

*Sodium Hyaluronate 60 mg/3ml and chondroitin sodium sulphate 90mg/3ml, solution for injection in pre-filled syringe – ORTHOFLEX ONE*

**CLINICAL INVESTIGATION**

**CODE: RA-CIR-001**

**FINAL REPORT**

Edition: 1  
Revision: 1  
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# **FINAL REPORT OF CLINICAL INVESTIGATION**

## *Clinical Investigation Report*

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**NAME OF CLINICAL INVESTIGATION:**

**“THE USE OF ORTHOFLEX ONE  
sterile solution for injection  
IN OSTEOARTHRITIS TREATMENT (OA)”**

**CODE OF CLINICAL INVESTIGATION:**

**RA-001**

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Clinical investigation monocentric incomparable

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**Clinical Investigation Plan**

**RA-CIP-001**

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Clinical investigation was performed according to standard

SR EN ISO 14155:2011

Date: 05 December 2014

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Dr. Dima Augustin

Primary doctor in Physiotherapy and Balneology

[signature and seal]

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## 1 SUMMARY

### 1.1. Title of Clinical Investigation

THE USE OF ORTHOFLEX ONE sterile solution for injection IN OSTEOARTHRITIS TREATMENT (OA)

### 1.2. Introduction

The purpose of this clinical investigation was to evaluate the performance and safety of intra-articular injection of sterile solution for injection ORTHOFLEX ONE in symptomatic treatment of osteoarthritis (OA) and to appreciate the acceptability of this product, from the perspective of the patient and medical staff.

### 1.3. Demographic data of patients

In this clinical investigation was included 21 subjects (patients); none of them abandoned the investigation. In statistical analysis were included all obtained data in case report forms.

Demographic data for those 21 patients, who received intra-articular injection of ORTHOFLEX ONE solution for injection, are shown in Table №1, below:

*Table №1 – Demographic data of subjects*

<b>DEMOGRAPHIC DATA</b>	
<b>Gender:</b>	
Male	<b>4</b> (19,05%)
Female	<b>17</b> (80,95%)
<b>The average ages</b>	61,81 years
<b>Domicile</b>	
Urban	<b>11</b> (52,38%)
Rural	<b>10</b> (47,62%)
<b>Occupation</b>	
Pensioner	<b>19</b> (90,48%)
Employee	<b>1</b> (4,76%)
Without occupation	<b>1</b> (4,76%)

To evaluate the performance and safety of intra-articular injection of ORTHOFLEX ONE solution for injection in treatment of OA were monitored: the pain felt by the patient in movement, severity of pain, joint mobility / joints affected and the incidence of adverse effects. To assess the acceptability, was assessed the ease use of ORTHOFLEX ONE solution for injection.

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## 1.4. Results

None of included patients presented any local undesirable effects after ORTHOFLEX ONE injection, so this solution for injection is one safe, without pain, edema, local warmth etc.

The ease of injection of ORTHOFLEX ONE solution is appreciated by the physicians of the investigation team as being very good, the product being acceptable from the user's point of view.

At 3 months after the injection of ORTHOFLEX ONE solution, the average pain felt by patients was of 4.81, and at 6 months after the injection, the pain was of 5.24, value meaning a pain determining a strong discomfort, but the relief is obvious compared to the initial pain, equal to 7.48 (pain close to 8, determining the patient's incapacity to perform the majority of activities). In fact, even at 6 weeks after the injection of ORTHOFLEX ONE solution, patients reported a decrease of intensity felt at a value equal to 5.86, close to 6 (determining patient's incapacity to perform only demanding activities) – improvement of symptoms being rapid and durable.

As regards the severity of pain felt by the subjects, the values of Lequesne functional index of OA treated with ORTHOFLEX ONE solution show that these disorders were extremely severe. At 6 weeks after the injection of ORTHOFLEX ONE solution, Lequesne index lowered by 13.7%, at 3 months after injection it lowered by 38.73%, and at 6 months after injection, Lequesne index presented a decrease by 35.18%, compared to the initial value, demonstrating the efficiency of injection.

The average value of initial Lequesne functional index, of 17.48, indicates extremely severe OA, which is also preserved 6 weeks after the injection of ORTHOFLEX ONE solution, but the decrease of Lequesne functional index is obvious. At 3 months after injection, the average Lequesne index is equal to 10.71, and at 6 months after injection, the average Lequesne index is equal to 11.33, indicating a very severe OA.

As regards the mobility of joints, at 6 weeks after the injection of ORTHOFLEX ONE solution, it increased by 17.8%, at 3 months after injection, the mobility increased by 31.15%, and at 6 months after injection it increased by 35.61%, compared to the initial value, thing having a special importance for the patients, they managing to perform more ample movements, reducing dependency on attendants, increasing the quality of life.

### Conclusions:

The data collected during the follow-up period (of 6 months starting from the injection) prove the safety of using ORTHOFLEX ONE solution, none of subjects reporting local or systemic adverse phenomena after the product injection, as well as the efficiency of injection as regards the improvement of OA symptoms.

Date of clinical investigation initiation: 10.03.2014

Date of clinical investigation completion: 07.11.2014

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## **2. INTRODUCTION**

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ORTHOFLEX ONE represents a medical device of class III, according to the Directive 93/42/EEC, amended by the Directive 2007/47/EC.

The clinical investigation was initiated to assess more precisely the safety and performance of intra-articular injection of sterile ORTHOFLEX ONE solution.

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### **3. ORTHOFLEX ONE DEVICE AND METHODS**

#### **3.1. Description of ORTHOFLEX ONE products**

ORTHOFFLEX ONE is a sterile, viscoelastic solution, containing sodium hyaluronate and sodium chondroitin sulphate.

Composition: sodium hyaluronate, sodium chondroitin sulfate, sodium chloride, sodium dihydrogen phosphate monohydrate, disodium phosphate dodecahydrate, sodium hydroxide and/or hydrochloric acid (for pH adjustment), water for injection preparations.

ORTHOFFLEX ONE solution is indicated for the symptomatic treatment of mild to severe osteoarthritis.

ORTHOFFLEX ONE solution treats pain and low mobility, as a result of degenerative or traumatic pathology at the level of the knee and other synovial joints (hip joint, ankle joint, shoulder, elbow, wrist, fingers, temporomandibular joint, and interapophysary joints).

ORTHOFFLEX ONE solution acts as a temporary substitute and as a supplement for the synovial fluid.

ORTHOFFLEX ONE solution improves joint pains, improves joint mobility and protects the cartilage.

ORTHOFFLEX ONE solution is also indicated for the diminishment of post-arthroscopy pains.

ORTHOFFLEX ONE solution is contra-indicated in children, pregnant or breastfeeding women.

#### **3.2. Clinical Investigation Plan**

The objectives of clinical investigation consisted in the assessment of performance and safety of intra-articular injection of sterile ORTHOFLEX ONE solution in symptomatic treatment of OA.

The clinical investigation was monocentric, non-comparative and it was carried out with the observance of ethical reasons, being obtained the endorsement of Ethics Commission attached to the National Institute for Rehabilitation, Physical Medicine and Balneoclimatology of Bucharest.

Quality provision was achieved by the representatives of the sponsor, S.C. Rompharm Company S.R.L, as well as by the monitor assigned by it, which checked the mode of storage and use of pre-filled syringes with ORTHOFLEX ONE injection solution during the investigation, but also the mode of collection/record and archiving the data collected with the occasion of assessment of subjects by the investigating physicians.

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### 3.2.1. Subjects of clinical investigation

The criteria of inclusion into the clinical investigation consisted in:

- Subject's acceptance by signing the consent form (RA-ICF-001);
- Age of subject: between 18 and 75 years old;
- Sex: male or female;
- Subject not falling within one of criteria of exclusion from the clinical investigation;
- Subject with IInd and IIIrd degree OA.

The criteria of subject exclusion from the clinical investigation:

- Subject's refusal to sign the consent form (RA-ICF-001);
- Subject being part of vulnerable populations, described in the clinical investigation plan (RA-CIP-001);
- Age of subject – less than 18 years old
- Subject suffering of:
  - ⇒ Septic arthritis;
  - ⇒ Paget disease, gout, major dysplasia;
  - ⇒ Patients suffering of Wilson's disease, acromegaly, ochronosis, hemochromatosis, Ehlers-Danlos syndrome, Charcot arthropathy, hyperparathyroidism, hypothyroidism, active synovitis;
  - ⇒ Patients suffering of rheumatoid arthritis;
  - ⇒ Patients with skin diseases at injection location.
- Patients which had traumas at the joint that is intended to be treated by ORTHOFLEX ONE injection or to which it was surgically intervened;
- Patients who were submitted to arthroscopy during the last year;
- Patients who benefited of intra-articular injection of steroids or HA during the last 6 months;
- Insufficient collaboration with the subject;
- Pregnant or breastfeeding women;
- The occurrence of some events excluding the subject from investigation inclusion criteria.

For the inclusion to the clinical investigation for the medical ORTHOFLEX ONE injection solution in pre-filled syringe of male or female subjects, with the maximum age of 75 years old, an amendment was brought to the Clinical Investigation Plan RA-CIP-001, Point 6.3. Subjects of Clinical Investigation, 6.3.1. Inclusion criteria for subject selection: extension of inclusion age from 70 years old up to 75 years old (Amendment no.1 to the Clinical Investigation Plan RA-CIP-001/10.03.2014).

21 patients were included. The Ethics Commission was notified by the Amendment no. 2 /29.05.2014 to the Clinical Investigation Plan RA-CIP-001 for the shortening of clinical investigation, by the enrolment of 21 patients instead of a number described in the Clinical Investigation Plan of 30 patients (Amendment no. 2 to Clinical Investigation Plan RA-CIP-001/29.05.2014).



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### 3.2.2. Procedures carried out by the subjects during clinical investigation

During the clinical investigation, the subjects were examined at the beginning of registration, as regards the pain felt upon movement of affected joint/joints, its severity, by the calculation of Lequesne functional index, Dreiser respectively (as the case may be), the mobility of affected joint/joints and their general health condition.

Subsequently, after the signature of the endorsed consent, the subjects benefited of an intra-articular injection, in a single dose, of ORTHOFLEX ONE sterile solution.

At 6 weeks, at 3 months and at 6 months after the intra-articular injection of ORTHOFLEX ONE sterile solution, the following parameters were assessed:

- Intensity of pain felt by the subject;
- Severity of pain felt by the subject (by the calculation of Lequesne index, Dreiser respectively, as the case may be);
- Joint mobility;
- Assessment of adverse phenomena incidence.

### 3.2.3. Concomitant treatments/medication

The subjects included in the present clinical investigation benefited of the following treatments, concomitantly with the injection of ORTHOFLEX ONE solution:

Table no. 2 – Concomitant subject treatment/medication

CONCOMITANT TREATMENT/MEDICATION	
Subject no./initials	Treatment/medication
1. RM	Nonsteroidal anti-inflammatory drugs (AINS)
2. VC	Nonsteroidal anti-inflammatory drugs (AINS), Treatment of comorbidities
3. MI	Physiotherapy
4.HE	Nonsteroidal anti-inflammatory drugs (AINS), Treatment of comorbidities, Electrotherapy
5.OM	Physiotherapy
6.ME	Treatment of comorbidities (Tertensiv, Prestarium, Aspenter)
7. BS	Paracetamol, Physiotherapy
8.GS	Nonsteroidal anti-inflammatory drugs (AINS), Treatment of comorbidities
9. UM	Nonsteroidal anti-inflammatory drugs (AINS), Treatment of comorbidities, Electrotherapy

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<b>CONCOMITANT TREATMENT/MEDICATION</b>	
<b>Subject no./initials</b>	<b>Treatment/medication</b>
10. AC	Nonsteroidal anti-inflammatory drugs (AINS), Physiotherapy
11. SF	Physiotherapy
12. CI	Physiotherapy
13. MI	Nonsteroidal anti-inflammatory drugs (AINS)
14. PM	Physiotherapy
15. GF	Physiotherapy
16. AT	Nonsteroidal anti-inflammatory drugs (AINS), Physiotherapy
17. LN	Nonsteroidal anti-inflammatory drugs (AINS), Physiotherapy
18. MV	Nonsteroidal anti-inflammatory drugs (AINS), Physiotherapy
19. UE	Nonsteroidal anti-inflammatory drugs (AINS), Physiotherapy
20. GM	Physiotherapy
21. CD	Physiotherapy

### **3.2.4. Duration of assessment of subjects**

The subjects were assessed for 6 months starting from the intra-articular injection of ORTHOFLEX ONE solution.

### **3.2.5. Statistical analysis**

More void hypotheses have been considered  $H_{01}$ ,  $H_{02}$ ..., as follows:

$H_{01}$  – the pain felt by subjects at 6 weeks, at 3 months and at 6 months after injection, using Wong-Baker scale, a combination between the visual scale and the numerical one (0 – without pain, 2 – pain which can be ignored, 4 – moderate pain, 6 – pronounced pain, 8 – severe pain and 10 – unbearable pain);  $H_{01}$  = intense pain, with admitted limit error  $r_1$  = moderate;

$H_{02}$  – the evolution of Lequesne index for the assessment of arthrosis of lower limbs at 6 weeks, at 3 months and at 6 months after injection. Thus,  $H_{02} = L_0$  (Initial Lequesne index), with admitted limit error:  $r_2 = 1\%$

$H_{03}$  – the evolution of Dreiser index for the assessment of arthrosis of upper limb at 6 weeks, at 3 months and at 6 months after injection. Thus,  $H_{03} = D_0$  (initial Dreiser index), with admitted limit error:  $r_2 = 1\%$

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H<sub>04</sub> – the evolution of joint (joints) mobility at 6 weeks, at 3 months and at 6 months after injection. Thus, H<sub>04</sub> = M<sub>0</sub> (initial joint mobility), with admitted limit error: r<sub>1</sub> = 1%;

H<sub>05</sub> – the occurrence of local or systemic undesirable phenomena (for example edema); H<sub>05</sub> = 100%; with admitted limit error r<sub>3</sub> = 5 %;

H<sub>06</sub> – the ease of injection of ORTHOFLEX ONE solution; H<sub>06</sub> = difficult; with admitted limit error r<sub>4</sub> = relatively easy.

The alternative hypotheses are the following:

H<sub>11</sub> – the pain felt by the subject at 6 weeks, at 3 months and at 6 months after injection, using Wong-Baker scale, a combination between the visual scale and the numerical one (0 – without pain, 2 – pain which can be ignored, 4 – moderate pain, 6 – pronounced pain, 8 – severe pain and 10 – unbearable pain), with significance threshold  $\alpha_1$  = pronounced;

H<sub>12</sub> – the evolution of Lequesne index for the assessment of arthrosis of lower limbs at 6 weeks, at 3 months and at 6 months after injection, with significance threshold  $\alpha_2$  = 1/4;

H<sub>13</sub> – the evolution of Dreiser index for the assessment of arthrosis of upper limb at 6 weeks, at 3 months and at 6 months after injection, with significance threshold  $\alpha_3$  = 1/4;

H<sub>14</sub> – the evolution of joint/joints mobility [degrees] at 6 weeks, at 3 months and at 6 months after injection, with significance threshold  $\alpha_4$  = 1/2;

H<sub>15</sub> – the occurrence of adverse phenomena caused by the injection of ORTHOFLEX ONE solution, with significance threshold  $\alpha_5$  = 5%;

H<sub>16</sub> – the ease of injection of ORTHOFLEX ONE solution, with significance threshold  $\alpha_6$  = mild.

The above hypotheses have been tested on all the subjects participating to the clinical investigation.

The calculation has been made on 21 subjects.

### 3.2.5.1. Intensity of pain felt by the subject upon movement

The medium initial pain was determined, before the injection, as well as at 6 weeks, at 3 months and at 6 months after injection of ORTHOFLEX ONE solution, the results being recorded in table no.6; subsequently being transposed into a graph.

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For the assessment of pain intensity by the subject, a scale was used representing a combination between the visual, numerical and facial scales (Wong-Baker Scale).

Before the assessment, the main clinical investigator or the clinical investigators of his team, as the case may be, explained to the subject the way of filling-in the form, as well as the meaning of symbols and figures used for the appreciation of pain intensity. Facial symbols are recommended to be used mainly in case of elderly subjects who might have not the ability to numerically appreciate their pain.

After the clinical investigator explained to the subject the meaning of figures, facial symbols respectively, he noticed on the scale the intensity of pain felt upon movement of affected joint/joints. The appreciation of pain intensity was avoided after a long time elapsed since the interruption of movements which had generated it, taking into consideration that the subject could appreciate and memorize a pain felt with a lower intensity than the real one.

#### 3.2.5.2. Pain severity

It was appreciated initially, before the injection of ORTHOFLEX ONE solution, as well as at 6 weeks, at 3 months and at 6 months after injection, by Lequesne index, Dreiser respectively, as the case may be, the results being recorded in table no. 7.

Thus, Lequesne functional index, used for the appreciation of pain severity in case of OA in lower limbs, was determined on the basis of subject's answers to the following questions:

<b>Pain or discomfort</b>	<b>Points</b>
A. At night	
Absent	0
Upon movement or in a certain position	1
Even without movement	2
B. Upon movements (morning stretching)	
Under 1 minute	0
Between 1 – 15 minutes	1
Over 15 minutes	2
C. In upright or sitting position for more than 30 minutes	
No	0
Yes	1
D. During walking	

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No	0
Only after a certain distance	1
Immediately after starting to walk and with rapidly increasing intensity	2
E. Upon rising from the chair, without using hands	
No	0
Yes	1
Total	0 - 8
<b>Maximum walking distance</b>	<b>Points</b>
Unlimited	0
Limited, but possible over 1 Km	1
Approximately 1 Km (about 15 minutes of walking)	2
500 – 900 m (8 – 15 minutes)	3
300 – 500 m	4
100 – 300 m	5
Under 100 m	6
Only with the walking stick or staff	+1
Only with 2 walking stocks, 2 staffs or walking frame	+2
Total	0 – 8
<b>Difficulties in carrying out usual actions</b>	<b>Points</b>
Climbing the stairs	0 – 2*
Descending stairs	0 – 2
Squat	0 – 2
Walking on uneven surface	0 – 2
Total	0 – 8
<b>GRAND TOTAL</b>	<b>0 – 24</b>

\*0 – without difficulty, 0,5-1,5 – depending on the level and 2 – impossible

Index greater than 13 indicates very severe OA,  
The index ranges from 11 to 13 indicates very severe OA,  
The index ranges from 8 to 10, indicates severe OA,  
The index ranges from 5-7 indicates moderate OA,  
The index ranges from 1 to 4, indicate a minor (mild) OA.

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### 3.2.5.3. The mobility of joints

Mobility of affected joint/joints M [degrees], quantitative parameter determined based on measurements using the goniometer at the beginning of clinical investigation before injecting the solution ORTHOFLEX ONE, denoted by  $M_{01}$ , in the case of the subject no.1  $M_{02}$ , in the case of the subject no.2 ... ..,  $M_{021}$  in the case the subject number 21.

For each subject mobility was noted after 6 weeks after injection ORTHOFLEX ONE,  $M_{1i}$ , then after 3 months after injection  $M_{2i}$ , and after 6 months after injection  $M_{3i}$ .

At the end, was calculated average joint mobility for each control using formulas:

$$M_{0m} = (M_{01} + M_{02} + \dots + M_{0i})/i;$$

$$M_{1m} = (M_{11} + M_{12} + \dots + M_{1i})/i;$$

$$M_{2m} = (M_{21} + M_{22} + \dots + M_{2i})/i;$$

$$M_{3m} = (M_{31} + M_{32} + \dots + M_{3i})/i;$$

Where, i = number of the subject.

The mobility of joint was evaluated by measuring the amplitudes of movement in all directions. The amplitude of joint movement expresses the mode of mobilization of a segment but not the degree of movement.

Evaluation of joint mobility by direct measurement using transparent goniometer:

- It was pursued that the subject is relaxed mentally and physically, comfortably seated, trained regarding the manoeuvres which will follow, known the fact that the state of contracture, fear, etc. limits the amplitude of passive movement and non-cooperation on the active movement;
- For each joint was defined a zero or neutral position from which was measured amplitude of the different movements. This position corresponds usually anatomical position and was specified at each joint individually;
- The goniometer was always applied on the side of the joint, with a few exceptions, namely, supination, pronation, inversion and eversion and in case of rotations of the shoulder and hip; goniometer centre corresponding as closely as possible to the joint centre, his arms overlapping longitudinal axis of the segments.

The data on the evolution of joint mobility / joints, for each subject were recorded in the table no. 8 later, based on the results, a graph was made.

For each subject was calculated rate of change of joint mobility, as follows:

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$$rMin(n-1) = M_{ni}/M_{(n-1)i} - 1, \text{ or detailed:}$$

$$rMi_{1/0} = M_{1i}/M_{0i} - 1$$

$$rMi_{2/1} = M_{2i}/M_{1i} - 1$$

.....

The average rate of change of mobility of joints, in case of all the subjects included in the clinical investigation, was calculated using the formula:

$$rMmn = (\Sigma rMin)/i,$$

where:

i = number of subject;

n = belongs to the set {0,1,2,3}

Data on the rate of change of the mobility of joints after 6 weeks, at 3 months and at 6 months from injection of ORTHOFLEX ONE for each subject, as well as those on the average values of the rate of variation were introduced in the Table no. 9 being transposed and graphically.

To check the correctness of measurements subsequently was calculated the **dispersion of mobility of joints**.

The dispersion of a size is defined as being the average square of deviations of the observed values from their mean and which is calculated according to the formula:

$$\sigma^2 = \Sigma (M_i - \bar{x})^2/n,$$

where: sum  $\Sigma$ , is calculated from 1 to n,

$M_i$  = measured value,

$\bar{x}$  = arithmetic mean of the values  $M_i$ , reported to the number of measurements =  $\Sigma M_i/n$ ,

n = number of made measurements

For this clinical investigation was calculated using the formula below:

- Dispersion of mobility of joints:  $\sigma^2 M = \Sigma (M_i - \bar{x})^2/n$ .

It was calculated Pearson's coefficient of asymmetry using the formula:

$$CaM = (xM - Mo) / \sigma$$

Where  $Mo$  = the most common characteristic value.

There may be three cases:

- CaM = 0 – when we have a perfect symmetry,
- CaM > 0 – when we have left positive asymmetry,

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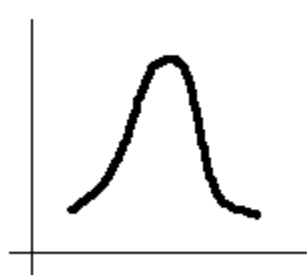
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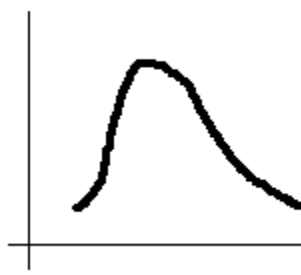
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c.  $CaM < 0$  – when we have a right negative asymmetry.

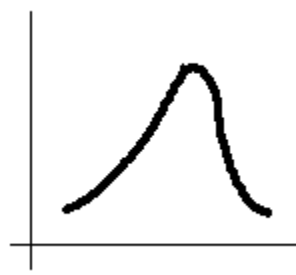
Graphically, the three cases are given below:



a) Symmetry



b)  $Mo < average$



c)  $Mo > average$

So that the joint mobility measurements believed to be accurate, we should be in one of the above situations, it is not permitted the presence of concomitant possibility of two or all three situations (perfect symmetry, concomitant with symmetry of the left and/or right).

The occurrence of undesirable phenomena, ease of use of the products ORTHOFLEX ONE

The data relating to: the appearance of local or systemic undesirable phenomena, as well as the ease of use of products ORTHOFLEX ONE were summarized in the Table no. 6.



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## 4. RESULTS

Date of beginning clinical of investigation: 10.03.2014

Date of end clinical of clinical investigation: 07.11.2014

### 4.1. The arrangement of subjects and products ORTHOFLEX ONE

#### 4.1.1. Demographic data on subjects

Table No. 1 – Demographic data on subjects

DEMOGRAPHIC DATA	
<b>Sex:</b>	
Male	4 (19,05%)
Female	17 (80,95%)
Average age	61,81 years
<b>Domicile</b>	
Urban	11 (52,38%)
Rural	10 (47,62%)
<b>Occupation</b>	
Retired	19 (90,48%)
Employee	1 (4,76%)
Unoccupied	1 (4,76%)

#### 4.1.2. Compliance with Clinical Investigation Plan, RA-CIP-001

All of the 21 subjects met the criteria for inclusion in clinical investigation.

### 4.2. Performance analysis provided in Clinical Investigation Plan, RA-CIP-001

Osteoarthritis (OA) is a degenerative process of wear and destruction of articular surfaces, caused by a congenital condition, age-related changes, vascular disorder of articular structures, traumatic injuries and other medical conditions or injuries in background. Regarding the ankle, osteoarthritis located on this level is less frequent than of the knee. It has almost always a known predisposing factor that will initiate joint changes. The best known is malalignment of articular surface after a fracture. Sometimes, joint change of the ankle is the primary element, of the debut of a disease of general nature.

Hyaluronic acid (HA) is a major component of synovial fluid and of cartilage and due to its viscoelastic and rheological properties is responsible for lubricating and amortization in joints. This decreases the friction between articular surfaces and protects the soft tissues from trauma, acting as a shock absorber. HA also has analgesic, anti-inflammatory, antioxidant and chondroprotective effects and stimulates proteoglycan synthesis.

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The quantity and quality of HA in the synovial fluid are reduced in patients with osteoarthritis because its synthesis by synovial cells and that of the cartilage is disrupted. So the protection of articular surfaces is strongly modified, the cartilage becomes vulnerable and exposed to structural damage due to friction and compression forces.

Chondroitin sulfate (CS) is a gel-substance and is already known for its properties, is mainly used for the relief of pain in the joints, associated with osteoarthritis and plays an important role in maintaining of the structural integrity of the tissue, as a major component of the external matrix, providing the resistance of the cartilage, so that the loss of it is one of the causes of osteoarthritis.

CS inhibits the processes that lead to the destruction of cartilage and stimulates the processes involved in the formation of a new cartilage.

#### 4.2.1. Subjects medical history

Table no. 3 – Subjects medical history

<b>MEDICAL HISTORY</b>	
<b>Cardiac</b>	
HBP (high blood pressure)	<b>12</b> (57,14%)
IHD (ischemic heart disease)	<b>11</b> (52,38%)
Heart failure (increased BNP)	<b>1</b> (4,76%)
CVI (chronic venous insufficiency) severe	<b>5</b> (23,80%)
Left fascicular block	<b>1</b> (4,76%)
<b>Diabetes</b>	<b>1</b> (4,76%)
<b>Smokers</b>	<b>2</b> (9,52%)
<b>Others</b>	<b>24</b>
Cervical spondylosis	<b>5</b> (23,81%)
Obesity Grade I and II	<b>6</b> (28,57%)
Lumbar discopathy IV	<b>4</b> (19,05%)
Gonarthrosis	<b>4</b> (19,05%)
Coxarthrosis	<b>1</b> (4,76%)
Osteoporosis	<b>1</b> (4,76%)
Anxiety-depressive disorder	<b>1</b> (4,76%)
Scapulohumeral periartthritis	<b>1</b> (4,76%)
Hepatic steatosis	<b>1</b> (4,76%)

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#### 4.2.2. Blood type

Table no. 4 – Blood type of the subjects

<b>BLOOD TYPE</b>	
<b>A</b>	<b>12 (57,14%)</b>
<b>B</b>	<b>3 (14,29%)</b>
<b>AB</b>	<b>1 (4,76%)</b>
<b>0</b>	<b>5 (23,81%)</b>

#### 4.2.3. Characteristics of Osteoarthritis (OA)

Table no. 5 – Characteristics of OA

<b>CHARACTERISTICS OF OA</b>	
<b>Affection (symptoms)</b>	
- Pain	<b>21 (100,00%)</b>
- Decreased mobility	<b>11 (52,38%)</b>
- Affection of walk scheme	<b>10 (47,62%)</b>
- Crackles	<b>14 (66,66%)</b>
<b>Average age [months / years]</b>	<b>7,90 years</b>
<b>Etiology</b>	
- Primary progressive	<b>20 (95,24%)</b>
- Unspecified	<b>1 (4,76%)</b>
<b>Location</b>	
Knee	<b>19 (90,48%)</b>
Bilateral coxarthrosis	<b>1 (4,76%)</b>
Ankle joint	<b>1 (4,76%)</b>

#### 4.2.4. Intensity of pain the subjects felt

Table no. 6 – Intensity of pain the subjects felt

<b>INTENSITY OF PAIN THE SUBJECTS FELT WHILE MOVING</b>					
<b>No. of subject/ the initials</b>	<b>No. of control</b>				<b>Average values of the intensity of pain/subject (without the initial pain, before injection)</b>
	<b>Before injection</b>	<b>At 6 weeks after injection</b>	<b>At 3 months after injection</b>	<b>At 6 months after injection</b>	
1. RM	8	6	5	6	<b>5,67</b>
2. VC	8	6	5	6	<b>5,67</b>
3. MI	8	7	5	6	<b>6,00</b>
4.NE	8	5	3	5	<b>4,33</b>

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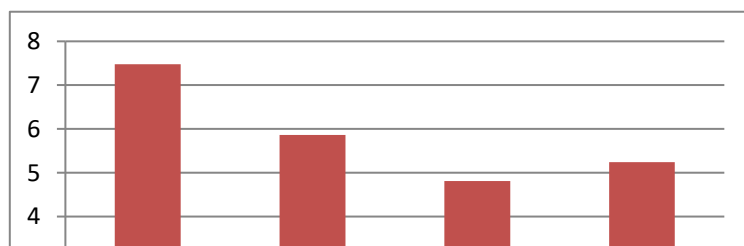
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<b>INTENSITY OF PAIN THE SUBJECTS FELT WHILE MOVING</b>					
<b>No. of subject/ the initials</b>	<b>No. of control</b>				<b>Average values of the intensity of pain/subject (without the initial pain, before injection)</b>
	<b>Before injection</b>	<b>At 6 weeks after injection</b>	<b>At 3 months after injection</b>	<b>At 6 months after injection</b>	
5.OM	6	5	3	5	<b>4,33</b>
6.ME	6	5	5	6	<b>5,33</b>
7. BS	6	5	4	5	<b>4,67</b>
8.GS	7	6	5	6	<b>5,67</b>
9. UM	8	6	5	5	<b>5,33</b>
10. AC	8	6	6	6	<b>6,00</b>
11. SF	7	6	5	5	<b>5,33</b>
12. CI	6	5	5	5	<b>5,00</b>
13. MI	8	6	5	5	<b>5,33</b>
14. PM	7	6	5	5	<b>5,33</b>
15. GF	9	7	6	5	<b>6,00</b>
16. AT	9	6	5	5	<b>5,33</b>
17. LN	8	6	5	5	<b>5,33</b>
18. MV	8	6	5	5	<b>5,33</b>
19. UE	8	7	5	5	<b>5,67</b>
20. GM	6	5	4	4	<b>4,33</b>
21. CD	8	6	5	5	<b>5,33</b>
<b>Average values of the intensity of pain</b>	7,48	5,86	4,81	5,24	<b>5,30</b>

Evolution of the average values of the intensity of pain felt by subjects (patients) at 6 weeks, at 3 months and at 6 months after injection ORTHOFLEX ONE solution is represented in the chart below:

**Intensity of pain**



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Before injection      at 6 weeks      at 3 months      at 6 months

The average pain intensity felt by the subjects at 6 weeks, 3 and 6 months after injection, showed a statistically significant reduction compared to average pain intensity felt by the subjects before injection ( $p < 0.001$ ).

It is found that, at 3 months after injection of the solution ORTHOFLEX ONE, the average value of pain felt by the patients was 4.81 and at 6 months after the injection, the average value of pain was 5.24 (pain resulting in strong discomfort), but compared to the initial intensity of 7.48, close to 8 (which determines the patient's inability to perform most of activities), the relief is evident. Moreover, even at 6 weeks after injecting the solution ORTHOFLEX ONE, patients reported a decrease in the intensity felt at a value equal almost to 5.86 close to 6 (which determines the patient's inability to perform demanding activities) - relieve of symptoms is fast and durable.

**4.2.5. Pain severity based on Lequesne functional index**

*Table no. 7– Pain severity felt by subjects*

<b>Pain severity</b>				
<b>No. subjects/ initials</b>	<b>Lequesne Index</b>			
	<b>Before injection</b>	<b>At 6 weeks after injection</b>	<b>At 3 months after injection</b>	<b>At 6 months after injection</b>
1. RM	17	13	10	13
2. VC	19	12	10	12
3. MI	17	12	11	14
4. NE	14	7	7	11

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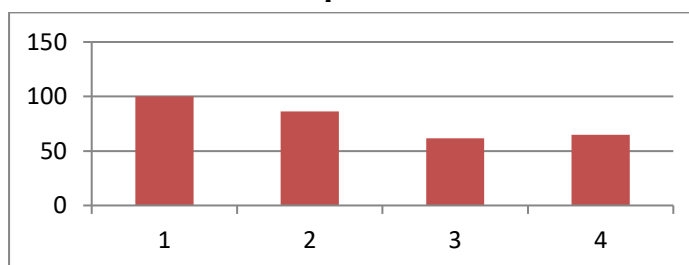
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<b>Pain severity</b>				
<b>No. subjects/ initials</b>	<b>Lequesne Index</b>			
	<b>Before injection</b>	<b>At 6 weeks after injection</b>	<b>At 3 months after injection</b>	<b>At 6 months after injection</b>
5.OM	12	8	8	10
6. ME	20	13	12	14
7. BS	15	10	9	10
8. GS	17	14	10	11
9. UM	15	17	10	10
10. AC	17	12	10	10
11. SF	21	16	12	12
12.CI	16	13	11	12
13. MI	21	16	14	12
14. PM	16	12	12	12
15. GF	19	14	12	11
16. AT	20	13	12	12
17. LN	18	12	11	11
18. MV	18	14	11	10
19. UE	21	15	13	12
20. GM	17	12	9	8
21. CD	17	13	11	11
<b>Average Lequesne index</b>	17,48	12,76	10,71	11,33
<b>Percentage</b>	100%	86,33	61,73	64,82

Graphical representation of the evolution Lequesne index is shown below:

**Lequesne Index**



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Before injection    at 6 weeks    at 3 months    at 6 months

Average index of OA treated by ORTHOFLEX ONE solution shows that these disorders were extremely severe.

It is acknowledged that 3 months after the injection of ORTHOFLEX ONE solution, the average value of pain felt by the patients was of 4.81, and 6 months after injection, the average value of pain felt was of 5.24 (pain resulting in a strong discomfort), but compared to the initial intensity of 7.48, close to 8 (resulting in patient's inability to perform most of activities), relief is evident. In fact, even at 6 weeks after the injection of ORTHOFLEX ONE solution, patients reported a decrease of intensity felt, at a value equal to 5.86, close to 6 (determining patient's incapacity to perform only demanding activities) – the amelioration of symptoms is fast and durable.

4.2.5. Pain severity based on Lequesne functional index

Table no. 7– Severity of pain felt by the subjects

<b>PAIN SEVERITY</b>				
<b>Subject no./initials</b>	<b>Lequesne index</b>			
	<b>Before injection</b>	<b>At 6 weeks after injection</b>	<b>At 3 months after injection</b>	<b>At 6 months after injection</b>
1. RM	17	13	10	13
2. VC	19	12	10	12
3. MI	17	12	11	14
4. NE	14	7	7	11
5.OM	12	8	8	10
6. ME	20	13	12	14
7. BS	15	10	9	10
8. GS	17	14	10	11
9. UM	15	17	10	10
10. AC	17	12	10	10

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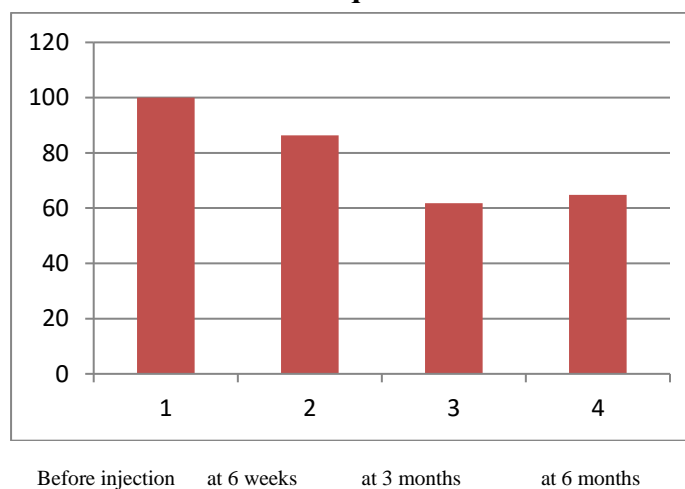
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<b>PAIN SEVERITY</b>				
<b>Subject no./initials</b>	<b>Lequesne index</b>			
	<b>Before injection</b>	<b>At 6 weeks after injection</b>	<b>At 3 months after injection</b>	<b>At 6 months after injection</b>
11. SF	21	16	12	12
12. CI	16	13	11	12
13. MI	21	16	14	12
14. PM	16	12	12	12
15. GF	19	14	12	11
16. AT	20	13	12	12
17. LN	18	12	11	11
18. MV	18	14	11	10
19. UE	21	15	13	12
20. GM	17	12	9	8
21. CD	17	13	11	11
<b>Lequesne index mean</b>	17.48	12.76	10.71	11.33
<b>Percentage</b>	100%	86.33	61.73	64.82

The evolution of Lequesne index is graphically represented below:

**Lequesne index**





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Average index of OA treated by ORTHOFLEX ONE solution shows that these disorders were extremely severe.

The average Lequesne index, at 6 weeks, at 3 and at 6 months after injection, shows a significant statistical decrease compared to the initial average Lequesne index, before injection ( $p < 0.001$ ).

It is acknowledged that at 6 weeks after the injection of ORTHOFLEX ONE solution, Lequesne index lowered by 13.7%, at 3 months after injection, lowered by 38.73%, and at 6 months after injection, Lequesne index presented a decrease by 35.18%, compared to the initial value, demonstrating the efficiency of injection.

The initial average Lequesne index, of 17.48, indicates extremely severe OA, which is also preserved at 6 weeks after the injection of ORTHOFLEX ONE solution, but the decrease of index is evident. At 3 months after injection, the average Lequesne index is equal to 10.71, and at 6 months after injection, the average Lequesne index is equal to 11.33, indicating a very severe OA.

#### 4.2.6. Mobility of joints

Table no. 8– Mobility of subject joints

<b>MOBILITY OF JOINTS [degrees]</b>				
<b>Subject no./initials</b>	<b>M<sub>0i</sub></b> Before injection	<b>M<sub>1i</sub></b> At 6 weeks after injection	<b>M<sub>2i</sub></b> At 3 months after injection	<b>M<sub>3i</sub></b> At 6 months after injection
1. RM	80 <sup>0</sup>	100 <sup>0</sup>	100 <sup>0</sup>	100 <sup>0</sup>
2. VC	80 <sup>0</sup>	100 <sup>0</sup>	110 <sup>0</sup>	110 <sup>0</sup>
3. MI	80 <sup>0</sup>	90 <sup>0</sup>	100 <sup>0</sup>	100 <sup>0</sup>
4. HE	80 <sup>0</sup>	100 <sup>0</sup>	140 <sup>0</sup>	140 <sup>0</sup>
5. OM	90 <sup>0</sup>	110 <sup>0</sup>	120 <sup>0</sup>	120 <sup>0</sup>
6. ME	70 <sup>0</sup>	90 <sup>0</sup>	100 <sup>0</sup>	100 <sup>0</sup>
7. BS	85 <sup>0</sup>	100 <sup>0</sup>	120 <sup>0</sup>	120 <sup>0</sup>
8. GS	75 <sup>0</sup>	100 <sup>0</sup>	110 <sup>0</sup>	110 <sup>0</sup>
9. UM	90 <sup>0</sup>	100 <sup>0</sup>	110	110 <sup>0</sup>
10. AC	60 <sup>0</sup>	80 <sup>0</sup>	90 <sup>0</sup>	90 <sup>0</sup>
11. SF	80 <sup>0</sup>	95 <sup>0</sup>	100 <sup>0</sup>	105 <sup>0</sup>
12. CI	85 <sup>0</sup>	100 <sup>0</sup>	120 <sup>0</sup>	120 <sup>0</sup>
13. MI	100 <sup>0</sup>	100 <sup>0</sup>	110 <sup>0</sup>	120 <sup>0</sup>
14. PM	85 <sup>0</sup>	100 <sup>0</sup>	110 <sup>0</sup>	120 <sup>0</sup>
15. GF	20 <sup>0</sup>	20 <sup>0</sup>	30 <sup>0</sup>	30 <sup>0</sup>
16. AT	80 <sup>0</sup>	90 <sup>0</sup>	100 <sup>0</sup>	100 <sup>0</sup>
17. LN	90 <sup>0</sup>	100 <sup>0</sup>	110 <sup>0</sup>	120 <sup>0</sup>
18. MV	75 <sup>0</sup>	90 <sup>0</sup>	100 <sup>0</sup>	110 <sup>0</sup>
19. UE	80 <sup>0</sup>	90 <sup>0</sup>	100 <sup>0</sup>	110 <sup>0</sup>
20. GM	100 <sup>0</sup>	120 <sup>0</sup>	110 <sup>0</sup>	130 <sup>0</sup>
21. CD	100 <sup>0</sup>	110 <sup>0</sup>	120 <sup>0</sup>	120 <sup>0</sup>
	<b>M<sub>0m</sub></b>	<b>M<sub>1m</sub></b>	<b>M<sub>2m</sub></b>	<b>M<sub>3m</sub></b>

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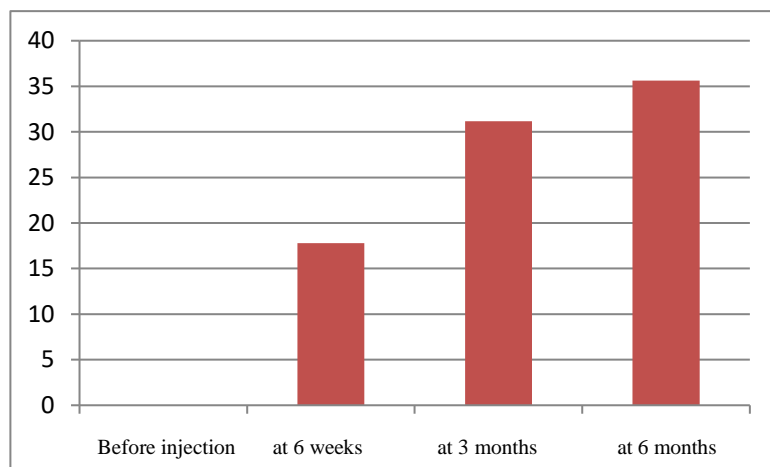
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<b>MOBILITY OF JOINTS [degrees]</b>				
<b>Subject no./initials</b>	<b>M<sub>0i</sub></b> Before injection	<b>M<sub>1i</sub></b> At 6 weeks after injection	<b>M<sub>2i</sub></b> At 3 months after injection	<b>M<sub>3i</sub></b> At 6 months after injection
<b>Average mobility</b>	<b>80.24 = 100%</b>	<b>94.52 = 117,80</b>	<b>105.24 =131.15%</b>	<b>108.81 = 135.61%</b>

The evolution of joint mobility of subjects having benefited of intra-articular injection of ORTHOFLEX ONE solution is graphically represented below:

**Joint mobility (%)**



The average joint mobility, at 6 weeks, at 3 and at 6 months after injection, shows a significant statistical decrease compared to the average joint mobility of subjects before injection ( $p < 0.001$ ). It is acknowledged that at 6 weeks after the injection of ORTHOFLEX ONE solution, the mobility of joints increased by 17.8%, at 3 months after injection, the mobility increased by 31.15%, and at 6 months after injection, the mobility increased by 35.61%, thing having a special importance for the patients, they managing to perform more ample movements, reducing dependency on attendants, increasing the quality of life.

Average variation rhythm of joint mobility of subjects

Data related to the variation rhythm of joint mobility, at 6 weeks, at 3 months and at 6 months after the injection of ORTHOFLEX ONE, for each subject, as well as those related to the average values of the variation rhythm are presented in the table below:

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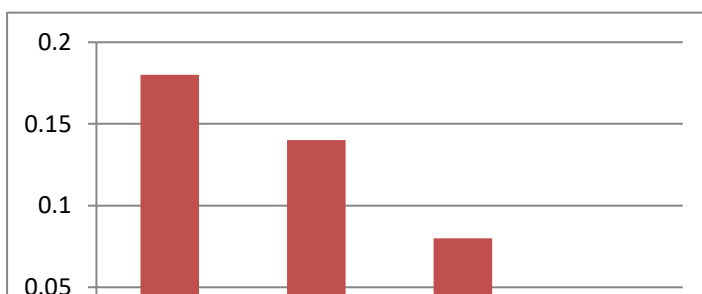
Table no. 9– Average variation rhythm of subject joints

Subject no./initials	rMi <sub>1/0</sub>	rMi <sub>2/1</sub>	rMi <sub>3/2</sub>
1. RM	0.25	0.00	0.00
2. VC	0.25	0.10	0.00
3. MI	0.13	0.11	0.00
4.HE	0.25	0.40	0.00
5.OM	0.22	0.09	0.00
6.ME	0.29	0.11	0.00
7. BS	0.18	0.20	0.00
8. GS	0.33	0.10	0.00
9. UM	0.11	0.10	0.00
10. AC	0.33	0.13	0.00
11. SF	0.19	0.05	0.05
12.CI	0.18	0.20	0.00
13. MI	0.00	0.10	0.09
14. PM	0.18	0.10	0.09
15. GF	0.00	0.50	0.00
16. AT	0.13	0.11	0.00
17. LN	0.11	0.10	0.09
18. MV	0.20	0.11	0.10
19. UE	0.13	0.10	0.10
20. GM	0.20	- 0.08	0.18
21. CD	0.10	0.09	0.00
Average variation rhythm of joint mobility	rmM <sub>1/0</sub>	rmM <sub>2/1</sub>	rmM <sub>3/2</sub>
	0.18	0.13	0.08

Average variation rhythm of joint mobility has positive values or equal to zero, meaning that the mobility of joints had an increasing tendency, after the injection of ORTHOFLEX ONE solution.

The average variation rhythm of joint mobility, after the injection of ORTHOFLEX ONE solution, is graphically represented below:

**Average variation rhythm of joint mobility**



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6 weeks/initial    3 months/6 weeks    6 months/3 months

**4.2.7. Tolerance and acceptability of ORTHOFLEX ONE solution**

Data related to: the occurrence of local/systemic undesirable phenomena, as well as the ease of use of pre-filled syringes with ORTHOFLEX ONE solution are centralized in the table below:

*Table no. 10– Undesirable phenomena/ease of use of ORTHOFLEX ONE*

<b>ORTHOFLEX ONE TOLERANCE AND ACCEPTABILITY</b>		
<b>SUBJECT</b>	<b>TOLERANCE</b>	<b>ACCEPTABILITY</b>
	<b>Occurrence of undesirable local phenomena[yes/no]</b>	<b>Ease of use [very easy/easy/difficult/very difficult]</b>
1. RM	No undesirable phenomena were signalled upon injection	Easy
2. VC	No undesirable phenomena were signalled upon injection	Very easy
3. MI	No undesirable phenomena were signalled upon injection	Very easy
4. HE	No undesirable phenomena were signalled upon injection	Easy
5. OM	No undesirable phenomena were signalled upon injection	Very easy
6. ME	No undesirable phenomena were signalled upon injection	Very easy
7. BS	No undesirable phenomena were signalled upon injection	Easy
8. GS	No undesirable phenomena were signalled upon injection	Very easy
9. UM	No undesirable phenomena were signalled upon injection	Easy
10. AC	No undesirable phenomena were signalled upon injection	Easy
11. SF	No undesirable phenomena were signalled upon injection	Very easy
12. CI	No undesirable phenomena were signalled upon injection	Very easy

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<b>ORTHOFLEX ONE TOLERANCE AND ACCEPTABILITY</b>		
<b>SUBJECT</b>	<b>TOLERANCE</b>	<b>ACCEPTABILITY</b>
13. MI	No undesirable phenomena were signalled upon injection	Very easy
14. PM	No undesirable phenomena were signalled upon injection	Easy
15. GF	No undesirable phenomena were signalled upon injection	Easy
16. AT	No undesirable phenomena were signalled upon injection	Very easy
17. LN	No undesirable phenomena were signalled upon injection	Very easy
18. MV	No undesirable phenomena were signalled upon injection	Very easy
19. UE	No undesirable phenomena were signalled upon injection	Very easy
20. GM	No undesirable phenomena were signalled upon injection	Very easy
21. CD	No undesirable phenomena were signalled upon injection	Very easy

No local undesirable phenomena have been signalled to any subject of the 21 included in the analysis of the present report with the occasion of injection of ORTHOFLEX ONE solution or after the injection, throughout the entire follow-up period of 6 months.

As regards the ease of use of ORTHOFLEX ONE solution phials, the members of the investigation team appreciated that the product is used very easily, in 66.67% of cases, respectively easily in 33.33%.

#### **4.2.8. Correctness of data recorded during clinical investigation**

Dispersion calculation for the joint mobility of subjects having benefited of the intra-articular injection of ORTHOFLEX ONE solution, as well as the calculation of Pearson's asymmetry coefficient, demonstrates that we are found in the case of a left (positive) asymmetry, thing demonstrating the correctness of measurements performed by the members of the clinical investigation team.

#### **4.3. Summary of adverse events and adverse effects**

Throughout the follow-up period of subjects (patients), no adverse events and/or adverse effects of ORTHOFLEX ONE solution injection were signalled, thing leading to the hypothesis of their low incidence in the large scale use.

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#### **4.4. Deficiencies of syringes pre-filled with sterile ORTHOFLEX ONE injection solution**

During the clinical investigation (use of products), no deficiencies of pre-filled syringes with ORTHOFLEX ONE injectable solution were signalled.

#### **4.5. Treatment mode of lost data, deviations, inclusively as regards the subjects**

a) lost subjects

Up to the completion, there were no cases of clinical investigation abandonment, all the subjects being assessed for 6 months starting from the injection of ORTHOFLEX ONE solution, as it was provided in the Clinical Investigation Plan. Moreover, there were no lost data or cases in which subjects did not collaborate accordingly with the members of the clinical investigation team.

b) subjects who withdrew, with justification

No enrolled subject withdrew from the clinical investigation, the data being fully analysed.

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## **5. DISCUSSIONS AND CONCLUSIONS**

### **5.1. Results regarding safety and performance**

Analysing the data collected during the present clinical investigation, it is acknowledged that the syringes pre-filled with ORTHOFLEX ONE injectable solution are safe for use, both for the patient and for the user. No serious adverse events were signalled which have undesired effects so that additional measures/treatment be imposed.

We appreciate that the syringes pre-filled with ORTHOFLEX ONE injectable solution are safe for use, and can be successfully used in the symptomatic treatment of osteoarthritis.

As regards the performance of intra-articular injection of ORTHOFLEX ONE solution, it is acknowledged a significant decrease of the intensity of pain felt by the subjects (patients), from 7.48 (according to Wong-Baker scale) – pain close to 8 (resulting in patient's inability to perform most of activities) to more reduced values, namely: 5.86 – at 6 weeks after injection, 4.81 – 3 months after injection and 5.24 – at 6 months after injection, values meaning pain with patient's inability only to perform demanding activities. Amelioration of symptoms was fast and durable.

As regards the severity of pain felt by the subjects, the average value of initial Lequesne functional index, of 17.48, indicates extremely severe OA, which is also preserved at 6 weeks after the injection of ORTHOFLEX ONE solution, but its reduction is evident. At 3 months after injection, the average Lequesne index is equal to 10.71, and at 6 months after injection, the average Lequesne index is equal to 11.33, indicating an OA amelioration, toward a very severe OA.

Data related to the evolution of joint mobility in subjects having benefited of the intra-articular injection of ORTHOFLEX ONE solution, highlight that at 6 weeks after injection, mobility of joints increased by 17.8%, at 3 months after injection, the mobility increased by 31.15%, and at 6 months after injection, the mobility increased by 35.61%, thing having a special importance for the patients, they managing to perform more ample movements, reducing dependency on attendants, increasing the quality of life.

### **5.2. Clinical relevance of data and results**

Osteoarthritis (OA) is a degenerative process, of wear and destruction of joint surfaces, determining a congenital disease, of age-related changes, vascular disorders of the joint structures, of traumatic lesions and of other pre-existing disorders or lesions. as regards the ankle, the osteoarthritis localised at this level is less frequent than that of the knee. She has almost always a known predisposing factor which will initiate the joint changes. The best known is the malalignment of joint surface after a fracture. Sometimes, the ankle joint changes represent the primary element, of onset of a general disease.

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Hyaluronic acid (HA) is a major component of the synovial fluid and the cartilage and, due to its viscoelastic and rheological characteristics, it is responsible of lubrication and amortisation in the joints. It reduces the friction between the joint surfaces and protects the soft tissues against the trauma, acting as an absorber of shock. HA has also analgesic, anti-inflammatory, anti-oxidative and chondroprotector effects, stimulates the proteoglycan synthesis.

HA quantity and quality in the synovial fluid are low in patients suffering of osteoarthritis because its synthesis by the synovial cells and of the cartilage is disturbed. Protection of joint surfaces is thus strongly changed, the cartilage becomes vulnerable and exposed to structural damages because of friction and compression forces.

Intra-articular administration of ORTHOFLEX ONE solution does not presuppose unacceptable risks for the patient and/or user, while the benefits exceed a lot the inherent risks of any medical procedure, including that of intra-articular injection.

Major benefits consisted in:

- pain relief;
- increase of joint mobility

both with a very important impact on the increase of patient's life quality.

### **5.3. Specific benefits or special precautions necessary to subjects or some subgroups**

As regards the benefits of intra-articular injection of ORTHOFLEX ONE solution, we can assert with certainty the following:

- It is acknowledged a significant relief of pain felt by the subjects (patients), relief appreciated on the evolution of pain intensity (according to Wong-Baker visual scale), as well as on the evolution of its severity (according to Lequesne index), with positive impact on patients' life quality;
- It is acknowledged an evident, substantial increase of mobility of joints to which ORTHOFLEX ONE solution was injected, thing having a special importance for the patients, they managing to perform more ample movements, reducing dependency on attendants, increasing the quality of patients' life;
- No special precautions are necessary as regards the intra-articular injection of ORTHOFLEX ONE solution, excepting the case in which the patient is allergic to one or more constituents of the solution;

We cannot conclude that certain patient subgroups (related to sex, age, blood type, occupation, etc.) would have additional benefits compared to other subgroups of patients, or additional risks.

### **5.4. Limitations of the clinical investigation**



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The present clinical investigation did not propose to analyse the performances of intra-articular injection of ORTHOFLEX ONE solution on subgroups of patients or different OA aetiologies.

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## **6. ABBREVIATIONS; TERMS AND DEFINITIONS**

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OA – Osteoarthritis  
HBP – High Blood Pressure  
IHD – Ischemic heart disease  
CVI – Chronic Venous Insufficiency  
SPOA – Spinal and Peripheral Osteoarthritis  
SHP – Scapulohumeral periarthritis  
CVA – Cerebrovascular accident  
HA – Hyaluronic acid

The terms and definitions used in the documentation of the clinical investigation [Investigator's Manual, Clinical Investigation Plan] are compliant with SR EN ISO 14155, SR EN ISO 13485 and SR EN ISO 14971.

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## **7. ETHICS**

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The clinical investigation plan was analysed by the Ethics Committee of the National Institute of Rehabilitation, Physical Medicine and Balneoclimatology of Bucharest, Romania, on 04.03.2014.

The Ethics Committee of the National Institute of Rehabilitation, Physical Medicine and Balneoclimatology of Bucharest, Romania was notified on the changes proposed to CIP by two amendments to the Clinical Investigation Plan (Amendment no. 1 /10.03.2014 and Amendment no. 2 /29.05.2014).

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## **8. INVESTIGATORS AND ADMINISTRATIVE STRUCTURE OF CLINICAL INVESTIGATION**

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### **8.1. Short description of clinical investigation organisation**

The clinical investigation has been carried out at the National Institute of Rehabilitation, Physical Medicine and Balneoclimatology of Bucharest, up to the enrolment of 21 subjects out of 30, number initially provided in the Clinical Investigation Plan RA-CIP-001.

No restrictions have been provided as regards the recruitment of subjects according to OA location.

### **8.2. List of investigators**

1. Principal clinical investigator: Doctor Dima Augustin, Board Certified Physician in Physiokinesitherapy and Balneology, National Institute of Rehabilitation, Physical Medicine and Balneoclimatology, Bucharest.
2. Clinical investigator: Reader Cinteza Delia, PhD, Board Certified Physician in Physiokinesitherapy and Balneology, National Institute of Rehabilitation, Physical Medicine and Balneoclimatology, Bucharest, Lecturer of Carol Davila University of Medicine and Pharmacy, Doctor of Medical Science.
3. Clinical investigator: Dr. Alexandru Cristea, Board Certified Physician in Physiokinesitherapy and Balneology, National Institute of Rehabilitation, Physical Medicine and Balneoclimatology, Bucharest.

### **8.3. Sponsor's name and address**

S.C. Rompharm Company S.R.L.  
Romania, Ilfov, 75100, Otopeni, Str. Eroilor, nr. 1A  
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web: [www.rompharm.ro](http://www.rompharm.ro)

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## **9. PAGE WITH SIGNATURES FOR THE CLINICAL INVESTIGATION REPORT**

I have read this report and I confirm it describes precisely the performance and the results of this clinical investigation.

Sponsor S.C. Rompharm Company S.R.L.	Managing Director S.C. Rompharm Company S.R.L. Atanasov Rossen	<i>Date and signature</i>
Principal Clinical Investigator National Institute of Rehabilitation, Physical Medicine and Balneoclimatology, Bucharest	Doctor Dima Augustin Board Certified Physician in Physiokinetotherapy and Balneology	<i>Date, signature and seal</i>
Monitor S.C. Rompharm Company S.R.L.	Pharm. Georgiana Marinică	<i>Date and signature</i>