

1. What is the purpose of the PROGRESS IV clinical trial?

This trial will compare the efficacy of autologous protein solution (APS), prepared using the investigational nSTRIDE® APS Kit, and saline in patients with early to moderate symptomatic knee osteoarthritis (OA), who have failed at least one prior conservative OA therapy (e.g. physiotherapy, simple analgesics).

2. What is the nSTRIDE APS Kit and is it currently available?

The nSTRIDE APS Kit is a self-contained, sterile-packaged, single-use device system. It is designed to separate anti-inflammatory cytokines and growth factors from whole blood. The device system is to be used at the point of care to create an autologous solution. The nSTRIDE APS Kit is not commercially available in the United States.

3. How does the nSTRIDE APS Kit work?

The nSTRIDE APS Kit uses a small sample of the patient's own blood to create an autologous solution. This device system consists of two parts: the nSTRIDE Cell Separator and the nSTRIDE Concentrator. The nSTRIDE Cell Separator utilizes centrifugal force to process the blood sample and separate the cellular components from plasma and red blood cells. The cell suspension is then loaded into the nSTRIDE Concentrator, which uses centrifugal filtration through polyacrylamide beads to concentrate the injectable output.

4. 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.ⁱ

5. What is the clinical trial design of the PROGRESS IV clinical trial?

The PROGRESS IV clinical trial is a double-blind, multicenter, randomized, controlled trial (RCT) with patients receiving either a single injection of APS or saline. During the injection visit, all patients will have a blood draw, from which the APS will be prepared for injection and for laboratory characterization. After all available joint fluid is aspirated, and appropriate to randomization group, approximately 2.5 mL of APS or saline will be injected into the joint. A blinding sleeve covering the contents of the syringe will be utilized to mask the group assignment from the patient and the injecting physician, and needle placement will be verified using ultrasound. Any adverse events associated with the blood draw and/or injection procedure will be recorded. All subjects should be instructed not to exceed the pre-injection level of activity for 14 days.

Efficacy and safety will be assessed at 1, 3, 6, and 12 months post-injection. An X-Ray and MRI will be obtained at baseline and at 12 months to assess anatomical changes. Upon completion of all 12 month follow-up evaluations, group allocation will be unblinded, and patients from both groups will be permitted to enter a one month open-label repeat injection phase if they had no major safety concerns due to the first injection.

6. What are the primary endpoints for this trial? Secondary?

The primary endpoints of the trial are the changes in pain and function from baseline to 12 months following injection of APS or saline. Secondary endpoints seek to demonstrate the superiority of APS over saline for improvement in stiffness and quality of life. Additionally, this trial will evaluate the safety of intra-articular injection of nSTRIDE APS compared to saline.

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7. What does the investigational procedure entail?

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8. Who is sponsoring the PROGRESS IV clinical trial?

Zimmer Biomet is sponsoring the PROGRESS IV clinical trial. Founded in 1927 and headquartered in Warsaw, Indiana, USA, Zimmer Biomet is a global leader in musculoskeletal healthcare. Zimmer Biomet designs, manufactures and markets orthopaedic reconstructive products; sports medicine, biologics, extremities and trauma products; spine, bone healing, craniomaxillofacial and thoracic products; dental implants; and related surgical products.

9. Where are the clinical trial sites? Who are the primary investigators?

The clinical trial sites for the PROGRESS IV clinical trial include some of the most highly respected medical institutions in the country, experienced in treating this condition. The coordinating investigator is Dr. Frederick Azar, MD, Campbell Clinic Orthopaedics. Visit www.zimmerbiomet.com/nstridetrial for a full list of clinical trial sites.

10. What patients qualify for the PROGRESS IV clinical trial?

Patients may be candidates if they meet the following inclusion criteria:

- ▶ Male or female ≥ 21 and ≤ 80 years old at time of injection
- ▶ Willingness and ability to comply with the trial procedures and visit schedules and ability to follow verbal and written instructions
- ▶ A standing radiograph of the knee showing a Kellgren-Lawrence grade of 2 to 4 and an absence of severe osteoarthritis (defined as advanced stage osteoarthritis, including large osteophytes, chronic fractures or bone remodeling, severe deformity or bone attrition, and/or bone-on-bone contact indicative of severe osteoarthritis/full thickness cartilage loss), as confirmed by the central imaging laboratory.
- ▶ Body mass index ≤ 40 kg/m²
- ▶ Has undergone at least one prior conservative osteoarthritis therapy without satisfactory pain relief
- ▶ Not have had recent intra-articular steroid injections (3 months) or hyaluronic acid (HA) or other joint injections (6 months) in the arthritic knee

11. Can my patient enroll both knees into the clinical trial?

Only patients who have symptomatic osteoarthritis in one knee may be enrolled in the trial.

12. What is the time commitment for my patient to participate?

The trial protocol requires a patient commitment of at least six total office visits, including the screening visit, injection procedure visit (within 28 days of screening), and four follow up visits. If, following completion of the 12 month visit, the patient elects to receive a second injection, this injection visit and a 1 month follow-up of the second injection will be conducted. Maximum trial duration is 16 months per patient.

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13. How can I stay informed of my patient's progress while in the trial?

The patient will remain under the care of their respective medical team for medical needs not directly related to the clinical trial. If your patient is eligible for the clinical trial, the site will notify you of the enrollment into the trial and treat your patient only for the purposes of the clinical trial. The medical institution conducting the trial will also work with you to ensure the highest quality medical care is provided to your patient at all times during the trial.

14. Will I be informed of my patient's trial results?

Once the trial is complete, it will take time for the trial sponsors at Zimmer Biomet to compile the results. When the results are complete, they are typically published for public knowledge and posted on clinicaltrials.gov. **Individual** patient results, however, will not be provided to you or made public.

15. What are the options following the trial if my patient receives saline?

Upon completion of all 12 month follow-up evaluations, group allocation will be unblinded, and patients from both groups will be permitted to enter a one month open-label repeat injection phase if they had no major safety concerns due to the first injection. One month after the second injection, patients will complete questionnaires for pain and function.

16. How will adverse events be treated during the course of the clinical trial?

All adverse events will be managed by the investigator depending on the type and severity.

17. How will the clinical trial track my patient's progress?

The clinical trial sites will track all participants' progress through four in-person follow-up visits after the procedure over the course of one year.

18. Will my patient be compensated for their time and travel?

Patients will not incur any extra costs for the medical care required for the trial and examinations that are not considered standard of care. Patients may incur costs associated with travel to their doctor's office. Extra visits to their doctor's office are required for follow up care throughout the trial. Patients will receive payment for participation in the trial. You may contact the trial site for details.

For trial protocol summary, additional inclusion and exclusion criteria, and a list of all trial site locations, please visit: www.zimmerbiomet.com/nstridetrial

REFERENCES

- i Woodell-May J, Matsuka A, Oyster M, et al. 2011. Autologous protein solution inhibits MMP13 production by IL-1beta and TNFalpha-stimulated human articular chondrocytes. *J Orthop Res.* 29(15): 1320-6.

Laboratory studies are not necessarily indicative of clinical results.

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