Kneed to Know Newsletter

nSTRIDE® APS Kit | Issue 1

Once OA Pain Starts, It's Hard to Stop.

In this edition of **Kneed to Know**, you will find:

An Interview with PROGRESS II Principal Investigator Dr. Elizaveta Kon

Dr. Elizaveta Kon, principal investigator of the PROGRESS II nSTRIDE Autologous Protein Solution (APS) clinical trial, presented the exciting results of the study at an Evening of Education event at the recent American Academy of Orthopaedic Surgeons (AAOS) Annual Meeting. The trial includes four European trial centers. PROGRESS II is no longer accepting patients, but data is still being collected for analysis.

Dr. Kon is an associate professor at Humanitas University and Research Hospital in Milan, Italy. The PROGRESS II clinical trial was the first time she conducted a trial comparing APS to saline, and she was pleased to find percent improvement in pain was significant in patients treated with APS versus saline (based on the Western Ontario and McMaster Universities Arthritis Index [WOMAC] and Visual Analogue Scale [VAS] pain scales). Further, that PROGRESS II demonstrated a promising adverse event profile for the nSTRIDE APS Kit.

"It was very exciting to document improvement in patients treated with APS over saline, and satisfying to find only a small number of adverse events," Dr. Kon said.[1] "The trial results will inform treatment of osteoarthritis in the future. I am very happy to have been involved and am looking forward to what is to come."

Both the nSTRIDE APS and platelet rich plasma (PRP) clinical trials with which Dr. Kon has been involved have studied intra-articular injections of potential autologous blood-derived therapies. A key difference between nSTRIDE APS and PRP is the content of leukocytes and associated anti-inflammatory cytokines in the therapies. She explained that leukocytes in PRP appear to create pro-inflammatory factors in vitro, but not in vivo. Characterization of APS in the PROGRESS II study reflected a high concentration of anti-inflammatory cytokines and low concentration of their inflammatory counterparts.[1]

"The presence of leukocytes has shown detrimental effects, but only in vitro. I did a study injecting leukocyte-rich PRP into the joint, and at the time of the second injection, which was seven days later, there was no increase in pro-inflammatory cytokines detected," Dr. Kon said. "APS is not leukocyte-rich PRP. It is a completely different product focused on the concentration of anti-inflammatory cytokines, so the results of PROGRESS II do not correlate with the leukocyte-rich PRP in vitro results."[1]

Though PROGRESS II had a limited patient population with patients ages ranging from 41 to 68, Dr. Kon believes

the patient population that would benefit from use of the nSTRIDE APS Kit is broader.

"Our PRP studies have shown that it works better in younger patients, and it would be interesting to see if the same is true for nSTRIDE APS," she said. "I hope to learn whether APS shows promise for other patient populations, especially in more severe cases of osteoarthritis."

Dr. Kon has been a valued partner to Zimmer Biomet, and we thank her for her dedication to nSTRIDE APS clinical trials.

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An Interview with Dr. Erik Rosenlund, an Innovator in the Use of the nSTRIDE Autologous Protein Solution (APS) Kit

Dr. Erik Rosenlund, Chief of Orthopaedics at Volvat Medical Center in Norway, recently spoke with Zimmer Biomet about his success with the nSTRIDE APS Kit in patients with knee osteoarthritis.

Dr. Rosenlund began practicing medicine in 1974 and has been a leader in the field of sports medicine in Norway for the past three decades. He began using blood-derived autologous therapies in 2006 and first used the nSTRIDE APS Kit in January 2016. He is at the forefront of surgeons in Norway utilizing the technology.

The nSTRIDE APS Kit concentrates cytokines and anabolic growth factors from the patient's blood. Dr. Rosenlund credits the anti-inflammatory properties of the solution with significantly decreasing pain and increasing function in patients with pain associated with knee OA.

"I'm very excited about patient results with the nSTRIDE APS Kit," Rosenlund said. "I'm consistently finding reduced fluid in the joints of patients treated with the APS and an increase in range of movement and activity level within 4-8 weeks following an injection."

Dr. Rosenlund has found that blood-derived autologous therapies can delay, and may negate, the need for knee replacement surgeries. Many of his patients who receive platelet-rich plasma (PRP) injections report a substantial improvement in pain and function following the initial injection. In his anecdotal experience, use of the nSTRIDE APS Kit produces quicker and more durable results than other autologous products.

Dr. Rosenlund believes the greatest benefit is often seen in younger patients who are not yet candidates for knee replacement but are finding their pain and loss of function a detriment in daily living. However, he also points to older patients who prefer not to have surgery and are finding the injections to be a very viable alternative when combined with weight and mobility training.

Most of Dr. Rosenlund's patients are advised to limit their physical activity for the first 3-4 days following an injection and to avoid strenuous training for up to a week, after which they can and do return to their normal activity. Given the record of success and quick recovery times, he anticipates more surgeons in Norway will begin offering the therapy.

"I currently treat a dozen or so patients per week, and I'm certain that number will go up," Dr. Rosenlund said. "As awareness of the nSTRIDE APS Kit spreads, I expect the demand at my practice and elsewhere will increase."

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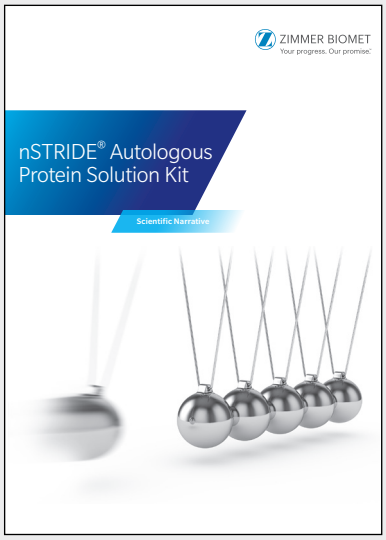
The nSTRIDE APS Kit Scientific Narrative Brochure

The nSTRIDE APS Kit represents an opportunity for Zimmer Biomet to apply its established technology and unique expertise in autologous therapies to address a pressing unmet medical need in osteoarthritis (OA) of the knee. The nSTRIDE APS Kit offers patients and their caregivers an effective option for the management of this common degenerative disorder.

The narrative reviews:

- The burden of OA on the knee
- How overall pathophysiology is based on changes occurring at the molecular level
- Medical and surgical treatments currently used in OA of the knee, and their respective efficacy and limitations
- The scientific basis for targeted therapy in OA
- The role of the nSTRIDE APS Kit in providing a treatment that can be delivered point-of-care to decrease inflammation and promote cartilage health



To receive a copy of the Scientific Narrative Brochure, **please contact Roel Brüll (Roel.Bruell@zimmerbiomet.com).**

The PROGRESS Clinical Story

Osteoarthritis (OA) is the most common joint disorder in humans with increasing prevalence between 2005 and 2015, yet there are no disease-modifying treatments available for the management of OA.[2] In fact, there is a growing treatment gap for patients with moderate to severe osteoarthritis who refuse or are not candidates for surgical intervention.[2] As a result, there is currently an unmet need for therapies that address the underlying disease process.

In an effort to address this need, Zimmer Biomet is executing a comprehensive series of clinical trials to better understand the potential role of a unique autologous therapy in the treatment of OA. The PROGRESS clinical trials are designed to demonstrate the effectiveness of the nSTRIDE APS Kit compared to saline or other injectable preparations with respect to globally recognized clinical measures. They also seek to clarify the role of APS as a potentially disease-modifying option for knee OA.

The clinical trial results obtained for the PROGRESS series to date represent a building body of evidence regarding the safety of the nSTRIDE APS Kit for production of APS, which is delivered via intra-articular (IA) injection for knee OA. PROGRESS I and II also demonstrated promising improvement in a variety of clinical measures related to OA pain and function.[1, 3, 4] PROGRESS III – V are designed to further explore the impact and role of the nSTRIDE APS Kit relative to saline and other OA treatments.

Zimmer Biomet is pleased to offer a product, the nSTRIDE APS Kit, which can improve OA symptoms and potentially delays surgery by promoting cartilage health. The company is hopeful that ongoing and future clinical studies will demonstrate disease-process modification, leading to longer and improved pain relief for patients who have failed conventional conservative therapies.

Study	Region/ Status	Design	Enrollment	Primary Completion Date	Results
First in Human	EU Complete	Open label, single injection safety study	11	June 2014	No serious adverse events. Avg. WOMAC pain change = 72% improvement from baseline to 6 months
PROGRESS I	US Complete	Open label, single injection safety study	10	October 2016	Avg. WOMAC pain change = 73% improvement from baseline to 12 months
nSTRIDE APS in Females With Primary Patellofemoral Osteoarthritis	EU Fully enrolled	Observational, single injection, treatment effects study	50	January 2018	TBD
PROGRESS II	EU Fully enrolled	Double-blind, randomized, single injection efficacy study	APS: 31 Saline: 15	October 2015	• Avg. WOMAC pain change = 65% improvement from baseline to 12 months (saline = 41%) • Avg. VAS pain change = 49% impovement from baseline to 12 months (saline = 13%) • Avg. WOMAC function change = 57% improvement from baseline to 12 months) (saline = 44%)
PROGRESS III	EU Fully enrolled	Prospective, observational, treatment effects study	78	February 2018	TBD
PROGRESS IV	US Enrolling	Double-blind, randomized, single injection efficacy study	APS: 123 Saline: 123	April 2019	TBD
PROGRESS V	EU Investigator Recruitment	Double-blind, randomized, single injection efficacy study	APS: 123 HA: 123	Estimated 2023	TBD

Spotlight on Zimmer Biomet Researchers

Jennifer Woodell-May, Ph.D.

Associate Research Director

Jennifer Woodell-May is currently Associate Director of Research in Biologics for Zimmer Biomet. After earning her PhD in Bioengineering from Clemson University, she joined Biomet Orthobiologics in 2001. Her responsibilities include management of research activities for currently marketed therapies as well as pre-clinical and regulatory efforts for new technologies. A well-published author on topics including the basic science and orthopedic uses for platelet-rich plasma, her research focuses on platelet-rich plasma, stem cells, demineralized bone matrix, and autologous anti-inflammatory concentrates. Jennifer also holds an adjunct faculty position in the Bioengineering department at Clemson University.

William King, Ph.D.

Research Principal Scientist

William King has been conducting regenerative medicine research for 15 years. While an undergraduate student, his work at several leading research institutions resulted in new ways of controlling stem cell differentiation and imaging analysis. His doctoral research at the University of Wisconsin focused on the interaction between stem cells, growth factors, and biomaterials. Subsequently, his postdoctoral research at the University of Michigan improved the process of genetically engineering stem cells. Bill joined Zimmer Biomet Biologics nearly 5 years ago to translate his work in regenerative medicine into new therapeutic approaches, like autologous protein solution, to address a variety of musculoskeletal conditions.

Highlighted Literature

Safety and Treatment Effectiveness of a Single Autologous Protein Solution Injection in Patients with Knee Osteoarthritis
Rogier AM van Drumpt, Walter van der Weegen, William King, Krista Toler, Mitchell M Macenski
2016 DOI: 10.1089/biores.2016.0014

Human Blood-Based Anti-Inflammatory Solution Inhibits Osteoarthritis Progression in a Meniscal-Tear Rat Study
William King, Alison Bendele, Taylor Marohl, Jennifer Woodell-May
2017 DOI: 10.1002/jor.23528

Frequently Asked Questions

What is the difference between nSTRIDE Autologous Protein Solution (APS) and platelet-rich plasma (PRP)?

Although APS and PRP are both blood-derived autologous products, the nSTRIDE APS Kit has been specifically designed to concentrate anti-inflammatory cytokines and anabolic factors. It is therefore an autologous anti-inflammatory solution and not a platelet-rich plasma, a classification agreed upon by the American Medical Association CPT Editorial Board.

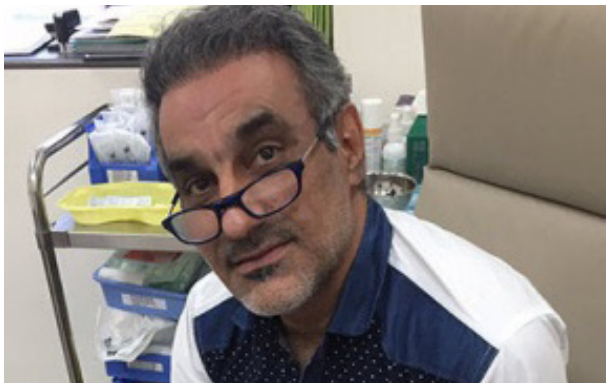
How many injections of nSTRIDE Autologous Protein Solution (APS) are required?

Human clinical studies have demonstrated the effectiveness of one injection. Studies suggest one injection can last at least 12 months in some patients.[1,4]

How soon does the treatment start to work?

Pain relief has been demonstrated within one to two weeks.

First nSTRIDE Autologous Protein Solution (APS) procedure in the Middle East and North Africa



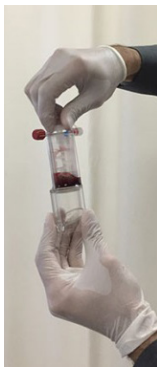
Dr. Ismail Jahromi, an orthopedic surgeon who operates at the Royal Bahrain Hospital in Manama, Bahrain, practices what he preaches. On March 27, the first nSTRIDE Autologous Protein Solution (APS) procedure in the Middle East and North Africa was performed—on Dr. Jahromi.

The nSTRIDE APS Kit is an autologous blood processing system designed to concentrate anti-inflammatory cytokines and anabolic growth factors to significantly decrease pain and promote cartilage health for patients.[5,6] It is part of Zimmer Biomet's early intervention joint preservation solutions program in Europe.

Dr. Jahromi has been using the Zimmer Biomet NexGen® Knee Replacement System in his practice for years and has confidence in Zimmer Biomet products. After reviewing research trials and clinical studies on the nSTRIDE APS Kit, Dr. Jahromi decided to become the first patient in the region to receive an nSTRIDE APS injection.

Dr. Jahromi had previously tried hyaluronic acid, platelet-rich plasma (PRP), steroid injections and arthroscopy and is relying on the nSTRIDE APS Kit to decrease his osteoarthritic knee pain and potentially promote cartilage health. He is also confident that the nSTRIDE APS Kit will benefit his patients suffering from early to moderate osteoarthritis.

"Zimmer Biomet only provides products based on scientific evidence," Dr. Jahromi said. "For that reason, when I read the nSTRIDE APS data provided, I was ready to proceed, even though it is an innovative product."



A total of 3ml of APS was injected into Dr. Jahromi's knee in a 25-minute procedure.

"This first case shows the trust that end users have in our innovation and the quality of our products," said Ayman Harb, Regional Sales Manager, Gulf and Iran. "We are excited to bring the innovative nSTRIDE APS Kit to patients in our region."

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Selected Centers of Excellence

BMI Healthcare
Bishopswood, United Kingdom
Vikas Vedi

Volvat Institute
Oslo, Norway
Erik Rosenlund

Institute Margalet
Barcelona, Spain
Eric Margalet

Royal Bahrain Hospital
Manama, Bahrain
Ismail Jahromi

Upcoming Events

NORDIC Evening of Education
Date: 11 September 2017
Location: Oslo, Norway
Please contact Roel Bruell at roel.bruell@zimmerbiomet.com if you are interested in attending

Zimmer Biomet Expect MORE Sports Medicine Symposium
Date: 23-24 November 2017
Location: Lisbon, Portugal
Please contact Roel Bruell at roel.bruell@zimmerbiomet.com if you are interested in attending

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References

[1.] Kon E, Engebretsen L, Verdonk P, Nehrer S, Filardo G Clinical outcomes of an autologous protein solution injection for knee osteoarthritis: a 1-year pilot double-blinded randomized controlled trial. Accepted for publication in American Journal of Sports Medicine, 2017.

[2.] Karsdal MA, Michaelis M, Ladel C, Siebuhr AS, Bihlet AR, Andersen JR, Guehring H, Christiansen C, Bay-Jensen AC, Kraus VB.," Disease-modifying treatments for osteoarthritis (DMOADs) of the knee and hip: lessons learned from failures and opportunities for the future. Osteoarthritis Cartilage. 2016 Dec;24(12):2013-2021.

[3.] van Drumpt RA, van der Weegen W, King WJ, Toler K, Macenski M. Safety and treatment effectivesness of a single autologous protein solution injection in patients with knee osteoarthritis. BioResearch Open Access. 2016;5(1):261-68.

[4.] Zimmer Biomet. A pilot study of a single intra-articular injection of autologous protein solution in patients with knee osteoarthritis. 2016. Report No.: IDE-15978.

[5.] Bertone AL, Ishihara A, Zekas LJ, et al. Evaluation of a single intra-articular injection of autologous protein solution for treatment of osteoarthritis in horses. Am J Vet Res. 2014;75(2):141-51.

[6.] Matuska A, O'Shaughnessey KM, King WJ, Woodell-May JE. Autologous solution protects bovine cartilage explants from IL-1a and TNFa induced cartilage degradation. J Orthop Res. 2013;31(12):1929-35.

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