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Revision History

No.	Date	Version	Changes
1	05/03/2019	1.0	New documents
2	13/07/2020	2.0	1. Corrections were added to FAS definition. 2. Data from the study termination form (CRF version 3.2 of 12/08/2019) were included. 3. Tables for AEs and SAEs resulting in the study termination were removed.

			4. Clarification was added to the scoring approach for KOOS and HOOS subscales in connection with the use of HOOS-physical short form (HOOS-PS) and KOOS-physical short form (KOOS-PS). 5. Table numbering was corrected; corrections of typos were made throughout the text.

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1. Definitions and 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

2. Introduction

Statistical Analysis Plan objectives:

- to define data preparation methods
- to describe analysis sets
- to describe endpoint calculation methods
- to describe statistical data processing methods
- to describe presentation of results of statistical data processing

The Statistical Analysis Plan (SAP) is prepared in accordance with the Good Clinical Practice Guideline of the International Conference on Harmonization (ICH GCP), the European Network of Centers for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology, BAYER Non-Interventional Study Protocol version 3.0 of 4 July 2018, ICF version 3.2 of 12 August 2019. This version of SAP is applicable to the final data analysis.

3. Study objectives and endpoints

3.1. Study objectives

Primary objective

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

Secondary objectives

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

3.2. Endpoints

Primary endpoints:

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

Secondary endpoints:

- 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
- Other medical/physical therapy for OA related pain (drugs/type of therapy, duration of use, dose, frequency)

4. Study design

4.1. Overall study design and plan

This is a single country, open-label multicenter non-interventional prospective study.

Figure 4.1:1 Overall Study Design and Plan

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

Table 4.1:1: 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

4.2. Randomization and blinding

The design of the study does not include randomization and “blinding”, and selection of patients does not depend on the strict criteria of inclusion/exclusion.

4.3. Sample size

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

5. General provisions

Tables for patients with knee osteoarthritis and for patients with hip osteoarthritis (DM domain, DMMHLOC variable) will be generated separately.

Data listings will include findings of scheduled and unscheduled visits, repeated examinations and data of prematurely withdrawn subjects.

6. Analysis sets

The following data sets will be included in the analysis:

1. All subjects who signed the informed consent (All screened subjects);
2. Full analysis set (FAS). FAS includes all patients from the All screened subjects population who received at least one dose of Theraflex® with available data for evaluation of at least one efficacy and/or safety parameter after the start of observation period.

7. Statistical assumptions

7.1. Standard descriptive statistics

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).

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.

The accuracy of descriptive statistics will be determined according to the following rules:

- mean, median, quartiles: 1 more decimal place than in the raw data;
- standard deviation: 2 more decimal places than in the raw data;
- minimum, maximum: the same number of decimal places as in the raw data;
- percentages: 1 decimal place;
- 95% CI: the same number of decimal places as in the parameter value for which CI is calculated.

The maximum number of decimal places used in a statistical report is 4. After applying the above rules, any descriptive statistics with higher accuracy will be rounded to four decimal places, if applicable.

7.2. Missing data

The per protocol analysis is planned to be performed using available data only with no missing data replacement methods. The exception will be incomplete dates for separation of prior and concomitant treatments, as well as for separation of AEs occurred during the study and AEs occurred prior to the initiation of the study (incomplete dates will not be replaced with any data during classification).

Prior/concomitant therapy with missing or incomplete dates of start and end of the event

Table 7.2:1 - Classification algorithm for prior, concomitant and post-treatment therapies with missing or incomplete dates of start and end of the event

Start date	End date	Actions
Known	Known	To be considered as prior therapy, if the end date is < the start date of the study drug To be considered as concomitant therapy, if the end date is >= the start date of the study drug and the start date is <= the end of treatment To be considered as post-treatment therapy, if the end date is >= the start date of the study drug and the start date is > the end of treatment
	Partially missing	The end date should be replaced with the latest date possible (i.e. the last day of the month, if the day is unknown, or December 31, if the day and the month are unknown), then: To be considered as prior therapy, if the end date is < the start date of the study drug To be considered as concomitant therapy, if the end date is >= the start date of the study drug and the start date is <= the last administration date To be considered as post-treatment therapy, if the end date is >= the start date of the study drug and the start date is > the end of treatment
	Missing	The event should not be considered as prior, if the end date is missing To be considered as concomitant therapy, if the start date is <= the last administration date To be considered as post-treatment therapy, if the start date is > the end of treatment
Partially missing	Known	The start date should be replaced with the earliest date possible (i.e. the first day of the month, if the day is unknown, or January 1, if the day and the month are unknown), then: To be considered as prior therapy, if the end date is < the start date of the study drug To be considered as concomitant therapy, if the end date is >= the start date of the study drug and the start date is <= the last dose date To be considered as post-treatment therapy, if the end date is >= the start date of the study drug and the start date is > the last administration date

Start date	End date	Actions
	Partially missing	The start date should be replaced with the earliest date possible (i.e. the first day of the month, if the day is unknown, or January 1, if the day and the month are unknown) and the end date should be replaced with the latest date possible (i.e. the last day of the month, if the day is unknown, and December 31, if the day and the month are unknown), then: To be considered as prior therapy, if the end date is < the start date of the study drug To be considered as concomitant therapy, if the end date is >= the start date of the study drug and the start date is <= the last administration date To be considered as post-treatment therapy, if the end date is >= the start date of the study drug and the start date is > the last administration date
	Missing	The start date should be replaced with the earliest date possible (i.e. the first day of the month, if the day is unknown, or January 1, if the day and the month are unknown), then: The event should not be considered as prior, if the end date is missing To be considered as concomitant therapy, if the start date is <= the last administration date To be considered as post-treatment therapy, if the start date is > the last administration date
Missing	Known	To be considered as prior therapy, if the end date is < the start date of the study drug To be considered as concomitant therapy, if the end date is >= the start date of the study drug Should not be considered as post-treatment therapy
	Partially missing	The end date should be replaced with the latest date possible (i.e. the last day of the month, if the day is unknown, or December 31, if the day and the month are unknown), then: To be considered as prior therapy, if the end date is < the start date of the study drug To be considered as concomitant therapy, if the end date is >= the start date of the study drug Should not be considered as post-treatment therapy
	Missing	To be considered as concomitant therapy

Adverse events with missing or incomplete dates of start and end of the event

Table 7.2:2 - Classification algorithm for AEs with missing or incomplete dates of start and end of the event

Day	Month	Year	Actions
missing	known	known	To be classified as treatment-emergent adverse event (TEAE), if the month and the year are ≥ the month and the year of the start date of the study drug; in other cases, to be classified as AE occurred prior to the initiation of the study treatment
missing	missing	known	To be classified as TEAE, if the year is ≥ the year of the start date of the study drug; in other cases, to be classified as AE occurred prior to the initiation of the study treatment
known	missing	known	
missing	known	missing	To be classified as TEAE
known	missing	missing	

missing	missing	missing	

7.3. Interim analysis and data monitoring

Interim analysis objectives

The main purpose of interim analyses is to assess the changes after the first course of treatment with Theraflex®. The final analysis will be performed after the end of the study which is the date when the analytical dataset is completely available.

7.4. Interim analysis scheme

It is planned to have an interim analysis/analyses after 50% of subjects (first 550 enrolled) have completed Visit 2 (V2).

Study termination

No early study termination is planned by the Protocol.

7.5. Multicenter studies

This is a multicenter study. For analysis purposes, data obtained from all study sites will be combined. Disposition data will be presented by study sites.

7.6. Multiple testing

No multiple testing is planned for the study.

8. Study data

8.1. Disposition of study subjects

Disposition of study subjects will be presented in tables and data listings with the following results:

- The number of screened and prematurely withdrawn subjects (overall and by study sites);
- The number of subjects with violations of inclusion/exclusion criteria;
- Reasons for early study withdrawal (overall and by study sites);

- The number and percentage of subjects in analysis sets;
- The number and percentage of subjects at each scheduled visit.

8.2. Protocol deviations

Protocol deviations will be presented in a listing. Protocol deviations will not result in inclusion or exclusion of subjects from analysis sets.

8.3. Demographics and baseline data

The following characteristics will be presented in tables and listings:

- demographic characteristics (for all subjects and separately for subjects with knee/hip osteoarthritis):
  - age (full years at the time of signing the IC): an automatically computed value in the CRF[1];
  - sex;
  - race (White, Black, Asian, not reported);
- anthropometric characteristics (for all subjects and separately for subjects with knee/hip osteoarthritis):
  - height (cm);
  - body weight (kg);
  - body mass index (BMI) (kg/m^2): computed value in the CRF[2];
- Risk factors:
  - hereditary diseases of bones and joints (description of hereditary diseases will be presented in listings only);
  - non-genetic (excess weight, hormonal disorders, malformations of the bones and joints, joint operations);
  - exogenous risk factors (professional activity, trauma, sports);
- OA staging according to Kellgren & Lawrence;

[1] Age calculation formula: [Date of informed consent signing - Date of birth].
[2] BMI calculation formula: [Body weight (kg)/(Height (m))^2].

Data on alcohol and tobacco use will be presented in listings only.

8.4. Concomitant diseases and medical conditions

All prior and concomitant diseases will be coded using the MedDRA dictionary (version 20.1 or later) according to the standard operating procedure of Data MATRIX LLC [4] and presented in separate tables by system organ class (SOC) and preferred term (PT).

Prior and concomitant diseases will be classified based on disease status at screening as recorded by investigators on the Medical History form in the CRF. Diseases with "Resolved" status will be considered as prior. Diseases having "Ongoing, positive dynamics", "Ongoing, negative dynamics", "Ongoing, no dynamics" status will be considered as concomitant.

Descriptive statistics for prior and concomitant diseases will reflect the number and percentage of patients with recorded diseases and relevant SOC and PT, as well as the number of these records. Patients with multiple diseases coded within the same SOC and PT will be counted only once within each SOC and PT. A patient may have multiple PTs within a SOC.

8.5. Prior and concomitant treatments

In accordance with the Protocol, 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
  - Hyaluronic acid
  - Diacerein
  - Unsaponifiable matters of avocado and soya
- Pain syndrome therapy
  - Analgesics
  - NSAID
- Topical pain therapy
  - Topical NSAID

- Intra-articular injections
- Manual therapy
- Surgery
- Physiotherapy

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

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

All treatments taken in addition to Theraflex® for any indication (initiated either before or during the study) are defined as concomitant and have to be documented.

Information on medications to be collected includes:

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

All prior and concomitant medications will be coded using the WHODD dictionary (version as of SEP 2017 or later) according to the standard operating procedure of Data MATRIX LLC [4] and presented in separate tables by pharmacological subgroup (3rd level) and chemical subgroup (4th level).

All treatments taken before the study start (initiated and stopped before the study start) are defined as prior treatments. Prior and concomitant treatments will be classified based on their start and end dates recorded by investigators on the Prior/Concomitant treatment form in the CRF:

– Prior treatment refers to medications started and stopped before the first dose of the study drug.

– Concomitant treatment refers to medications started after the first dose of the study drug, but before the end of treatment.

– Post-treatment refers to medications started after the last dose of the study drug.

In case of missing or incomplete dates of start and end of treatment, the rules specified in section 7.2 will be applied(Table 7.2:1). If it is impossible to clearly determine whether the therapy was taken before, during, or after the study treatment, such therapy is defined as concomitant.

Descriptive statistics for prior, concomitant and post-treatment therapies will reflect the number and percentage of patients with prescribed treatments and relevant pharmacological and chemical subgroups, as well as the number of these records. Patients with multiple prescribed treatments coded within the same pharmacological and chemical subgroups will be counted only once within each pharmacological and chemical subgroup. A patient may have multiple chemical subgroups within a pharmacological subgroup.

9. Primary and secondary endpoint analysis

Primary and secondary endpoint analysis will be conducted in the Full Analysis Set (FAS).

For each visit, results will be presented descriptively by subscales and changes from Visit 1 for HOOS and KOOS questionnaires separately.

The results for secondary endpoints will be presented by subgroups of patients with knee osteoarthritis, patients with hip osteoarthritis and in a combined table (three types of tables will be presented).

9.1. Primary efficacy endpoint analysis

Primary endpoints:

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

Results for “Pain”, “Symptoms” and “Quality of Life” KOOS subscales will be calculated as [100 – (Mean score for all subscale questions * 100) / 4]. In case of more than 50 % of missing answers for any sub-scale, results will be considered unknown for such sub-scale.

Table 9.1.1 will be used to determine resulting scores for the KOOS-PS Function subscale. [6] All 7 questions of this scale must be answered to determine the result for functional activity.

Table 9.1.1: Conversion table for total scores on the KOOS-PS questions using a scale ranging from 0 (extremely difficult) to 100 (no difficulty).

Total scores (0-28)	Resulting scores for KOOS-PS (from 0 to 100)
0	100
1	94.4
2	89.5
3	85.2
4	81.4
5	78.0
6	75.1
7	72.5
8	70.3
9	68.2
10	66.4
11	64.7
12	63.0
13	61.4
14	59.7
15	58.0
16	56.0
17	53.9
18	51.5
19	48.8
20	45.6
21	42.1

22	38.0
23	33.4
24	28.2
25	22.3
26	15.7
27	8.2
28	0.0

Results for “Pain”, “Symptoms” and “Quality of Life” HOOS subscales will be calculated in a similar manner.

For HOOS-physical short form (HOOS-PS), results will be determined based on the total scores from answers given to 5 questions of this scale using Table 9.1.2. [6] All 5 questions of this scale must be answered to determine the result for functional activity.

Table 9.1.2: Conversion table for total scores on the HOOS-PS questions using a scale ranging from 0 (extremely difficult) to 100 (no difficulty).

Total scores (0-20)	Resulting scores for HOOS-PS (from 0 to 100)
0	100
1	95.4
2	91.2
3	87.3
4	83.6
5	80.0
6	76.6
7	73.1
8	69.6
9	66.1
10	62.3
11	58.3

12	53.9
13	49.2
14	44.1
15	38.4
16	32.1
17	25.2
18	17.6
19	9.2
20	0.0

Endpoints will be descriptively summarized by visits (n, mean calculated using 95% CI for mean, SD, minimum, maximum, quartile, median). Individual subject data with primary endpoint results will be presented in listings.

9.2. Secondary efficacy endpoint analysis

Secondary endpoints:

- Drug utilization of Theraflex® therapy as reported by the patient to their physician:
  - frequency table with assessment of treatment duration will be presented as an assessment of the drug utilization. The results will be presented by the following categories:
    - patients treated with Theraflex® for up to 1 month inclusive: (the assessment will be performed using the collected start and end dates of treatment, this category includes patients falling under the following time period: [0 days < duration for a patient ≤ 30.42 days]);
    - patients treated with Theraflex® for 1-3 months: this category includes patients falling under the following time period: [30.42 days < duration for a patient ≤ 91.25 days];
    - patients treated with Theraflex® for 3-6 months: this category includes patients falling under the following time period: [91.25 days < duration for a patient ≤ 182.50 days];
    - patients treated with Theraflex® for more than 6 months: this category includes patients falling under the following time period: [duration for a patient > 182.50 days];
  - frequency table with the investigator's assessment of compliance with recommendations for duration of treatment with Theraflex/Theraflex Advance (Mostly complied with/Mostly not complied with).

- Patient satisfaction measured with a Likert response scale:

- Frequency and shift tables based on the results of the scale assessment [*very dissatisfied, dissatisfied, neither satisfied nor dissatisfied, satisfied, very satisfied]* presented overall and separately for patients with knee and hip osteoarthritis;

- Descriptive statistics for results and changes form Visit 1 (as the Likert scale data are best described by the median, not the mean, 95% CI is additionally provided for the median).

- Use of analgesics for symptomatic treatment of osteoarthritis:

  - Data will be presented on the patient's additional analgesic treatment of pain in the target joint (no/occasionally/regularly, topical agents/systemic agents/combined treatment) at the time of starting the chondroprotector (Theraflex/Theraflex Advance), at the time of study completion, as well as the investigator's assessment of the dynamics of the analgesic treatment of pain in the target joint from the start of the chondroprotector (Theraflex/Theraflex Advance) until the patient's discontinuation from the study (not changed/increased/decreased/pain treatment was discontinued) and time until complete cessation of analgesic treatment (1 month/ 2 months/ 3 months/ 6 months/ 12 months after the start of the chondroprotector), if it was completely discontinued;

  - Tables similar to those described in section 8.5 will be presented by pharmacological subgroup (3rd level) and chemical subgroup (4th level) for various indications [Symptomatic treatment with analgesics for target joint OA/ Other medication for target joint OA related pain/ Other therapy for target joint OA];

Individual subject data will be presented in listings.

9.3. Exploratory efficacy analysis

In addition to the primary and secondary endpoints specified in the Protocol, this statistical analysis plan provides for an extended analysis. This exploratory analysis will be carried out in the Full Analysis Set (FAS).

List of parameters to be analyzed:

Additional treatment-related analysis:

- The percentage of patients with no progression of arterial hypertension, diabetes mellitus and obesity at the end of observation[3]

[3] According to the "MEDICAL DATA COLLECTION AT THE END OF OBSERVATION" form.

- The percentage of patients with no need for analgesic treatment of pain in the target joint from the start of Theraflex/Theraflex Advance until the end of study participation[4];
- The percentage of patients with a complete withdrawal of analgesic treatment of pain in the target joint[5];
- The percentage of patients with no need for surgical intervention/ at the end of observation[6];
- The percentage of patients with no need for an emergency visit due to persisting joint pain during the study[7];
- The percentage of patients who required intra-articular[8] injections of glucocorticosteroids[9] during the observation period;
- The percentage of patients who required intra-articular injections of hyaluronic acid[10] during the observation period;
- The percentage of patients who required PRP injection therapy[11] during the observation period.

Additional KOOS subscale assessment:

- The percentage of patients with a ≥ 20% reduction in pain intensity at Visits 2, 3 and 4 in the group of patients with knee OA as assessed using the relevant KOOS subscale.
- The percentage of patients with a ≥ 20% improvement in symptoms at Visits 2, 3 and 4 in the group of patients with knee OA as assessed using the relevant KOOS subscale.
- The percentage of patients with a ≥ 20% improvement in functional activity at Visits 2, 3 and 4 as assessed using the relevant KOOS subscale in the group of patients with knee OA.
- The percentage of patients with a ≥ 20% improvement in quality of life at Visits 2, 3 and 4 in the group of patients with knee OA as assessed using the relevant KOOS subscale.
- Changes for each KOOS question presented in a shift table.

Additional HOOS subscale assessment:

- The percentage of patients with a ≥ 20% reduction in pain intensity at Visits 2, 3 and 4 in the group of patients with hip OA as assessed using the relevant HOOS subscale.

[4] According to the "MEDICAL DATA COLLECTION AT THE END OF OBSERVATION" form.
[5] According to the "MEDICAL DATA COLLECTION AT THE END OF OBSERVATION" form.
[6] According to the "MEDICAL DATA COLLECTION AT THE END OF OBSERVATION" form.
[7] According to the "MEDICAL DATA COLLECTION AT THE END OF OBSERVATION" form.
[8] Route of administration will be provided in the CM domain, CMROUTE = "OTHER" or "intra-articular".
[9] A list of glucocorticosteroids will be determined using the CM domain: incomplete ATC code H02AB
[10] A list of hyaluronic acid agents will be determined using the CM domain: ATC code M09AX
[11] As agreed with the Sponsor and with the help of a medical writer, patients who received platelet-rich plasma treatment from the date of enrollment will be specified.

- The percentage of patients with a ≥ 20% improvement in symptoms at Visits 2, 3 and 4 in the group of patients with hip OA as assessed using the relevant HOOS subscale.
- The percentage of patients with a ≥ 20% improvement in functional activity at Visits 2, 3 and 4 as assessed using the relevant HOOS subscale in the group of patients with hip OA.
- The percentage of patients with a ≥ 20% improvement in quality of life at Visits 2, 3 and 4 in the group of patients with hip OA as assessed using the relevant HOOS subscale.
- Changes for each HOOS question presented in a shift table.

10. Safety analysis

Safety endpoints:

- Review of drug utilization.
- AEs and SAEs.
- Vital sign measurement results.
- Physical examination results.

10.1. Study drug administration

The following information about Theraflex and Theraflex Advance utilization should be captured in the CRF:

- Start/end of treatment
- Dose/frequency of treatment

For each subject, the following parameters representing the extent of exposure will be calculated:

- Treatment duration.
- Cumulative dose.

Treatment duration (in days) will be calculated using the formula: [(end date - start date) + 1].

The resulting cumulative treatment dose will be calculated as the number of capsules taken during the study.

10.2. Adverse events

All AEs recorded by investigators on the Adverse event form in the CRF will be coded using the MedDRA dictionary (version 20.1 or later) according to the standard operating procedure of Data MATRIX LLC [4] and presented in separate tables by system organ class (SOC) and preferred term (PT).

Classification algorithm for AEs with missing or incomplete dates of start and end of the event is provided in section 7.2 (Table 7.2:2). If it is impossible to determine whether AE has occurred before, during, or after the study treatment, such AE will be classified as treatment-emergent AE.

Descriptive statistics for AEs will reflect the number and percentage of patients with at least one recorded AE with the relevant SOC and PT, as well as the number of these records. Patients with multiple AEs coded within the same SOC and PT will be counted only once within each SOC and PT. A patient may have multiple PTs within a SOC.

The following tables for AE data will be generated:

- Adverse events (AEs)
- AEs by intensity/severity
- AEs by relationship to the study drug
- AEs resulting in treatment discontinuation
- AEs resulting in dose reduction
- Serious AEs (SAEs)
- SAEs by intensity/severity
- SAEs by relationship to the study drug
- SAEs resulting in treatment discontinuation
- SAEs resulting in dose reduction

10.3. Only AEs classified as a treatment-emergent AEs will be included in tables. All AEs will be presented in listings. Pregnancy

No pregnancy data are collected in the study.

10.4. Laboratory data

No laboratory data are collected in the study.

10.5. Other safety measurements

10.5.1. Vital signs

The following vital signs will be collected and analyzed in this clinical study:

- Systolic blood pressure (SBP) (mm Hg)
- Diastolic blood pressure (DBP) (mm Hg)
- Heart rate (bpm)
- Body temperature (°C)

Vital sign assessments will be performed at Visits 1, 2, 3, 4.

Measurements of vital signs will be presented in the following tables:

- Descriptive statistics for actual values by study visits with changes from baseline by treatment group and overall.
- Frequency and shift tables based on clinical evaluation of measurements relative to baseline levels (Normal/ Clinically insignificant deviation/ Clinically significant deviation).

The baseline for vital sign measurements will be the values obtained at Visit 1.

10.5.2. Physical examination

The following physical examination results will be collected and analyzed in this clinical study:

Physical examination assessments will be performed at Visits 1, 2, 3, 4.

Physical examination results will be presented in the following table:

- Frequency and shift tables based on clinical evaluation of measurements relative to baseline levels (Normal/ Clinically insignificant deviation/ Clinically significant deviation).

The baseline for physical examination will be the assessment performed at Visit 1.

11. Presentation of results

The results will be presented by diagnosis (for patients with knee and hip osteoarthritis) and for all patients in the relevant population.

12. Technical details

SAS 9.4 will be used for statistical analysis and statistical report preparation. Results will be presented in tables, data listings and figures.

The statistical report will be presented in Microsoft Office Word format (*.docx*).

13. Description of protocol deviations

There are no study protocol deviations to report.

14. References

1) Committee for Proprietary Medicinal Products (CPMP). International Conference on Harmonisation (ICH) Topic E9: Note for Guidance on Statistical Principles for Clinical Trials; September 1998.
2) DataMatrix_SOP_STAT001_Statistical Principles_ver.2.0_June 2016.
3) OCT-OP-CL043/001-November 2015_Protocol Deviation Management.
4) DataMatrix_SOP_DM010_Dictionary Management and Data Coding_ver.2.0_August 2015.
5) The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP). Guide on Methodological Standards in Pharmacoepidemiology (Revision 5). EMA/95098/2010
6) http://www.koos.nu/index.html