Kneed to Know Newsletter

nSTRIDE® APS Kit | Issue 2

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

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

An Interview with PROGRESS Researcher Dr. Peter Verdonk

Dr. Peter Verdonk, an orthopaedic surgeon, researcher and international lecturer, recently spoke with our Kneed to Know editor about his decision to become involved with the nSTRIDE Autologous Protein Solution (APS) research program.

Why did you choose to get involved with the research program for nSTRIDE APS?
I was invited to the program by Dr. Elizaveta Kon, principal investigator of the PROGRESS II nSTRIDE APS trial. I have always been very skeptical of injectable therapies, but Zimmer Biomet was doing some very good research around its nSTRIDE product. I was excited for the opportunity to be part of a robust clinical research program.

What are some of the key learnings from your involvement in the clinical study of nSTRIDE APS in females with primary patellofemoral osteoarthritis?
At this point, it is very early on. I have received some preliminary data that is encouraging and supports the findings from the PROGRESS II study. Basically, we have seen a number of patients improve, experiencing less pain and becoming more active.

Peter Verdonk, MD, PhD, is a full time consultant orthopaedic knee surgeon at the Antwerp Orthopaedic Center (Monica Hospitals) and researcher at the Antwerp University and the Monica Research Institute. He is also a visiting surgeon at the Aspetar Hospital in Doha, Qatar and an attending surgeon at the Antwerp University Hospital. His clinical and research interests are knee surgery and arthroplasty with a particular focus on meniscus substitution and cartilage repair.

Dr. Verdonk was an international traveling fellow of the International Cartilage Repair Society in 2004 and of the European Society of Sport Traumatology Knee Surgery and Arthroscopy in 2007. He is author of more than 100 peer reviewed papers and has lectured internationally. He is also involved in a number of national and international scientific organizations, including ICRS, ISAKOS, ESSKA, ABA, BVOT and BKS. More information on Dr. Verdonk is available at www.verdonk.be.

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Why did you feel this patient population was well-suited to treatment with nSTRIDE APS?
Many of these patients are in their 50s and 60s and are looking for alternatives to surgery that will allow them to remain active. This treatment makes sense both for their lifestyles and for the pathology of their disease. Primary patellofemoral osteoarthritis is often associated with an inflammatory response – with joint inflammation and swelling. The anabolic effect from the growth factors with the anti-inflammatory cytokines in APS seems to address this.

What further learnings do you hope to gain through participation in the PROGRESS V trial?
I would like to help identify a treatment protocol that includes the exact patient population for which this product makes the most sense. OA is a very common disease, and many patients want to avoid surgery. I'd love to help them do this and remain active.

How have you identified PROGRESS V trial participants?
All have come from within my own practice. I see about 5,000 patients per year, and the trial is a possibility for a subset of these – those who have symptomatic OA and prefer it over other non-surgical interventions, such as physical therapy and bracing. Belgians tend to be early adapters of new medical technologies. The recent publication of PROGRESS data in the American Journal of Sports Medicine has provided scientific support for the discussions I have with patients about nSTRIDE APS.

What do you foresee as the role for nSTRIDE APS in the treatment of knee OA?
I appreciate that Zimmer Biomet is doing the research required to substantiate the value of and need for nSTRIDE APS within the knee OA patient population. As the research bears out, I look forward to the continued commercialization of the product and the opportunity to use nSTRIDE APS to keep patients active and healthy.

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Insights from nSTRIDE APS Kit Veteran Dr. Vikas Vedi

Dr. Vikas Vedi, an orthopedic surgeon in the U.K, was among the first to become active utilizing the nSTRIDE APS Kit. He is currently an investigator in the PROGRESS III clinical trial, which is documenting treatment effects, changes in quality of life and complications following an APS injection. He also offers the nSTRIDE APS Kit to individuals not participating in PROGRESS III through his highly successful clinical practice. Dr. Vedi recently shared his views on the efficacy of nSTRIDE APS, its appeal to patients and its potential as an osteoarthritis (OA) treatment.

"I have been collecting data using a number of health outcome scores to determine OA patients' knee function and symptoms of their suffering with certain activities and movements," Dr. Vedi said. "We have been using baseline and repeat patient questionnaires at regular intervals to assess whether there are functional benefits to nSTRIDE APS. Anecdotally, I've seen positive results in many of my nSTRIDE APS patients, even though my data includes results from patients with very severe OA. I expect doctors who treat mostly patients with more moderate OA may have even greater improvement rates."

Dr. Vedi said he typically sees improvement in pain, stiffness and function within two weeks of an nSTRIDE APS injection followed by continued improvement for several months. Some patients ultimately achieve complete resolution of their symptoms, while others see improvement, but continue to experience some symptoms. While he prefers to use nSTRIDE APS for patients with moderate OA, Dr. Vedi also uses the treatment for certain patients with more severe OA who wish to explore all available non-surgical treatments before moving on to arthroplasty.

> "Anecdotally, I've seen positive results in many of my nSTRIDE APS patients..."

Dr. Vedi spends considerable time with each of his patients explaining the pros and cons of the treatment options available to them. He addresses conservative approaches such as analgesics, activity modification, knee supports and physiotherapy, as well as injectable therapies including steroids, hyaluronic acid and nSTRIDE APS.
"I explain that steroids are an anti-inflammatory to reduce swelling and pain, and that they don't alter or slow the disease process," Dr. Vedi said. "I discuss the mechanism of action of hyaluronic acid, which acts as a lubricant, and also does nothing to alter the disease process. And then I explain the mechanism of action of nSTRIDE APS, which seems to target the arthritic process."

In the end, his patients usually have very few concerns about the nSTRIDE APS procedure.

"They are reassured that anesthesia is not required, that it's a walk-in/walk-out procedure and that the procedure uses their own blood," Dr. Vedi said. "I take time to explain the science behind the procedure and reference the clinical studies that have been done. I let them know that, while outcomes have been very good, there is no guarantee of success."

With respect to the injection site, Dr. Vedi prefers to use the interior aspect of the knee, where he would normally make an arthroscopy incision, into the anteromedial portal. He avoids the suprapatellar pouch, where other clinicians might make steroid injections. Instead, he goes right into the joint space. Dr. Vedi's clinic has been organizing evening events with general practitioners to educate them about the use of nSTRIDE APS. He said attendees are often surprised to learn about the simplicity of the procedure and are enthusiastic about the science and possible applications of autologous therapies beyond OA.

Dr. Vedi has spoken to the media about his experiences with nSTRIDE APS, and this has generated public excitement about the procedure and its potential.

"I gave an interview to the Daily Mail in 2016, in which I suggested an APS injection could negate the need for keyhole surgery for OA of the knee in the future," Dr. Vedi said. "This led to a lot of interest, and it has been gratifying to see that for some of my patients, APS has shown very promising long-term results in terms of pain relief and functional improvement. In others with more severe OA, it is delaying the need for surgery."

Dr. Vedi stresses the need for more data, but is excited about the long-term benefit associated with nSTRIDE APS.

We thank Dr. Vedi for his time and insights.

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Positive Results of PROGRESS I Trial Published in BioResearch Open Access

The clinical body of evidence to support the potential role of nSTRIDE APS for OA is expanding with the recent publication of the positive results of the PROGRESS I clinical trial in BioResearch Open Access. The first in the PROGRESS series of trials, PROGRESS I built on the strong foundation of pre-clinical studies and initial first in human study of nSTRIDE APS to evaluate the safety of a single injection of APS in patients with painful unilateral knee OA who had not achieved satisfactory pain relief with other treatments. The PROGRESS I trial demonstrated a single intra-articular injection of APS in patients with knee OA can be considered safe and resulted in significant improvement in pain scores measured by the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) along with other well-established measures.

Highlights of the PROGRESS I clinical study:

- 62.5 percent improvement in WOMAC pain score six months post-injection; 72.5 percent improvement 12 months post-injection
- 100 percent of subjects were OMERACT-OARSI responders
- Patient-reported global impression scores improved 12 months post-injection
- Concentration of WBC in APS significantly correlated with WOMAC pain improvement

The PROGRESS I trial was a prospective, single-center, single-arm, non-randomized safety study that enrolled 11 patients with unilateral knee OA pain who had not achieved satisfactory pain improvement with other treatments. One patient was withdrawn prior to treatment due to insufficient blood draw. Ten patients received a single injection of APS prepared by the nSTRIDE APS Kit and completed 12-month's of follow-up. Safety and efficacy measures were evaluated during post-injection visits one day after treatment, at one week and one, three, six and 12 months post-injection. Clinical efficacy was assessed by several measures including WOMAC, Knee Injury and Osteoarthritis Outcome Index (KOOS), and Numerical Rating Scale (NRS). Subjects were also evaluated according to the Outcomes Measures in Rheumatology – Osteoarthritis Research Society International (OMERACT-OARSI) responder scale. MRI assessments and X-ray assessments were reviewed for structural changes from baseline to 12 months. All adverse events (AEs) that occurred during the 12-month period were reported.

APS contains high concentrations of white blood cells and anti-inflammatory cytokines and low concentrations of inflammatory cytokines. Treatment with nSTRIDE APS resulted in improvement in pain scores across WOMAC, KOOS and NRS measures, which improved consistently from interval to interval over the duration of the study and achieved significant

improvement compared to baseline at each interval. Twelve months post-injection, subjects had a mean 72.5% WOMAC pain-improvement and 100 percent were OMERACT-OARSI responders.

"We are pleased the results of the PROGRESS I study demonstrate the safety of nSTRIDE APS and look forward to further exploring the potential for this approach in the treatment of knee OA through ongoing clinical studies in the PROGRESS series," said Jennifer Woodell-May, PROGRAM DIRECTOR, ADVANCED OSTEOARTHRITIS THERAPIES, Biologics, Zimmer Biomet.

Authors of the publication are Jason Hix, MD, Mark Klaassen, MD, Ryan Foreman, MD, Edith Cullen, MD, Krista Toler, MS, William King, PhD and Jennifer Woodell-May, PhD.

The publication is available online at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5738995/.

Positive PROGRESS II Trial Second Year Results from A Single Injection of nSTRIDE APS Presented at Expect More Meeting in Lisbon, Portugal

Zimmer Biomet recently demonstrated its power and willingness to conquer Europe's growing sports medicine market by hosting the largest sports medicine event in EMEA in Lisbon, Portugal. More than 300 surgeons and team members attended the event, which supported the theme "Expect More."

The curriculum covered a range of topics, from conservative care and early intervention to arthroscopic interventions in knee and shoulder. Breakout sessions, which focused on hip, foot and elbow interventions, provided an opportunity to discuss treatment of those joints as well. The Subchondroplasty® procedure, nSTRIDE APS and the latest in knee and shoulder arthroscopy were special focuses.

Highlighted at the meeting, Professor Elizaveta Kon of Humanitas University in Milan, Italy and Principal Investigator for the PROGRESS II study (a multicenter, randomized, double-blind, saline controlled study with nSTRIDE APS) presented study results. Twelve-month time point data was recently published in the American Journal of Sports Medicine.[1] At the 12 month follow-up visit, patients were asked to consent for long term follow-up. Long term efficacy data will be collected up to 5 years or until receipt of another invasive treatment for the OA of the treated knee, whichever occurs first. Subjects treated with nSTRIDE did not receive a second injection but continued to report outcome measures.

It was exciting to see that 23 of the original 31 patients had not sought other treatments or dropped out of the study (one patient could not attend the 24-month time-point assessments but attended the 36-month post-injection assessments). Of the 22 patients with 24-month data, an average of 69.7% improvement in WOMAC pain compared to their baseline scores was reported (Figure 1).

Prof. Kon is continuing her evaluation of nSTRIDE APS as the Principle Investigator of the PROGRESS V trial, a multicenter trial across Europe comparing the effects of nSTRIDE APS against a single injection Hyaluronic Acid injection.

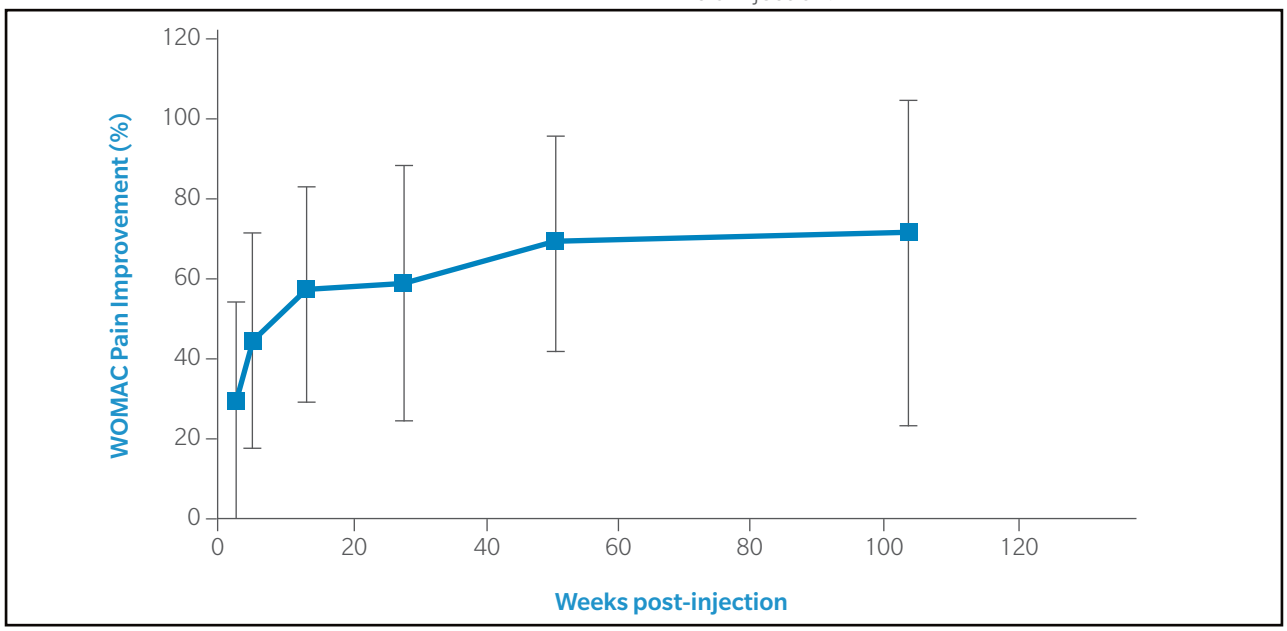


Figure 1. WOMAC percent improvement in the Group 1 (APS). Error bars represent standard deviation, n = 22. 69.7% improvement, $p < 0.0001$) 24 months post-injection.

Positive Results of PROGRESS II Trial Published in American Journal of Sports Medicine

Zimmer Biomet is pleased to announce the positive results of the PROGRESS II clinical trial have been published online by the American Journal of Sports Medicine. A predecessor to the PROGRESS IV trial, PROGRESS II evaluated the ability of one intra-articular injection of APS produced with the nSTRIDE APS Kit compared to saline to reduce pain and improve function in patients affected by knee osteoarthritis (OA). The one-year study found significant improvement in percent change from baseline in pain scores measured by the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), as well as comparable safety to saline.

The PROGRESS II trial was a prospective, randomized, double-blind, saline-controlled pilot study that enrolled 46 patients with unilateral, mild-to-moderate, symptomatic knee OA pain at four trial sites across Europe. Patients were randomized 2:1 to receive either a single injection of APS prepared by the nSTRIDE APS Kit (n=31), or a single saline injection (n=15). Patient-reported outcomes and adverse events were assessed at two weeks, and at one, three, six and 12 months post-injection. Clinical effectiveness was measured using the Visual Analog Scale, the WOMAC, and the Knee Injury and Osteoarthritis Outcome Score. X-ray and magnetic resonance imaging evaluations were taken at baseline as well as three and 12 months following treatment.

"After nearly a decade of preclinical and clinical research on the use of autologous anti-inflammatory cytokines and growth factors to treat osteoarthritis pain, we were pleased to demonstrate that APS, prepared with the nSTRIDE APS Kit, may be a promising, safe and viable new treatment for patients living with OA of the knee," said Elizaveta Kon, MD, associate professor, Humanitas University, Milan, Italy, and lead investigator of the PROGRESS II trial.

"The positive results of the PROGRESS II trial not only reinforce the safety and clinical value of the autologous anti-inflammatory solution prepared with the nSTRIDE APS Kit, but also lay the groundwork to advance our regulatory efforts in the United States," said Joel Higgins, development senior director, Biologics, Zimmer Biomet.

Authors of the publication are Elizaveta Kon, MD, Prof., Lars Engebretsen, MD, Prof., Peter Verdonk, MD, Prof., Stefan Nehrer, MD and Giuseppe Filardo, MD, PhD.

The publication is available online at https://doi.org/10.1177/0363546517732734.

Top-line results showed that patients treated with APS demonstrated:

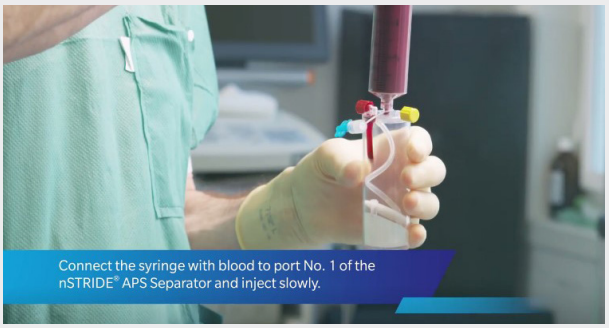
- A 65 percent change in WOMAC pain score from baseline to 12 months compared to a 41 percent change in the saline group ($p = 0.02$)
- A 49 percent improvement in VAS pain scores compared to a 13 percent improvement in the saline group ($p = 0.06$)
- No procedure- or device-related serious adverse events, and comparable frequency, severity and relatedness of adverse events as compared to the saline group

Additional Research Updates

- The primary completion date for the nSTRIDE APS trial in females with primary patellofemoral OA is May 2018
- The nSTRIDE APS PROGRESS IV and PROGRESS V trials are continuing to enroll patients

New on Zimmer Biomet TV

Dr. Eric Rosenlund from the Volvat Clinic in Oslo, Norway shares his personal experience with the nSTRIDE APS Kit. Dr. Rosenlund explains how nSTRIDE APS has allowed his patients to increase their range of motion, move about more freely and see an increase in activity level. Patients have told him that nSTRIDE APS works better and quicker than PRP, resulting in Dr. Rosenlund treating about 30 patients per week. Click here to view the video.



You can now view a complete nSTRIDE APS Kit procedure. This video includes detailed video footage and step-by-step instructions on how to successfully conduct the nSTRIDE procedure from start to finish. This is an excellent resource for refreshing experienced technicians prior to a procedure in addition to training technicians who will perform the procedure for the first time. Click here to view the video.

FAQs

How long will the benefits of nSTRIDE APS last?

Based on clinical results, patients may expect to see benefits up to 24 months.[1-3]

How does APS work and why?

The proposed APS mechanism of action is a process of reducing OA-related upregulated inflammatory cytokines by introducing antagonistic cytokines which inhibit the inflammatory cytokine activity. APS has been shown to reduce production of proteins associated with osteoarthritic inflammation and pain responses in vitro.[4]

Are there differences between nSTRIDE APS and Orthokine ACS?*

There are considerable differences between nSTRIDE APS and Orthokine ACS.

- nSTRIDE APS is a single injection treatment and is point of care. It's processed in under 20 minutes, while the Orthokine ACS processing lasts 6 to 24 hours and requires up to 6 injections.[5, 6]
- The nSTRIDE APS output has a much broader anti-inflammatory profile and has much higher anti-inflammatory concentrations than Orthokine.[4, 5,6] For example, nSTRIDE APS has significantly more IL-1ra than Orthokine (APS was 54,922.1 ± 32,750.7 (pg/ml), Orthokine ACS was 1,618.0 ± 674.7 (pg/ml)).[5,6] In fact, the concentration of IL-1ra in the output of the Orthokine ACS system was significantly less than the IL-1ra concentration in whole blood (5664.5 ± 2,317.6 pg/ml ($p < 0.05$)).[5,6] Higher concentrations of IL-1ra and the ratios of IL-1ra:IL-1 in nSTRIDE APS have clearly correlated with lower knee pain scores after treatment with APS.[2]
- Based on clinical results, patients may expect to see benefits in pain relief and function improvement up to 24 months.[1-3]

*Orthokine® is a trademark of Orthogen AG.

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Announcements

PARTNERSHIP WITH INTERNATIONAL CARTILAGE REPAIR SOCIETY (ICRS)

Zimmer Biomet has partnered with the ICRS to participate in the Global ICRS Patient Registry. We encourage doctors to sign up for the registry and track intra-articular injection patient data in the registry. nSTRIDE APS injections are categorized as Autologous Anti-Inflammatories (AAI) within the registry. You can register at the following URL: https://cartilage.org/society/icrs-patient-registry/

nSTRIDE AT AMERICAN ACADEMY OF ORTHOPAEDIC SURGEONS

nSTRIDE APS will be displayed at the American Academy of Orthopaedic Surgeons (AAOS) meeting March 6-10 in New Orleans, Louisiana. If you are in New Orleans, please stop by the booth.

nSTRIDE HIGHLIGHTED AT ICRS WORLD CONGRESS

nSTRIDE APS and the Subchondroplasty procedure will be highlighted at a lunch industry symposium at the 14th World Congress ICRS meeting in Macau, China on April 10

- Jennifer Woodell-May, Ph.D. – The science behind nSTRIDE APS
- Elizaveta Kon, M.D. – Developing second generation biologics
- Amon Ferry, M.D. – The treatment of chronic, painful subchondral BML defects using the Subchondroplasty procedure

Highlighted Centers of Excellence

Klinikin
Reykjavik, Iceland
Hjálmar Torsteinsson

Midland Knee Clinic, Spire Little Aston Hospital
Sutton Coldfield, West Midlands, United Kingdom
Rik Kundra

NewMed
Warsaw, Poland
Prof. Janusz Płomiński

Upcoming Events

AAOS
Date: 6-10 March 2018
Location: New Orleans, LA

ORS
Date: 10-13 March 2018
Location: New Orleans, LA

17th Congress of the Japanese Society for Regenerative Medicine
Date: 21- 23 March 2018
Location: Yokohama, Japan

ICRS World Congress
Date: 9-12 April 2018
Location: Macau, China

ESSKA
Date: 9-12 May 2018
Location: Glasgow, Scotland

EFORT
Date: 30 May -1 June 2018
Location: Barcelona, Spain

Termis
Date: 4-7 September 2018
Location: Kyoto, Japan

ICRS Focus Meeting
Date: 13-14 December 2018
Location: Milan, Italy

References

[1.] Kon E, Engebretsen L, Peter Verdonk P, Nehrer S and Filardo G. "Clinical Outcomes of Knee Osteoarthritis Treated with an Autologous Protein Solution. A 1-year Pilot Double-Blinded Randomized Control Trial. American Journal of Sports Medicine, Oct. 2017.

[2.] Van Drumpt RA, van der Weegen W, King WJ, Toler K, Macenski M. Safety and treatment effectiveness of a single autologous protein solution injection in patients with knee osteoarthritis. BioResearch Access, Vol 5.1, 2016.

[3.] Kon E, Engebretsen L, Verdonk P, Neher S, Andriolo L, Filardo G. "An Autologous Protein Solution Injection Reduces Knee Osteoarthritis Pain in a Saline-Controlled RCT: 2 year Outcomes," 14th World Congress of the International Cartilage Repair Society, Macau, China, Program #13.3.5 (#9663), Apr 9-12, 2018.

[4.] Woodell-May J, Matuska A, Oyster M, et al. Autologous protein solution inhibits MMP-13 production by IL-1beta and TNFalpha-stimulated human articular chondrocytes. J Orthop Res 2011 Sep 15;29:1320-6.*

[5.] Wehling P, Moser C, Frisbie D, et al. Autologous conditioned serum in the treatment of orthopedic diseases: the orthokine therapy. BioDrugs 2007;21(5):323-32.

[6.] King WJ, Woodell-May JE., "Comparison of the cellular and cytokine concentrations in the output of the Autologous Protein Solution, Orthokine, and Onoccomed 2 device systems," OARSI, #. 335, Apr. 24-27 2014, Paris, France.

Disclaimers

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*In vitro data is not necessarily indicative of clinical performance.