FRANKSTON
PAIN MANAGEMENT

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Dear Colleagues;

I would like to invite your interest and assistance in a first-in-human study that I lead to evaluate the safety of a novel genicular nerve block device. BXT-786 Focused Cold Therapy has been designed to impart a longer lasting, easy to administer, and non-pharmacological (non-addictive) genicular nerve block. From prior animal studies, investigators have reported rat sciatic nerve blocks for up to approximately 90 days with complete neuronal regeneration and function. The BXT-786 Focused Cold Therapy is administered via injections much like diagnostic knee blocks today, and all "cold therapy" fluid constituents are classified as GRAS (Generally Regarded As Safe) and are existing parenteral materials.

I ask for your help to find and refer eligible patients. General inclusion/exclusion criteria include:

- patients 21-70 years old with pain due to Grade 3-4 Knee OA who are eligible for TKA
- have normal knee nervous architecture (i.e., have not had invasive genicular neurological procedures on the treatment knee such as radiofrequency, chemical, or other genicular nerve ablation, destruction, or other invasive intervention or genicular neuropathology)

The study received ethical approval from the St Vincent's Hospital Melbourne HREC (Ref: HREC D 065/22) on 17 May 2022. Inclusion/exclusion criteria is attached as Appendix A.

I am particularly excited about this new analgesic therapy/device as it may fill a gap in our pain management armamentarium and be an option for those patients that must endure extended surgical wait times, help those with comorbidities that might contraindicate surgery including delaying primary TKA in young patients, those with existing or the potential for drug abuse disorder, those who are too old, too sick, and more. If human outcomes mirror those seen in animals, this investigational therapy might bring your patients extended pain relief before surgery that may improve mobility, pre-surgery habilitation, and, therefore, post-surgery outcomes.

Thank you.

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Lead Principal Investigator, BXT-786-KPM-01 first-in-human study
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Appendix A

Inclusion Criteria:
Subjects meeting **ALL** of the following criteria will be considered eligible for clinical trial entry:

1. Age 21 to 70 of any gender
2. Average baseline pain intensity ≥4 on Numeric Rating Scale (NRS), despite current treatment
3. A decrease of ≥50% from highest NRS score with diagnostic genicular nerve block
4. Meets criteria for primary, unilateral total knee arthroplasty (TKA):
    - Criteria 1: Severe osteoarthritis of the knee (K-L stage 3 or 4) on plain x-rays AND
    - Criteria 2: Failed conservative treatments (NSAID, acetaminophen, PT, cortisone inj.)
5. Willing/able to understand informed consent form, provide written informed consent, and able to complete outcome measures
    - Must have access to device/equipment with internet capabilities (for Video telehealth visits and recording pain scores)

Exclusion Criteria:
Subjects meeting **ANY** of the following criteria will **NOT** be considered eligible for clinical trial entry:

1. Known allergy to any component of BXT-786 (glycerol and/or phosphate buffered saline)
2. History of cryoglobulinemia
3. History of paroxysmal cold hemoglobinuria
4. History of cold urticaria
5. History of Raynaud's disease
6. Open and/or infected wounds at or near treatment site
7. History of significant renal or hepatic insufficiency
8. History of vascular surgery involving femoral vessels on the injection side
9. History of surg. Proc. to affected limb that, per Investigator, impact the integrity of genic. nerves
10. History of arrhythmia or seizures
11. History of low blood pressure or uncontrolled high blood pressure
12. Currently on anticoagulants or antibiotics
13. Active infection
14. Currently taking >40mg of morphine equivalent daily oral dose
15. Severe psychiatric or neurological disease that prevents subject from reporting pain assessment
16. History of local tumor-related disease
17. Pre-existing lower limb neurology that, per Investigator, impairs assessment of safety and/or pain
18. History of systemic inflammatory conditions such as rheumatoid arthritis
19. Previous recipient of cryoneurolysis, radiofrequency ablation, or phenol injection for the knee
20. Use of hyaluronic acid, prolotherapy, autologous blood, or PRP injections w/in previous 30 days
21. Injection of corticosteroid within the previous 3 months
22. Difficulty comprehending health status/pain questionnaires
23. Subjects who may not be able to cooperate with post-injection follow-ups/regimen
24. A history of medical conditions that would hamper block or be exacerbated by block (i.e. medical conditions requiring blood thinners; poorly managed diabetes/diabetic neuropathy; alcohol or drug addiction, COPD; paradoxical adipose hyperplasia, etc.)
25. Known contraindication to use of a regional block
26. Pregnant/breastfeeding persons
27. Any condition or circumstance that, in the opinion of the investigator, would compromise the safety of the subject or the quality of study data
28. Participation in any clinical study of an investigational product within 30 days prior to enrollment and through completion of study participation
29. No scheduled surgeries until all study visits are completed (3 months)