physical Examination
- Weight (kg)
- Vital Signs
    - Blood Pressure
    - Body Temperature (axillary temperature)
    - Heart rate
- Review of Theraflex® drug utilization

- Start / End of treatment
- Dose/frequency of treatment

- KOOS or HOOS Questionnaire (PRO)
- Patient satisfaction with Theraflex®
- Concomitant disease(s)
- Concomitant non-medication therapies (e.g. physiotherapy, surgery)
- Adverse events

All examinations are performed according to the local routine clinical practice as indicated by the attending physician. PRO should be completed at the time of the visit at the physician by the patient.

Premature end of therapy does not automatically imply end of documentation: the patient should be followed up until the end of the observation period (64 weeks) or until no longer possible.

Table 2: Tabulated overview on variables collected during the study

	Prior to inclusion to the study	Visit 1 Inclusion into the study	Visit 2 & 3 Follow-up visit	Visit 4 Final Visit / End of Observation
		First Visit after starting treatment with Theraflex® [not more than 2 weeks]	Week 16-24 Week 36-44 after start of treatment with Theraflex®	Week 56-64 after start of treatment with Theraflex®
Assessment of inclusion / exclusion criteria		X		
Information about the study	X			
Written Informed Consent		X		
Patient demographic data		X		
Physical Examination*		X	X	X
Height /Weight**		X	X	X
Vital signs		X	X	X
OA Staging according to Kellgren & Lawrence*		X		
Lifestyle		X		
Concomitant therapies other than drug		X	X	X
Medical history /concomitant diseases		X	X	X

Concomitant medication		X	X	X
Adverse events		X	X	X
Review of Theraflex® drug utilization		X	X	X
KOOS or HOOS Questionnaire (PRO)		X	X	X
Patient satisfaction (PRO)		X	X	X

**performed in accordance with local practice*
*** Height at Visit 1 only*

9.3 Variables

The investigator collects historic data (demographic and clinical characteristics) from medical records if available, or else by interviewing the patient. Likewise, the investigator collects treatment related data during initial visit and follow-up visits. The investigator documents the study-relevant data for each patient in the case report form (CRF). The CRF is available upon request (see Table 3, Annex 1).

9.3.1 Variables to determine the primary endpoint(s)

The variable(s) for primary objective(s) is/are:

- Changes in pain, other symptoms, functions and knee related quality of life assessed KOOS in patients with knee OA from the first assessment throughout the observation period
- Changes in pain, others symptoms, functions and hip related quality of life assessed by HOOS in patients with hip OA from the first assessment throughout the observation period

9.3.2 Variables to determine the secondary endpoint(s)

The outcome variable(s) for secondary objective(s) is/are:

- Drug utilization of Theraflex® therapy as reported by the patient to their physician
- Patient satisfaction measured with a Likert response scale (from 1-very dissatisfied to 5 – very satisfied)
- Type, frequency and length of painkiller for the symptomatic treatment of hip OR knee OA for an observation period up to 64 weeks
- Other medical/physical therapy for OA related pain (drugs, duration of use, dose, frequency)

9.3.3 Detailed description of variables collected

9.3.3.1 Date of Visit

- Date (Day, Month, Year) of visit

9.3.3.2 Patient demographic data

For demographic/socio-demographic assessment, the following data will be recorded:

- Year of birth

- Age
- Gender
- Race (e.g. White, Black or African American, Asian, not reported)

9.3.3.3 Vital signs

Information on vital signs to be documented, (if such data are available and the colletion of this data is the routine clinical practice of the Investigator) include:

- Temperature
- Blood pressure
- Heart rate

9.3.3.4 Physical Examination

Physical examination performed in accordance with routine clinical practice. Information on normal/abnormal findings after physical examination, height (at Visit 1 only) and weight. In the absence of the height meter and scale in the doctor's office.height and weight can be registered from the patient's words.

9.3.3.5 Lifestyle

- alcohol and tobacco use during the last 3 months prior to the visit

9.3.3.6 Disease history

Disease history describes any medical findings that are relevant to the underlying disease and were present before inclusion into the study. Findings and diagnosis meeting the criteria listed below have to be documented:

- Date of diagnosis
- Disease status at study start
- Risk factors, such as:
    - hereditary diseases of bones and joints
    - non-genetic (age, excess weight, hormonal disorders, malformations of the bones and joints, joint operations)
    - exogenous risk factors (professional activity, trauma, sports)

9.3.3.7 OA Classification according to Kellgren & Lawrence

The Kellgren and Lawrence system (Kellgren J.H., 1957 P. 494–501) is a method of classifying the severity of OA into five grades. Grade I to III as indicated in the label for Theraflex® is referring to this classification. In case it is normal clinical practice at the site to do the grading without using the Kellgren and Lawrence system, the subject can be still included in the study.

Has the Kellgren Lawrence scale being used for the diagnosis?

☐ Yes, if yes please indicate below which grade is diagnosed according to Kellgren and Lawrence:

- **grade 0**: no radiographic features of OA are present
- **grade 1**: doubtful joint space narrowing (JSN) and possible osteophytic lipping
- **grade 2**: definite osteophytes and possible JSN on anteroposterior weight-bearing radiograph
- **grade 3**: multiple osteophytes, definite JSN, sclerosis, possible bony deformity
- **grade 4**: large osteophytes, marked JSN, severe sclerosis and definite bony deformity

☐ No

9.3.3.8 KOOS or HOOS questionnaire (PRO)

Depending on the diagnosis (knee vs. hip OA), one of the two following questionnaires will be used.

Knee injury and Osteoarthritis Outcome Score (KOOS)

The KOOS questionnaire should be completed during the visit at the physician by the patient.

KOOS consists of 5 subscales; Pain, other Symptoms, Function in daily living (ADL), Function in sport and recreation (Sport/Rec) and knee related Quality of life (QOL). The previous week is the time period considered when answering the questions. Standardized answer options are given (5 Likert boxes) and each question is assigned a score from 0 to 4.

KOOS has been validated in patients with mild to moderate OA (Kellgren and Lawrence grades I-III) of thee knee hence a similar populations as observed in the study (Tanner, 2007).

KOOS is patient-administered, the format is user friendly, and takes about 10 minutes to complete.

The original KOOS Questionnaire contains a total of 42 questions. To reduce the number of questions to 27 the KOOS- physical short form (KOOS-PS) containing 7 Questions on function replaces the two subscales functions, daily living with 17 questions (A1-A17) and functions, sports and recreational activities with 5 questions (SP1-SP5).

The proposed questionnaire for the patient with knee OA would contain following elements therefore:

- Symptoms: 5 questions (S1-S5) from KOOS
- Stiffness: 2 Questions (S6- S7) from KOOS
- Pain: 9 Questions (P1-P9) from KOOS
- Function: 7 questions from KOOS-PS
- Quality of life: 4 Questions (Q1-Q4) from KOOS

Link for further information: http://www.koos.nu/index.html

Hip disability and Osteoarthritis Outcome Score (HOOS)

The HOOS questionnaire should be completed during the visit at the physician by the patient.

HOOS consists of 5 subscales; Pain, other Symptoms, Function in daily living (ADL), Function in sport and recreation (Sport/Rec) and hip related Quality of life (QOL). The last week is taken into consideration when answering the questions. Standardized answer options are given (5 Likert boxes) and each question gets a score from 0 to 4.

According to the user guidance published on their homepage, HOOS validation work is ongoing.

HOOS is patient-administered, the format is user friendly, and takes about 10 minutes to fill out. A Russian version of the questionnaire is not available.

The original HOOS Questionnaire contains a total of 40 questions. To reduce the number of questions to 24 the HOOS- physical short form (HOOS-PS) containing 5 Questions on function replaces the two subscales functions, daily living with 17 questions (A1-A17) and functions, sports and recreational activities with 4 questions (SP1-SP4)

- Symptoms: 3 questions (S1-S3) from HOOS
- Stiffness: 2 Questions (S4- S5) from HOOS
- Pain: 10 Questions (P1-P10) from HOOS
- Function: 5 questions from HOOS-PS
- Quality of life: 4 Questions (Q1-Q4) from HOOS

Link for further information: http://www.koos.nu/index.html

9.3.3.9 Patient satisfaction with Theraflex®

The Satisfaction question should be completed during the visit at the physician by the patient. Patient satisfaction measured with a Likert response scale (from 5 – very satisfied to 1-very dissatisfied).

How satisfied are you with your treatment with Theraflex® ?

- Very satisfied
- Satisfied
- Neither satisfied nor dissatisfied
- Dissatisfied
- Very dissatisfied

Guidance to the patients what the individual categories mean will be provided by the investigator.

9.3.3.10 Co-morbidities (medical history, concomitant diseases)

Co-morbidities are any medical findings, whether or not they pertain to the study indication, that were present before start of therapy with Theraflex® independent on whether or not they are still present. They have to be documented in the Medical History/Concomitant Diseases section.

For any co-morbidity, the diagnosis, the start and the stop date/ongoing have to be documented.

9.3.3.11 Drug Utilization

At every visit after start of the treatment with Theraflex® the physician should collect in detail start and end as well as frequency of Theraflex® treatment as reported by the patient into the CRF

To evaluate the drug utilization of the Theraflex® treatment the physician should also specifically ask how often Theraflex® is taken in average during a treatment.

- Start Date of Theraflex®
- End Date of Theraflex®
- Change of dosing/reason for change
- Dose
    - 3 capsules per Day
    - 2 capsules per Day
    - 1 capsules per Day

- The duration of the period without Theraflex®

The first three weeks which do have a different posology (3 capsules per day) according to the label should be entered as a distinct period to the treatment period with a recommended posology of 2 capsules per day.

9.3.3.12 Prior and concomitant treatments

All treatments obtained before study start (initiated and stopped before study start) is defined as prior treatments. Prior treatments meeting the criteria listed below are considered to be relevant to the study indication have to be documented:

- Slow-acting drugs
  - Glucosamine
  - Chondroitin
  - Gialuronic acid
  - Diacerein
  - Unsaponifiable matters of avocado and soya
- Pain syndrome therapy
  - Analgesics
  - NSAID
- Topical pain therapy
  - Topical NSAID
- Intra-articulararticular injections
- Manual therapy
- Surgery
- Physiotherapy

Treatment of comorbid diseases (Diabetes mellitus, Hypertension, Obesity)

- Antihypertensive drugs
- Drugs for treatment of diabetes
- Anticoagulants
- Other

All treatments obtained in addition to Theraflex® for any indication (either initiated before study start or during the study) is defined concomitant treatments and has to be documented.

Information to be collected for medication includes:

- Trade name or INN
- Start date, stop date/ongoing
- Dose
- Unit
- Frequency
- Application route
- Indication

9.3.3.13 Laboratory parameters

No laboratory parameters will be collected.

9.3.3.14 End of observation

If available the primary reason for end of observation/study discontinuation should be stated:

- Regular end of observation
- Patient lost to follow up
- Consent withdrawn by patient
- Investigator decision
- (Serious) Adverse Event/Adverse Drug Reaction
- Pregnancy
- Lack of efficacy
- Patient died
- Change to another Gl+Ch therapy (which therapy and reason for switch)
- Site closed
- Study terminated

9.3.3.15 Adverse events/Adverse events of special interest

(Serious) Adverse Events need to be collected as described in section 11.2. Information collected includes:

- Diagnosis of AE, or symptom (if diagnosis unknown)
- Start and stop date
- Seriousness
- Relatedness to therapy
- Action taken
- Event outcome
- Other specific treatment(s) of AE

9.4 Data sources

The investigator collects historic data (demographic and clinical characteristics) from medical records if available. Likewise, the investigator collects treatment related data during visits that take place in routine practice. Each patient is identified by a unique central patient identification code, which is only used for study purposes. For the duration of the study and afterwards, only the patient's treating physician or authorized site personnel is able to identify the patient based on the patient identification code.

9.5 Study size

The study will be analyzed descriptively. Therefore the study is not statistically powered. It is planned to enroll 1100 subjects into the study.

9.6 Data management

A Contract Research Organization (CRO) will be selected and assigned for EDC system development. The CRF will be part of the EDC system which allows documentation of all outcome variables and covariates by all participating sites in a standardized way. Information on the EDC system is available upon request (Table 3, Annex 1). Detailed information on data management, including procedures for data collection, retrieval and preparation are given in the Data Management Plan (DMP), which is available upon request (see Table 3, Annex 1).

For information on quality control, refer to section 9.8.

9.7 Data analysis

All variables will be analysed in an exploratory manner with appropriate descriptive statistical methods: categorical variables by frequency tables (absolute and relative frequencies) and continuous variables by sample statistics (i.e. mean, standard deviation, minimum, median, quartiles and maximum).

Statistical analyses will be performed using validated statistical software (e.g. SAS, SAS Institute Inc.).

All statistical details including calculated variables and proposed format and content of tables will be detailed in the statistical analysis plan (SAP). The SAP will be finalized before study database lock. The analysis will be performed in accordance with the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology.

9.7.1 Statistical considerations

Statistical analyses will be of explorative and descriptive nature.

All variables will be analyzed descriptively with appropriate statistical methods: categorical variables by frequency tables (absolute and relative frequencies) and continuous variables by sample statistics (i.e. mean, standard deviation, minimum, median, quartiles and maximum). Continuous variables will be described by absolute value and as change from baseline per analysis time point, if applicable.

Additionally, measured HOOS/KOOS subscales values and changes from baseline will be presented using 95% CI.

All analyses will be performed for the total study population (overall analysis). Patients receiving at least one dose of Theraflex® will be included in the analysis. Whenever reasonable, data will be stratified by subgroups (e.g. age, gender, baseline characteristics).

Sample size and disposition information by analysis time point will be displayed in a frequency table.

All therapies documented will be coded using the World Health Organization – Drug Dictionary (WHO-DD). Medical history, any diseases and AEs will be coded using the latest Medical Dictionary for Regulatory Activities (MedDRA) version.

All statistical details including calculated variables and proposed format and content of tables will be detailed in the Statistical Analysis Plan (SAP). The SAP will be finalized before study database lock. The SAP is available upon request.

It is planned to have 1 interim analysis after 50% of (first 550 enrolled) subjects have completed V2. The main purpose of Interim analyses to assess the changes after the first course of treatment with Theraflex®. The final analysis will be performed after end of the study which is the date the analytical dataset is completely available.

9.8 Quality control

9.8.1 Data quality

Before study start at the sites, all investigators will be sufficiently trained on the background and objectives of the study and ethical as well as regulatory obligations. Investigators will have the chance to discuss and develop a common understanding of the study protocol and the CRF.

A CRO will be selected and assigned for EDC system development, quality control, verification of the data collection, data analysis and data transfer to Bayer.

All outcome variables and covariates will be recorded in a standardized CRF. After data entry, missing or implausible data will be queried and the data will be validated. A check for multiple documented patients will be done.

Detailed information on checks for completeness, accuracy, plausibility and validity are given in the Data Management Plan (DMP). The same plan will specify measures for handling of missing data and permissible clarifications. The DMP is available upon request (see Table 3: List of stand-alone documents, Annex 1).

Medical Review of the data will be performed according to the Medical Review Plan (MRP). The purpose of the Medical Review is to verify the data from a medical perspective for plausibility, consistency, and completeness and to identify potential issues that could affect the robustness of the collected study data or the progress of the study. Detailed information on the Medical review will be described in the MRP, which is available upon request (see Table 3, Annex 1).

National and international data protection laws as well as regulations on observational studies will be followed. Electronic records used for capturing patient documentation (eCRF) will be validated.

9.8.2 Quality review

In a subset of patients source data verification will be conducted. The purpose is to review the documented data for completeness and plausibility, adherence to the study protocol and verification with source documents.

The data quality will be assured by using by telephone interview and quality review visit:

Telephone interview

During the telephone interview the officer, responsible for the telephone interview:

- Ensures adherence to NIS protocol and any amendments

Quality review visit in the study centers

The individual, responsible for data review will have an access to the data of the patients in the centers. The quality review will consist of two parts: interview and verification of the compliance of the data presented in the Case Report Forms with the data of the primary documentation.

During conduction of the NIS the person responsible for the quality review:

- controls observance of the protocol and amendments to it;
- controls completeness and accuracy of entry of the data into CRF and their compliance with the data of the primary documentation;
- shall have an access to any documentation related to the NIS.

Detailed measures for quality reviews will be described in the Quality Review Plan (QRP). The QRP is available upon request (see Table 3, Annex 1).

9.9 Limitations of the research methods

The non-interventional study design was chosen to allow evaluation (or assessment) of current clinical practices. In contrast to clinical studies, the design of non-interventional studies (NIS) does not include randomization and "blinding", and selection of patients does not depend on the strict criteria of inclusion/exclusion. There are also limitations to this design (e.g. no possibility for comparison), but for the purpose of the objectives in this study this methodology shall provide sufficient data.

Non-interventional studies are a valuable instrument as they allow analysis samples of patients without special selection during routine clinical practice.

A prospective non-interventional study, in contrast to a retrospective one, makes it possible to plan in advance the design, procedure of gathering and processing of data, which considerably increases validity of the results.

10. Protection of human subjects

10.1 Ethical conduct of the study

This study is an observational study where Theraflex® is recommended in the customary manner in accordance with the terms of the marketing authorization. There is no assignment of a patient to a particular therapeutic strategy. The treatment recommendation falls within current practice and the recommendation of the medicines is clearly separated from the decision to include the patient in the study. The final decision on which product the patient will take is done by the patient through the purchase of the product at a pharmacy.

No additional diagnostic or monitoring process is required for participation or during the study.

Epidemiological methods will be used for the analysis of the collected data.

10.2 Regulatory authority approvals/authorizations

The study will be carried out within an approved indication and in accordance with the routine clinical practice.

Although the study is conducted in the Russian Federation, the study design is in accordance to the definition of a non-interventional study as defined in the European Clinical Trials Directive (2001/20/EC) which are further discussed in details in the “consideration on the definition of NIS trials” by the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP, 2011).

Recommendations for NIS studies given by European Federation of Pharmaceutical Industries and Associations (EFPIA, Oct 2007) will be followed as well as ICH-GCP guidelines whenever possible.

Collection and handling of personal data in this study will be done in accordance with current local legislation (Federal Law # 152-FZ of 27.07.2006 “About personal data”)

Ethical assessment will be done by expert Independent review board (IRB), specialized in NIS assessment. Protocol related documentation to be submitted to IRB for the approval, located atInter-University Ethics Committee.

10.3 Independent ethics committee (IEC) or institutional review board (IRB)

Ethical assessment will be done by expert Independent review board (IRB), specialized in NIS assessment. Protocol related documentation to be submitted to IRB for the approval, located at Inter-University Ethics Committee:

PPD
e-mail: PPD
Mobile: PPD

10.4 Audit and Inspection

To ensure compliance regulatory requirements, a member of the sponsor's (or a designated CRO's) quality assurance unit may arrange to conduct an audit to assess the performance of the study at the study site and of the study documents originating from there.

The investigator/institution will be informed of the audit outcome.

In addition, inspections by regulatory health authority representatives and IEC(s)/IRB(s) are possible. The investigator should notify the sponsor immediately of any such inspection.

The investigator/institution agrees to allow the auditor or inspector direct access to all relevant documents and allocate his/her time and the time of his/her staff to the auditor/inspector to discuss findings and any issues. Audits and inspections may occur at any time during or after completion of the study.

11. Patient information and consent

Before documentation of any data, informed consent is obtained by the patient in writing. In countries where required by law or regulation, the investigator must have the IECs/IRB written approval/favorable opinion of the written informed consent form and any other written information to be provided to patients prior to the beginning of the observation.

11.1 Patient insurance

In this study, data on routine treatment of patients in daily practice are documented and analyzed with the help of epidemiological methods. Treatment including diagnosis and monitoring of therapy follows exclusively routine daily practice. Current medical daily practice is observed, and for the patient no risks beyond regular therapy exist – there is no additional hazard arising from study participation. As no study related risks exist, there is no need to protect the patient additionally by a patient insurance. The general regulations of medical law and the professional indemnity insurance of the investigators and, respectively, the institutions involved provide sufficient protection for both patient and investigator.

No study medication will be provided to participants. Thus, product insurance is covered by the existing product liability.

11.2 Confidentiality

Bayer as well as all investigators ensure adherence to applicable data privacy protection regulation. Data are transferred in encoded form only. The entire documentation made available to Bayer does not contain any data which, on its own account or in conjunction with other freely available data, can be used to re-identify natural persons. The investigators are obligated to ensure that no documents contain such data.

All records identifying the subject will be kept confidential and will not be made publicly available. Patient names will not be supplied to the MAH. If the patient name appears on any document, it must be obliterated before a copy of the document is supplied to the MAH. Study findings stored on a computer will be stored in accordance with local data protection laws.

The investigator will maintain a list to enable patients' records to be identified in case of queries. In case of a report of a serious adverse event (SAE), the responsible pharmacovigilance person may ask for additional clarification. In that case, the company is not allowed to directly contact the patient. All additional information will be provided by the investigator.

12. Management and reporting of adverse events/adverse reactions

12.1 Definitions

An adverse event (AE) is any untoward medical occurrence in a patient administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (e.g. an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to this medicinal product [9].

The term also covers laboratory findings or results of other diagnostic procedures that are considered to be clinically relevant (e.g. that require unscheduled diagnostic procedures or treatments or result in withdrawal from the study). The AE may be:

- A new illness
- Worsening of a sign or symptom of the condition under treatment or of a concomitant illness
- An effect of the study medication
- An effect of the comparator product
- Off label use, occupational exposure, lack of drug effect, medication error, overdose, drug abuse, drug misuse or drug dependency itself, as well as any resulting event
- An effect related to pre-existing condition improved (unexpected therapeutic benefits are observed)
- Product exposure via mother/ father (exposure during conception, pregnancy, childbirth and breastfeeding)

As mentioned above no causal relationship with a product is implied by the use of the term "adverse event".

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 Theraflex®.

Causal relationship: The assessment of the causal relationship between an AE and the administration of treatment is a clinical decision based on all available information at the time of the completion of the CRF. The assessment is based on the question whether there was a "reasonable causal relationship" to the study treatment in question. Possible answers are "yes" or "no".

An assessment of "no" would include:

The existence of a clear alternative explanation (e.g. mechanical bleeding at surgical site)

Non-plausibility (e.g. the subject is struck by an automobile when there is no indication that the product caused disorientation that may have caused the event; cancer developing a few days after the first product administration)

An assessment of "yes" indicates that there is a reasonable suspicion that the AE is associated with the use of the study treatment. Factors to be considered in assessing the relationship of the AE to study treatment include:

The temporal sequence from product administration: The event should occur after the product is given. The length of time from product exposure to event should be evaluated in the clinical context of the event.

Recovery on product discontinuation (de-challenge), recurrence on product re-introduction (re-challenge): Subject's response after de-challenge or subjects response after re-challenge should be considered in the view of the usual clinical course of the event in question.

Underlying, concomitant, intercurrent diseases: Each event should be evaluated in the context of the natural history and course of the disease being treated and any other disease the subject may have.

Concomitant medication or treatment: The other products the subject is taking or the treatment the subject receives should be examined to determine whether any of them may be suspected to cause the event in question.

The pharmacology and pharmacokinetics of the study treatment: The pharmacokinetic properties (absorption, distribution, metabolism and excretion) of the study treatment, coupled with the individual subject's pharmacodynamics should be considered.

An AE is serious (SAE) if it:

- Results in death
- Is life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization (see exceptions below)
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect
- Is medically important.

Death is usually the outcome of an underlying clinical event that causes it. Hence, it is the cause of death that should be regarded as the SAE. The one exception to this rule is 'sudden death' where no cause has been established. In this instance, 'sudden death' should be regarded as the AE and 'fatal' as its reason for being 'serious'.

Life-threatening: The term "life-threatening" in the definition of "serious" refers to an AE in which the subject was at risk of death at the time of the event. It does not refer to an AE which hypothetically might have caused death if it were more severe.

Hospitalization: Any AE leading to hospitalization or prolongation of hospitalization will be considered as serious, unless the admission is:

- planned before subject's inclusion in the study (i.e. elective or scheduled surgery) or
- ambulant (shorter than 12 hours) or
- part of the normal treatment or monitoring of the studied disease (i.e. not due to a worsening of the disease)

However it should be noted that invasive treatment during any hospitalization may fulfill the criteria of 'medically important' and as such may be reportable as a SAE dependent on clinical judgment. In addition where local regulatory authorities specifically require a more stringent definition, the local regulation takes precedent.

Disability means a substantial disruption of a person's ability to conduct normal life's functions.

Congenital anomaly (birth defect), i.e. any congenital anomaly observed in an infant, or later in a child, should be regarded as a SAE when:

- The mother had been exposed to a medicinal product at any stage during conception or pregnancy or during delivery
- The father was exposed to a medicinal product prior to conception

Other medically important serious event: any adverse event may be considered serious because it may jeopardize the patient and may require intervention to prevent another serious condition. Medically important events either refer to or might be indicative of a serious disease state. Such reports warrant special attention because of their possible association with serious disease state and may lead to more decisive action than reports on other terms.

12.2 Collection

Starting with the first application of Theraflex® after enrollment into the study, all non-serious adverse events (AE) must be documented on the AE Report Form or in the CRF/EDC system and forwarded to the MAH within 7 calendar days of awareness. All serious AEs (SAE) must be documented and forwarded immediately (within 24 hours of awareness). For each AE, the investigator must assess and document the seriousness, duration, relationship to product, action taken and outcome of the event.

The questionnaire related information (as it is primary and secondary endpoints) should be exempted from AE reporting.

For the reasons stated below, the following AEs are exempt from reporting in this study and will therefore not be documented in the AE Report Form in the CRF/eCRF.

* If a pregnancy occurs during the study, although it is not a serious adverse event itself, it should be documented and forwarded to the MAH within the same time limits as a serious adverse event. The result of a pregnancy will be followed-up according to applicable Bayer SOPs. Any data on abnormal findings concerning either the mother or the baby will be collected as adverse events.

* The documentation of any AE/SAE ends with the completion of the observation period of the patient. However, any AE/SAE - regardless of the relationship and the seriousness - occurring up to
<30 days after the last dose of Theraflex® within the study period has to be documented and forwarded to the MAH within the given timelines, even if this period goes beyond the end of observation.

* As long as the patient has not received any Theraflex® within the frame of the study AEs /SAEs do not need to be documented as such in this observational study. However, they are part of the patient's medical history.

* For any serious product-related AE occurring after study end, the standard procedures that are in place for spontaneous reporting have to be followed.

12.3 Management and reporting

* Non-serious AEs

* The outcome of all reported AEs will be followed up and documented. Where required, investigators might be contacted directly by the responsible study staff to provide

further information.

* For non-serious ARs occurring under non-Bayer products the investigator has to account for and comply with the reporting system of the product's Marketing Authorization Holder within the frame of local laws and regulations as well as other locally applicable laws and regulations.

* Serious AEs

* Any SAE or pregnancy entered into the CRF/EDC system will be forwarded immediately (within one business day of awareness) to the pharmacovigilance country person being responsible for SAE processing. The outcome of all reported SAEs (resolution, death etc.) will be followed up and documented. Where required, investigators might be contacted directly by the pharmacovigilance country person in charge to provide further information.

* Submission to the relevant authorities according to national regulations will be done by the MAH for SAEs related Theraflex® treatment; however, all investigators must obey local legal requirements.

* For any serious drug-related AE occurring after study end, the standard procedures that are in place for spontaneous reporting have to be followed.

* For SAEs that occurred while administering non-Bayer products the investigator has to account for and comply with the reporting system of the product's Marketing Authorization Holder within the frame of local laws and regulations as well as other locally applicable laws and regulations.

Submission of SAEs related to non-Bayer products to the relevant authorities according to national regulations will be done by the MAH

12.4 Evaluation

* Whenever new important safety information is received, e.g. case reports from an investigator, the reports are processed and entered into the global pharmacovigilance safety database. These reports will be reviewed on a regular basis (for information on collection, management and reporting of case reports, refer to section 11.2 and 11.3). If a potential safety signal is suspected, an investigation of the suspected potential signal will be performed according to internal standard operating procedures, for further evaluation within the context of benefit risk.

13. Plans for disseminating and communicating study results

This study will be registered at "www.clinicaltrials.gov". Results will be disclosed in a publicly available database within the standard timelines.

14. References

Clegg DO. et al. (2006). Glucosamine, chondroitin sulfate, and the two in combination for painful knee osteoarthritis. . *N Engl J Med. 2006*, Feb 23;354(8):795-808.

EFPIA. (Oct 2007). Code on the Promotion of Prescription-Only Medicines to and Interactions with Healthcare Professionals.

EMA. (05 Nov 2010). ENCePP guide on methodological standards in pharmacoepidemiology. .

EMA. (08 Sep 2014). GPV Module VI - Management and reporting of adverse reactions to medicinal products (Rev 1). *Guideline on good pharmacovigilance practices (EMA/8731138/2011_Rev1)*.

EMA. (19 Apr 2013). GPV Module VIII - Post-authorisation safety studies (Rev 1). *Guideline on good pharmacovigilance practices (EMA/813938/2011_Rev1)*.

EMA. (19 Apr 2013). GPV Module VIII Addendum 1 - Member States' requirements for transmission of information on non-interventional post-authorisation safety studies (Rev 1). *Guideline on good pharmacovigilance practices (EMA/395730/2012_Rev 1)*.

ENCePP. (2011). *Definition of non-interventional trials under the current legislative framework.* ENCePP.

EU. (20 Jun 2012). Commission implementing regulation (EU) No 520/2012 of 19 June 2012 on the performance of pharmacovigilance activities provided for in Regulation (EC) No 726/2004 and Directive 2001/83/EC of the European Parliament and of the Council. *Official Journal of the European Union*.

EU. (2008). Eudralex - Volume 9A of the Rules Governing Medicinal Products in the European Union: the Guidelines on Pharmacovigilance for Medicinal Products for Human Use.

FDA. (01 Apr 2012). Code of Federal Regulations. *Title 21, Volume 1. 21CFR11: Electronic records; electronic signatures.*

Graf, C., Battisti, W. P., Bridges, D., Bruce-Winkler, V., Conaty, J. M., Ellison, J. M., et al. (2009). International Society for Medical Publication Professionals. Research Methods & Reporting. Good publication practice for communicating company sponsored medical research: the GPP2 guidelines. *BMJ*.

ICH. (Nov 2003). ICH Harmonized Tripartite Guideline: Clinical Safety Data Management: Definitions and Standards for Expedited Reporting (E2D).

Jordan, K. M. (2003). EULAR Recommendations 2003: an evidence based approach to the management of the knee osteoarthritis: Report or a Task force of the Standing Committee for International Clinical Studies Including Therapeutic Trials (ESCISI). *Ann Rheum Dis*, 33(11), 2271–2279.

Kellgren J.H., L. J. (1957 P. 494–501). *Radiographic assessment of osteoarthritis* . Ann. Rheum. Dis.

Lapane KL. et al., 2. L. (2012). Use of complementary and alternative medicine among patients with radiographic-confirmed knee osteoarthritis. *Osteoarthritis Cartilage.*, Jan;20(1):22-8.

Lippielo, L. W. (1999). Beneficial effect of cartilage structure modifying agents tested in chondrocyte and rabbit instability model ostearthrosis. . *Arthritis Rheum.*, (42), 256.

McAlindon TE. et al., 1. M. (1992). Knee pain and disability in the community. *Br J Rheumatol.* , Mar;31(3):189-92.

Nuesch, E. D. (2011). All cause and disease specific mortality in patients with knee or hip osteoarthritis: population based cohort study. *BMJ*, (3342), 1165–1173.

Qiu GX., W. X. (2005). A multi-central, randomized, controlled clinical trial of glucosamine hydrochloride/sulfate in the treatment of knee osteoarthritis. *Zhonghua Yi Xue Za Zhi*, Nov 16;85(43):3067-70.

Sawitzke, A. (2010). Clinical efficacy and safety of glucosamine, chondroitin sulphate, their combination, celecoxib or placebo taken to treat osteoarthritis of the knee: 2-year results from GAIT. . *Ann Rheum Dis,.*, 69(8), 1459-64.

von Elm, E., Altman, D. G., Egger, M., Pocock, S. J., Gøtzsche, P. C., & Vandenbroucke, J. P. (2008). STROBE-Initiative. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting of observational studies. J Clin Epidemiol. 2. *J Clin Epidemiol.*

Zegels B., C. P. (2013). Equivalence of a single dose (1200 mg) compared to a three-time a day dose (400 mg) of chondroitin 4&6 sulfate in patients with knee osteoarthritis. Results of a randomized double blind placebo controlled study. *Osteoarthritis Cartilage*, Jan;21(1):22-7.

Annex 1: List of stand-alone documents

Table 3: List of stand-alone documents

Document Name	**Final version and date (if available)***
Investigator list	Tbd
CRF	Tbd
EDC System	Tbd
Data Management Plan	Tbd
Statistical Analysis Plan	Tbd
EDC System Validation>	Tbd
Quality Review Plan (QRP)	Tbd
Medical Review Plan (MPP)	Tbd

* Draft versions are indicated by <draft> in brackets and date. "tbd" indicates documents that are not available at the time of protocol creation, but will be issued at a later stage

Annex 2: Additional information

Not applicable

Annex 3: Description of amendments

Version 1 / N/A

Amendment 1

Correction of exclusion criteria was conducted, in order to minimize the risk of including patient s with different baseline level of OA treatment. At the same time it became obvious that with initial exclusion criteria slow patient recruitment is predictable.

9.2.3. Exclusion criteria

Exclusion criteria:

- Patients who have both Hip and Knee OA and OA of any other location.

is deleted

Exclusion criteria:

- Patients who completed a treatment with Theraflex® or another combination of Gl+ Ch less than 5 months before start of the current treatment

is changed to:

- Patients who completed a treatment with Theraflex® or the other Symptomatic Slow-Acting drug in Osteoarthritis (SYSADOA) less than 5 months before start of the current treatment

Exclusion criteria:

- Patients who completed intra-articular corticosteroids treatment in the last 3 months to exclusion criteria.

is changed to :

- Patients who completed intra-articular corticosteroids treatment in the last 3 months before enrollment.

Exclusion criteria:

- Patients who completed hyaluronic injections of the lower limbs in the last 6 months.

is changed to:

- Patients who completed hyaluronic injections and/or platelet-rich plasma (PRP) therapy of the lower limbs in the last 6 months

The approach for completing the questionnaire was clarified in case the patient has multiple joint OA or bilateral Knee/Hip OA.

In the section **9.2.7.2 Visit 1: Enrollment/Initial visit**

The following text is added : “If the patient has multiple joint OA or double-sided (bilateral) Knee/Hip OA, only one «target» joint to be selected for the evaluation, where the patient experiences the most severe pain at the time of enrollment. Filling in a questionnaire, the patient needs to associate his/her responses with the "target" joint only during the entire follow-up period»

In the section **9.2.7.3 Follow-up Visits I & II**

The following text is added :

« If patient switches to another Symptomatic Slow-Acting drug in Osteoarthritis (SYSADOA), the observation of the patient is terminated ».

« The patient needs to assess the outcome of joint treatment, which was selected as the "target" at the first visit ».

In the section **9.2.7.4 Final Visit / End of Observation**

The possible window for the visit is corrected in accordance with the schedule of visits

The following text is added : "Final visit should be performed during the time frame week 56-64 ».

The patient needs to assess the outcome of joint treatment, which was selected as the target at the first visit.

Requirements for collection of vital signs and data of physical examination were clarified.

In section **9.3.3.3 Vital signs**

the following text was added : « if such data are available and the colletion of this data is the routine clinical practice of the Investigator »

In section **9.3.3.4 Physical Examination**

The following text is added :

« In the absence of the height meter and scale in the doctor's office.height and weight can be registered from the patient's words ».

In section **9.3.3.9 Patient satisfaction with Theraflex®**

The following text was added :

« Patient satisfaction measured with a Likert response scale (from 5 – very satisfied to 1-very dissatisfied) ».

Information about the Independent Ethics Committee responsible for protocol related documentation review and approval was updated

In the section **10.2 Regulatory authority approvals/authorizations**

the text has been changed from:

« located at PPD ».

to:

«located atInter-University Ethics Committee ».

Some errors and typos were corrected.,

In the section **10.3 Independent ethics committee (IEC) or institutional review board (IRB)**

The contact infromation has been changed from :

«located at PPD ».

To :

" located at Inter-University Ethics Committee:

PPD

e-mail: PPD

Mobile: PPD »

Amendment 2

The number of patients is reduced from 1500 patients to 1100 patients.
Justification: Originally planned to conduct an observational study of the Theraflex product in 80 study centers of Moscow, St. Petersburg and Yaroslavl regions. In connection with the additional administrative barrier on the part of the Moscow Health Care Department, instead of 40 centers planned for opening in the Moscow region, the number of study centers in Moscow has dropped to 20. Thus, the total number of study centers will not exceed 60, which is 75% of the planned number of clinical centers. In proportion with reduced number of study centers, the number of patients in the study is also reduced by 25%, which in numerical terms approximately corresponds to 1100 patients.

In order to calculate the indicator of "patients lost to follow-up subjects", was made a simple analysis of the V2 frequency on the group of the first 10% of subjects included into the study. The analysis was carried out after 3-6 months from the date of patients recruitment, which corresponds to allowable time-window for the second visit. As a result of this analyses, "patients lost to follow-up" index is about 7%, which is significantly lower than initially assumed figure for this indicator (In the Study Risk Register this risk factor was registered as 20% and above). This additionally makes possible to reduce the study population to 1100 subjects without negative effect on the result of the whole study.

Since the analysis of all variables in the study will be carried out using appropriate methods of descriptive statistics, a decrease in the number of patients cannot have a negative impact on the representativeness.

Initially It was planned to have interim analysis after all subjects have completed V2. With this amendment the starting point is changing – Interim analysis will be conducted after 50% of subjects (first 550 enrolled) have completed V2 in order to assess the changes after the first course at the half of the study population.

In connection with these changes, following text correction of protocol took place:

In the synopsis in the the population and study size sections

text "Approximately 1500 subjects are planned to enrolled in the study in about 80 study centers in Russia"

changed to:

"Approximately 1100 subjects are planned to enrolled in the study in about 60 study centers in Russia.

text: "It is planned to enroll approximately 1500 patients into the study"

change to:

"It is planned to enroll approximately 1100 patients into the study".

In section 9.2.1 Eligibility

text : "Approximately 1500 subjects are planned to be included in the study in about 80 study centers in Russia".

Changed to:

Approximately 1100 subjects are planned to be included in the study in about 60 study centers in Russia.

In section 14.1.1 Statistical considerations

In the last paragraph text: "It is planned to have 1 interim analysis after all subjects have completed V2".

Changed to:

It is planned to have 1 interim analysis after 50% of (first 550 enrolled) subjects have completed V2.

Annex 4: Signature pages

Not applicable