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JOURNAL	World Science
p-ISSN	2413-1032
e-ISSN	2414-6404
PUBLISHER	RS Global Sp. z O.O., Poland
ARTICLE TITLE	POSTMARKETING, PROSPECTIVE, MULTICENTRE, SINGLE-ARM STUDY OF SUBJECTS WHO RECEIVE AN INJECTION OF A MEDICAL DEVICE BASED ON HYALURONIC ACID: CLINICAL STUDY REPORT
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ARTICLE INFO	Nazar Vadzyuk. (2024) Postmarketing, Prospective, Multicentre, Single-Arm Study of Subjects Who Receive an Injection of a Medical Device Based on Hyaluronic Acid: Clinical Study Report. <i>World Science</i> . 1(83). doi: 10.31435/rsglobal_ws/30032024/8127
DOI	https://doi.org/10.31435/rsglobal_ws/30032024/8127
RECEIVED	23 February 2024
ACCEPTED	27 March 2024
PUBLISHED	29 March 2024
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POSTMARKETING, PROSPECTIVE, MULTICENTRE, SINGLE-ARM STUDY OF SUBJECTS WHO RECEIVE AN INJECTION OF A MEDICAL DEVICE BASED ON HYALURONIC ACID: CLINICAL STUDY REPORT

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DOI: https://doi.org/10.31435/rsglobal_ws/30032024/8127

ARTICLE INFO

Received: 23 February 2024

Accepted: 27 March 2024

Published: 29 March 2024

KEYWORDS

Hyaluronic Acid, Intra-Articular Injection, Knee Osteoarthritis, Joint Pain.

ABSTRACT

Introduction: Viscosupplementation with an intra-articular injection of hyaluronic acid (HA) is widely used around the globe for pain management in patients with osteoarthritis (OA). Safety and clinical outcomes are debated for decades. First, products have been designed for multiinjections (3–5 injections at 1-week intervals); newer products and treatment schemes are developing continuously. Elevated concentration or dose, additional components, and chemical bonds can provide better and prolonged effects of treatment. All these features could give an advantage like single-injection treatment, prolonged time between injections and better pain management. With the use of a single injection one can get advantages such as the reduction of visits to the doctor and less interventions with their associated risks. For this purpose, a benefit/risk profile of the novel HA formulation was investigated. This study contributes to knee osteoarthritis (KOA) treatment.

Methods: Postmarketing, prospective, multicentre, single-arm study of subjects with knee OA grades II to IV according to the Kellgren and Lawrence classification was used who received a single injection of medical HA-based device was performed. The study has been scheduled in the form of Visit 1 (month 0), Visit 2 (month 1), Visit 3 (month 2), Visit 4 (month 3), Visit 5 (month 4), Visit 6 (month 5) and Visit 7 (month 6). The changes in the WOMAC questionnaire have been evaluated upon treatment initiation for up to 6 months. The incidences of adverse events have been recorded throughout the study.

Results: The clinical study was conducted in Ukraine and Poland by 5 clinical sites; 55 persons who met the study inclusion criteria were involved in the investigation. The age of subjects ranged from 36 to 80 years with mean age of 52.02 years. The score of the WOMAC questionnaire findings resulted in the improvement of pain and function after 1, 2, 3, 4, 5, 6 months compared to the population's baseline data (mean reduction from baseline 13.62, 18.31, 22.79, 22.18, 21.25, 21.55 points, respectively ($p < 0.001$)).

Conclusion: This study showed HA's tolerability and safety in a single-injection application for at least 24 weeks, resulting in a promising treatment option for patients with KOA for whom conventional therapy has failed.

Citation: Nazar Vadzyuk. (2024) Postmarketing, Prospective, Multicentre, Single-Arm Study of Subjects Who Receive an Injection of a Medical Device Based on Hyaluronic Acid: Clinical Study Report. *World Science*. 1(83). doi: [10.31435/rsglobal_ws/30032024/8127](https://doi.org/10.31435/rsglobal_ws/30032024/8127)

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Introduction.

According to the Osteoarthritis Research Society International (OARSI) definition, OA is a disorder involving movable joints characterized by cell stress and extracellular matrix degradation initiated by micro- and macro-injury that activates maladaptive repair responses including pro-inflammatory pathways of innate immunity [1]. Numerous treatment guidelines are provided by leading professional societies for OA across the world [2, 3]. At the same time, different methodologies have been used historically to develop these treatment guidelines. It can be concluded that management of osteoarthritis is still focused primarily on symptom management due to the lack of approved pharmacologic agents that halt the disease progression. That's why there is still no definitive treatment for OA. The entirety of the factors involved in the development and progression of the OA should be taken into account.

Treatment of OA includes non-pharmacological and pharmacological approaches, and currently available modalities provide pain relief for most patients. Paracetamol and nonsteroidal anti-inflammatory drugs (NSAIDs) are the most frequently prescribed medications, but resistance or intolerance to NSAIDs is common [4]. Those who have weak response or cannot tolerate a conservative approach need to turn to surgery. For patients that have failed pain-killing therapy HA is a valuable symptom-modifying alternative, and it may be used to forestall surgery. The safety and, mostly, efficacy of HA are the topics for clinical study as previous findings often showed differences in results [5].

Numerous functions have been attributed to synovial fluid hyaluronic acid, including lubrication of the soft tissues, e.g., adjacent fronds of synovial villi, and provision of a surface layer on the articular cartilage [6].

During the last years, the use of viscosupplementation has grown as a treatment of moderate-degree osteoarthritis [7]. Viscosupplementation is a minimally invasive technique that involves replacement of synovial fluid by intraarticular injection of HA. HA products are safe and efficacious in patients with symptomatic knee osteoarthritis by restoring its concentration and molecular weight in joint cavity [8].

This study was designed to confirm the safety, tolerability and effectiveness of the investigational medical device (IMD) based on the new HA formulation (registered under trademarks Diart One in Ukraine and Easygo One in Poland) administered intraarticularly to patients affected by knee osteoarthritis.

Methods.

This clinical study was performed in accordance with the requirements of the CIP provided by the Sponsor, requirements of applicable current state regulations, European Council Directive 93/42/EEC of 14 June 1993 on medical devices, taking into consideration the requirements of MDR Regulation (EU) 2017/745 on medical devices, ISO 14155:2020 "Clinical investigation of medical devices for human subjects — Good clinical practice" and in compliance with the ethical principles of the Declaration of Helsinki (64th World Medical Association. World Medical Association Declaration of Helsinki and the conditions established by the Ethics Committees at the Investigation Sites) [9].

The study was scheduled in the form of monthly visits from 1 to 6 (end of follow-up, 6 months). The changes in the WOMAC questionnaire were evaluated upon treatment initiation for up to 24 weeks. The incidences of adverse events were recorded throughout the study. The enrolled subjects received 1 injection of the HA-based IMD. Only one of the subject's knee joints was treated during the investigation. Accuracy of the injection was confirmed through the use of ultrasound guidance.

The new formulation of the HA-based IMD manufactured by Diaco Biofarmaceutici S.R.L., Italy has been administered intraarticularly to patients affected by knee osteoarthritis.

Objectives of the study included the following: 1. Evaluate the effectiveness of a medical device by analysing the effect on pain intensity by the WOMAC index pain subscale score (5-point Likert-type scale, 0-20 for Pain). 2. Evaluate the effectiveness of a medical device by analysing the effect on WOMAC index sum score (Likert-type scale, total 0-96: 0-20 for Pain, 0-8 for Stiffness, 0-68 for Physical Functioning). 3. Investigate safety and tolerability of the medical device application. The original variation of the Kellgren and Lawrence classification system was used [10].

The subject had to meet all of the following criteria for the inclusion to the study:

1. Age ≥ 21 years.
 2. Body mass index $\geq 18.5 \text{ kg / m}^2$, $< 35 \text{ kg / m}^2$.
 3. The subject had manifestations of KOA confirmed by radiographic methods (Kellgren-Lawrence grades II-IV).
 4. The subject agreed to participate in the study and signed the Informed Consent Form.
- Subjects with at least one exclusion criterion were not included in the study:
1. Age < 21 years.
 2. Body mass index $< 18.5 \text{ kg / m}^2$, $\geq 35 \text{ kg / m}^2$.
 3. Pregnancy and lactation.
 4. The subject had no evidence of injury or degenerative diseases, such as osteoarthritis, confirmed by radiographic methods (Kellgren-Lawrence score – 0-1).
 5. Hypersensitivity to HA, its metabolites, or to the excipients in the injectable implant.
 6. Confirmed infectious diseases of the joint.
 10. Systemic connective tissue diseases (including confirmed active rheumatoid arthritis, confirmed ankylosing spondylitis).
 11. Non-OA arthritis.
 12. Planned total arthroplasty of the target knee joint.
 13. Gait disorders of neurological origin.
 14. Injections of HA at the IMD application site for 3 months before inclusion in the study.
 15. Surgery, orthopaedic surgery on the affected joint for the last 3 months.
 16. Cancer.
 17. Decompensated diabetes mellitus.
 18. Haematological diseases.
 19. Refusal or suspicion of inability of the subject to comply with the requirements of the CIP.
 20. The subject has difficulty understanding the language in which the informed consent is written.
 21. Any other reason that the Investigator believes prevents the subject from participating in the study.
 22. The subject takes part in another study.

Visits 0 and 1 were outpatient visits with the evaluation of test results and eligibility. If the IMD was prescribed in accordance with the instructions for use, the subject was invited to participate in the clinical study and signed an Informed Consent Form. At visit 1 (Day 1), a clinical evaluation and the WOMAC index evaluation were carried out, and dose and volume were determined, as well as injection of the IMD was performed, device defects, adverse events before and after the procedures and device adverse effects were registered. At the discretion of the Investigator, the procedures of visit 0 and visit 1 could be carried out in one day. If these visits occurred separately, the WOMAC index evaluation was carried out on both visits. Visits 2, 3, 5, 6 (Days 30 ± 5 , 60 ± 5 , 120 ± 5 , 150 ± 5 , respectively) were conducted by telephone; visit 4 (Day 90 ± 5) as an outpatient visit. Visit 7 (Day 180 ± 5) was a telephone visit or outpatient visit at the discretion of the Investigator. A clinical evaluation (in case of an outpatient visit), the WOMAC index evaluation, interview for indicating adverse events and device adverse effects were carried out. Primary effectiveness endpoint included the following: 1. Changing the score of the WOMAC index Pain subscale (5-point Likert-type scale, 0-20 for Pain) after 3 months compared to baseline. Secondary effectiveness endpoints included the following: 1. Changing the score of the WOMAC index Pain subscale (5-point Likert-type scale, 0-20 for Pain) after 1, 2, 4, 5, 6 months compared to baseline. 2. Changing the sum score of the WOMAC index (Likert-type scale, total 0-96: 0-20 for Pain, 0-8 for Stiffness, 0-68 for Physical Functioning) after 1, 2, 3, 4, 5, 6 months compared to baseline.

Primary effectiveness endpoint was the changings of the WOMAC index Pain subscale (5-point Likert-type scale, 0-20 for Pain) after 3 months compared to baseline. Secondary effectiveness endpoints were, first, changings of the WOMAC index Pain subscale (5-point Likert-type scale, 0-20 for Pain) after 1, 2, 4, 5, 6 months compared to baseline; second, changings of the sum score of the WOMAC index (Likert-type scale, total 0-96: 0-20 for Pain, 0-8 for Stiffness, 0-68 for Physical Functioning) after 1, 2, 3, 4, 5, 6 months compared to baseline.

Safety endpoints were the following: registration of all device defects observed during the study by the Investigator; registration of all adverse events and all device adverse effects observed during the study with the description of their predictability, duration, severity, seriousness, course,

consequences, relation to the application of the IMD, the need to take additional measures to eliminate them by the Investigator.

The safety and tolerability of the IMD have been assessed during the application of the IMD and throughout the follow-up period. The tolerability of the IMD have been assessed based on subjective data and objective data obtained by the Investigator during the use of the IMD and during the follow-up period, the overall tolerability assessment given by the Investigator and the subject (separately).

The safety assessment was based on the assessment of adverse events: data collection on adverse events; data collection on the concomitant treatment; physical examination.

The number, frequency, predictability, duration, severity, seriousness, course, consequences, relation to the application of the IMD, adverse events (AE) and device adverse effects (DAE), the need to take additional measures to eliminate them were considered for the purpose of the analysis: number, frequency, predictability, duration, severity, seriousness of all AEs, which were identified during the study; number, frequency, predictability, duration, severity, seriousness of all DAEs, which were identified during the study; number, frequency, predictability, duration, severity, seriousness of all DAEs and AEs leading to the withdrawal of the subject from the study.

Results.

The population who met the criteria (55 subjects) included both female and male subjects with a percentage ratio of 54.5% to 45.5%; subjects enrolled in Ukraine (24 subjects, 43.6%) and Poland (31 subjects, 56.4%). The age of subjects ranged from 36 to 80 years old with the mean age of 52.02 (95% CI 55.07-60.97). The subject had BMI from 21.97 to 34.82 with the mean BMI of 29.77 (95% CI 28.89-30.66). 33 subjects (60.0%) had at least one chronic disease (except osteoarthritis) at baseline (visit 1). In total, 60 different cases of chronic diseases were registered in the population, among which the most common was hypertension (23 cases, 38.34%, pooled from "patient reports"). Osteoarthritis has been diagnosed in the population subjects in period from 1980 to 2021; 30.9% of subjects from the population were diagnosed with osteoarthritis in 2021. 33 subjects (60.0%) from the population took concomitant medication (except for the osteoarthritis treatment) at baseline (visit 1). Only 2 patients (2.22%) of 55 had a history of an allergic reaction (or/and individual intolerance) namely to vitamin B12 and local oedema after Penicillin intake. 21 subjects (38.2%) from the population took medication for the knee osteoarthritis treatment at visit 1. 9 subjects (16.4%) had surgeries for the knee osteoarthritis treatment.

There were 3 types of surgeries for the knee osteoarthritis treatment done previously in population: arthroscopy (5), arthrotomy (1), arthroplasty (3). First-degree or/and second-degree relatives of 11 (20.0%) subjects from the population also had OA. Both knees were affected by osteoarthritis in 20 subjects (36.4%), only left knee in 16 subjects (25.4%) and only right knee in 19 subjects (30.2%). In addition to the knee joints of both legs, the other joints were affected in some of the subjects, among them different sections of the spine (1 case, 1.6% - cervical spine; 4 cases, 6.3% - lumbosacral spine), left ankle (1 case, 1.6%) and small joints of the hands (1 case, 1.6%) and both feet (1 case, 1.6%). The left knee pain was present in 34 subjects (61.8%), 16 of them described this pain as moderate (29.1%) and 35 subjects (63.6%) reported pain in the right knee, the most frequent intensity of pain also was moderate (in 22 subjects - 40.0% of the population). Subjects noticed the pattern to the onset of pain (50.9% for the left knee localization pain and 47.3% for the right knee). 43 subjects reported stiffness (78.2%), 7 of them reported stiffness in both knees (12.7%), 19 (34.5%) subjects reported stiffness in left knee, 17 (30.9%) subjects reported about stiffness in the right knee. 14 subjects (25.5%) noted the absence of physical activity limitations in any knee and 41 subjects (74.5%) had different types of physical activity limitation in both knees (6 subjects, 10.9%), in left knee (16 subjects, 29.1%) and in right knee (19 subjects, 34.5%). 2 cases (3.6%) of swelling were reported (one in a left knee - slight swelling of periarticular tissues, synovitis, and another in a right knee - suprapatellar pouch) and no information about redness and heat was reported. The X-ray examination was done for 51 subjects (92.7%), the MRI examination for 3 subjects (5.5%) and the ultrasound for 1 subject (1.8%). 7.3% (4 subjects) reported Grade 1 (doubtful), 36.4% of subjects (20 subjects) had Grade 2 (minimal), 16.4% of subjects (9 subjects) had Grade 3 (moderate), 7.3% (4 subjects) had Grade 4 (severe) in Kellgren-Lawrence score for the left knee. For the right knee also 7.3% (4 subjects) had Grade 1 (doubtful), 32.7% (18 subjects) had Grade 2 (minimal), 27.3% (15

subjects) had Grade 3 (moderate), and 1.8% (1 subject) had Grade 4 (severe) in Kellgren-Lawrence score. First-degree or/and second-degree relatives of 11 subjects (20.4%) also had OA.

According to the analysis of mean of the WOMAC index total score we could report about 22.79 points (56.59%) reduction from visit 1(baseline) to visit 4 (after 3 months) and slight increase in value from visit 4 (after 3 months) to visit 7 (after 6 months) – 1.24 points (7.09%) (Figure 1).

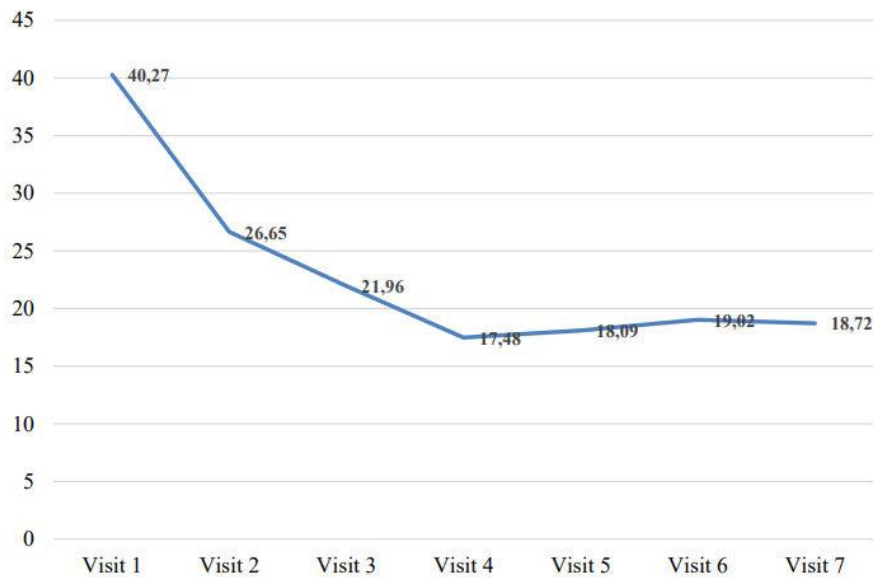


Figure 1. Mean of the WOMAC index total score.

According to the sensitivity analysis of mean of the WOMAC index total score, after replacement of the outliers with the dataset median, we could report 24.08 points (60.58%) reduction from visit 1 (baseline) to visit 4 (after 3 months) and slight increase in the value from visit 4 (after 3 months) to visit 7 (after 6 months) – 0.14 points (0.89%) (Figure 2).

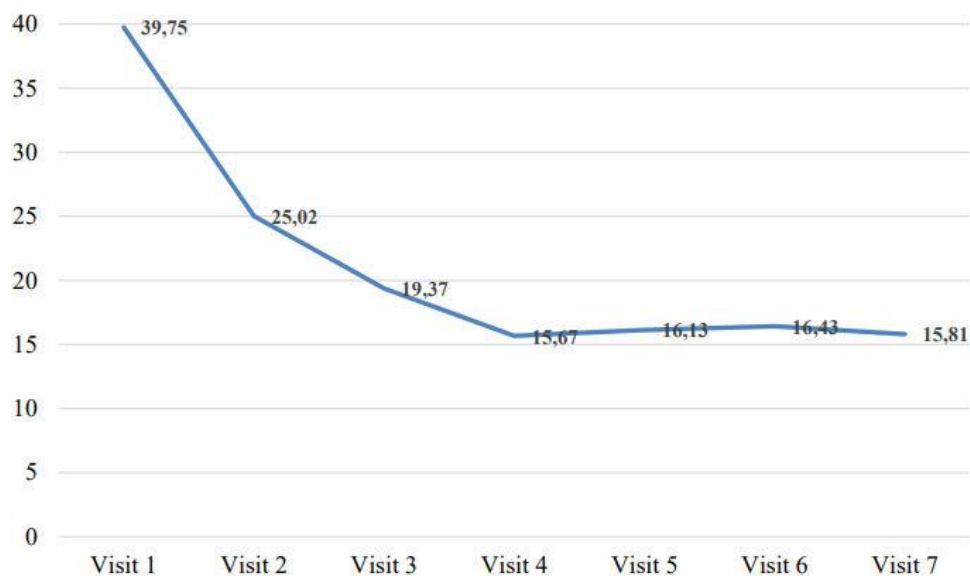


Figure 2. Mean of the WOMAC index total score after replacement of the outliers with the dataset median.

For statistical significance of means, additional analysis of the primary effectiveness variable was applied since most of the WOMAC index total score data was not distributed normally

($p \leq 0,001$). Non-parametric Friedman test followed by post hoc analysis using Wilcoxon signed-rank test was applied. According to the test results, we can report that most of the pain subscale total score of WOMAC at all visits of the study (Visit 1 – Visit 7) had statistically significant difference ($p \leq 0,025$) except Visit 6 compared with Visit 3 ($p=0.037$), Visit 7 compared with Visit 3 ($p=0.090$), Visit 5 compared with Visit 4 ($p=0.341$), Visit 6 compared with Visit 4 ($p=0.187$), Visit 7 compared with Visit 4 ($p=0.546$), Visit 6 compared with Visit 5 ($p=0.441$), Visit 7 compared with Visit 5 ($p=0.988$), Visit 7 compared with Visit 6 ($p=0.581$).

The final statistical analysis corroborates high safety and tolerability of the HA as only 8 non-serious adverse events, 2 DAEs and 1 serious adverse event were registered during the study from Visit 1 till Visit 7 (6-months follow-up). As for causal relationship with the IMD, only one AE was classified as possible, unlikely; another AE was classified as unknown. These events were registered as DAEs. The severity of 1 DAE was mild; the other one DAE was of moderate severity. 1 DAE continued and 1 DAE was resolved. 1 of the DAEs required actions taken due to the development of the DAE (removal of exudate). The severity of AEs was mild but 3 AEs with moderate severity were discovered. 1 of the AEs continued, 2 were in process of recovery and 5 AEs resolved. 4 subjects were treated by concomitant medications for AEs. SAE was classified as not related to the use of the IMD. It was resolved. The subject was treated by concomitant medications for SAE.

Discussion.

Viscosupplementation with intra-articular HA is an option for the treatment of the OA. Available papers doesn't show unequivocally effectiveness, but some of them show promising results. Exogenous HA can enhance chondrocytes' hyaluronan synthesis and prevent degradation of the cartilage. Moreover, it can reduce the production of proinflammatory mediators and matrix metalloproteinases involved in OA pathogenesis.

This postmarketing, prospective, multicentre, single-arm study demonstrated the sustained tolerability and safety of treatment with HA in subjects with OA in terms of improvement of patient-reported outcomes related to pain and functioning. These beneficial effects developed in the form of increasing physical activity and showed low incidence of adverse events.

These effects might be achieved due to physicochemical properties of the novel formulation of HA chains that may prolong maintenance of its molecules in the joint - viscosity, elasticity, lubrication and a high capacity for holding water. Due to indicated above properties of HA one can expect anti-oxidative, anti-inflammatory, and analgesic effects in OA treatment.

After treatment initiation, the WOMAC score gradually and significantly decreased across the visits in the cohort to month 3. Considering its clinical and structural effectiveness and tolerability, therapy with hyaluronic acid can be regarded as a long-term therapy.

Conclusion.

As final statistical analysis corroborated high safety and tolerability of the IMD (Diar One/EasyGo One) proven by statistically significant reduction of OA symptoms and functional limitations per WOMAC index detected at every time point covered by the analysed follow-up period, the benefit/risk ratio might be deemed positive.

This postmarketing, prospective, multicentre, single-arm study demonstrated the sustained effectiveness and safety of the used HA, improvement outcomes related to pain and functioning. OA is a degenerative condition where treatment is mainly based on symptomatic or surgical interventions. After treatment initiation, the WOMAC score of pain decreased across the visits. Importantly, a 22-point reduction in pain was observed gradually till month 4 after treatment initiation and slight increase in value from visit 4 (after 3 months) to visit 7 (after 6 months).

Our findings described in this study suggest that intraarticular injections of new HA formulation are not associated with serious adverse events and can be used safely and effectively in reducing pain and improving functionality of the knee joint.

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