
Platform
Therapeutics™

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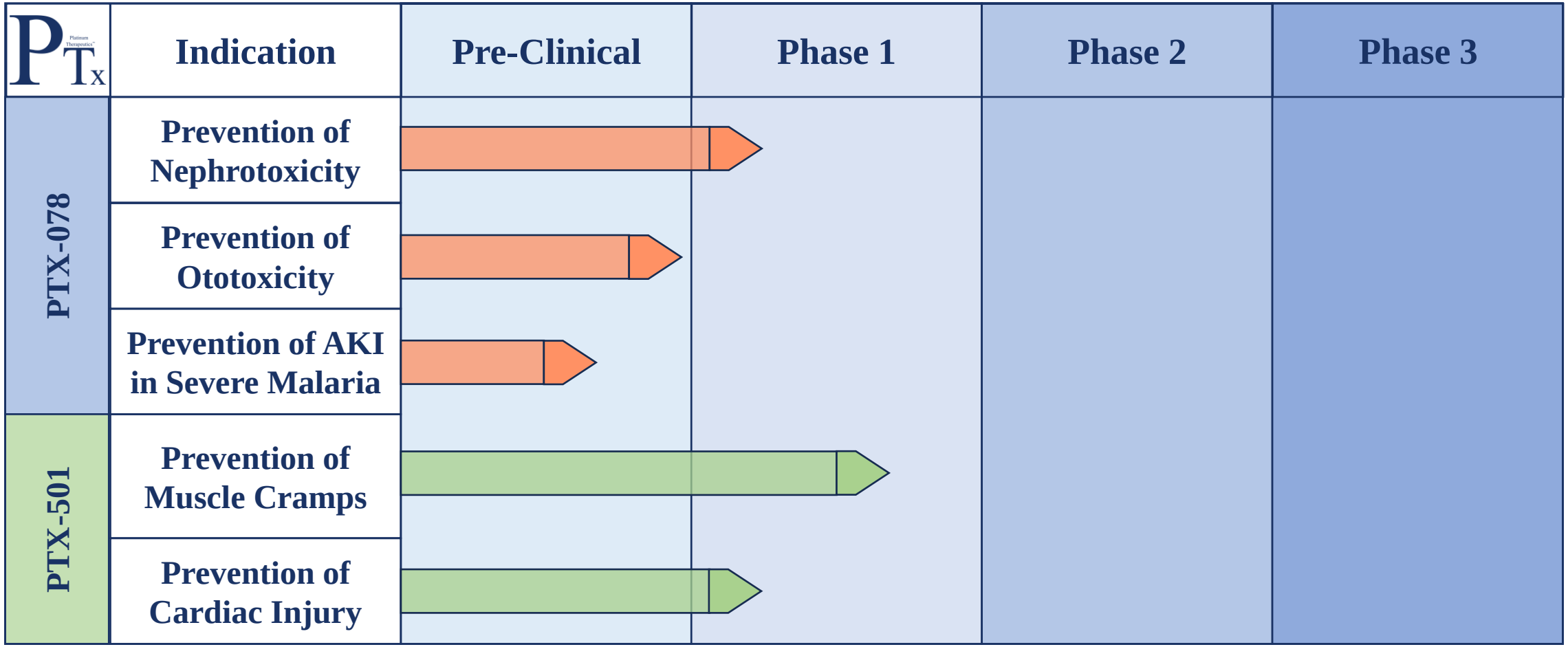
PTX Pipeline



Problem: Intradialytic Painful Muscle Cramps

- 785,883 Americans with kidney failure in 2018 [1]
- 554,038 were on IHD (intermittent hemodialysis) [1]
- ~98 million dialysis sessions in the US in 2024
- $49.2 billion cost to Medicare alone [1]
- PTX-501 is designed to prevent painful intradialytic muscle cramps
  - Over 1/3 of hemodialysis patients cramp and they continue to cramp [2]
  - Extremely painful and a major cause of early termination of dialysis occurring in ~5 million procedures per year in the US
- $733 million market in the US
- Eligible for ESRD PPS TDAPA [3]

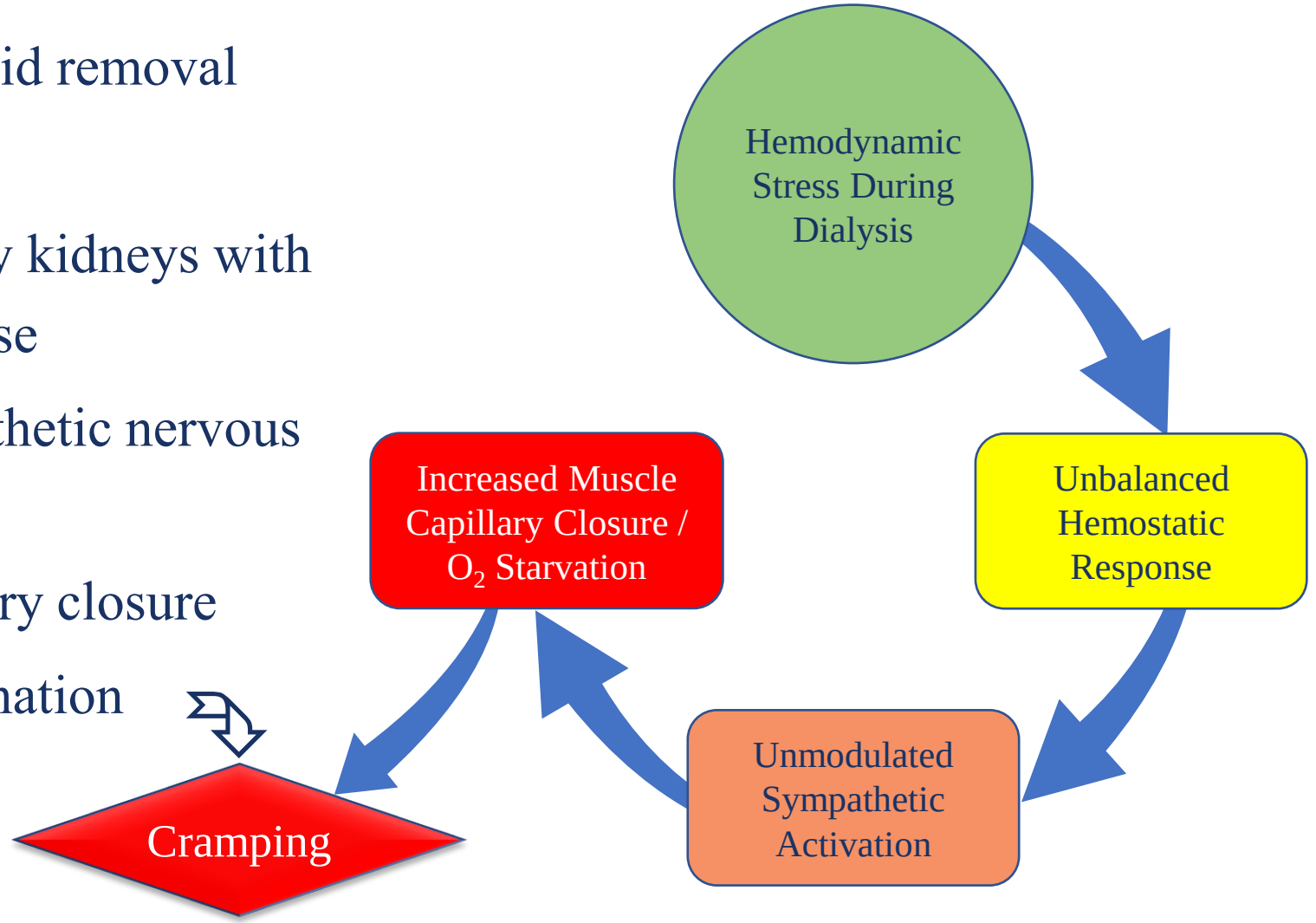
Source: https://evofitness.at/en/avoiding-muscle-cramps-during-exercise/

Sources: 1) https://www.kidney.org/news/newsroom/fsindex; 2) Rocco MV, Burkart JM. Prevalence of missed treatments and early sign-offs in hemodialysis patients. J Am Soc Nephrol. 1993 Nov;4(5):1178-83. 3) The Transitional Drug Add-On Payment Adjustment (TDAPA) supports payment and patient access to new therapies introduced to the End-Stage Renal Disease (ESRD) Prospective Payment System (PPS).

Cause of Intradialytic Muscle Cramps

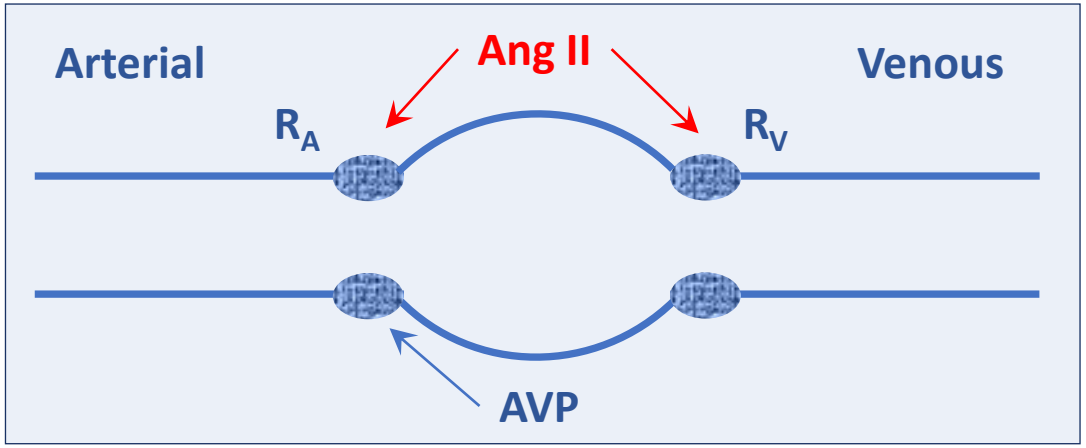
Extracorporeal circulation + fluid removal

- Hemodynamic stress
  - ↓ renin production by kidneys with ↓ angiotensin response
  - Unmodulated sympathetic nervous system response
    - ↑ muscle capillary closure
    - ↓ muscle oxygenation



Pathophysiology

- Arginine vasopressin (AVP) and norepinephrine act solely on arterial resistance (R_A) resulting in closure of some capillaries.
- Renal endocrine function declines along with renal excretory function, so the renin-angiotensin response to hemodynamic stress is impaired in dialysis patients.
- Angiotensin II (Ang II) acts on both venous and arterial resistance (R_V and R_A) in such a way that the ratio of R_V/R_A is sufficient to modulate NE effects and maintain capillary patency and functional surface area.
- Human and animal studies support the hypothesis that the use of Ang II will modulate the NE response of patients undergoing dialysis and will prevent muscle cramps.



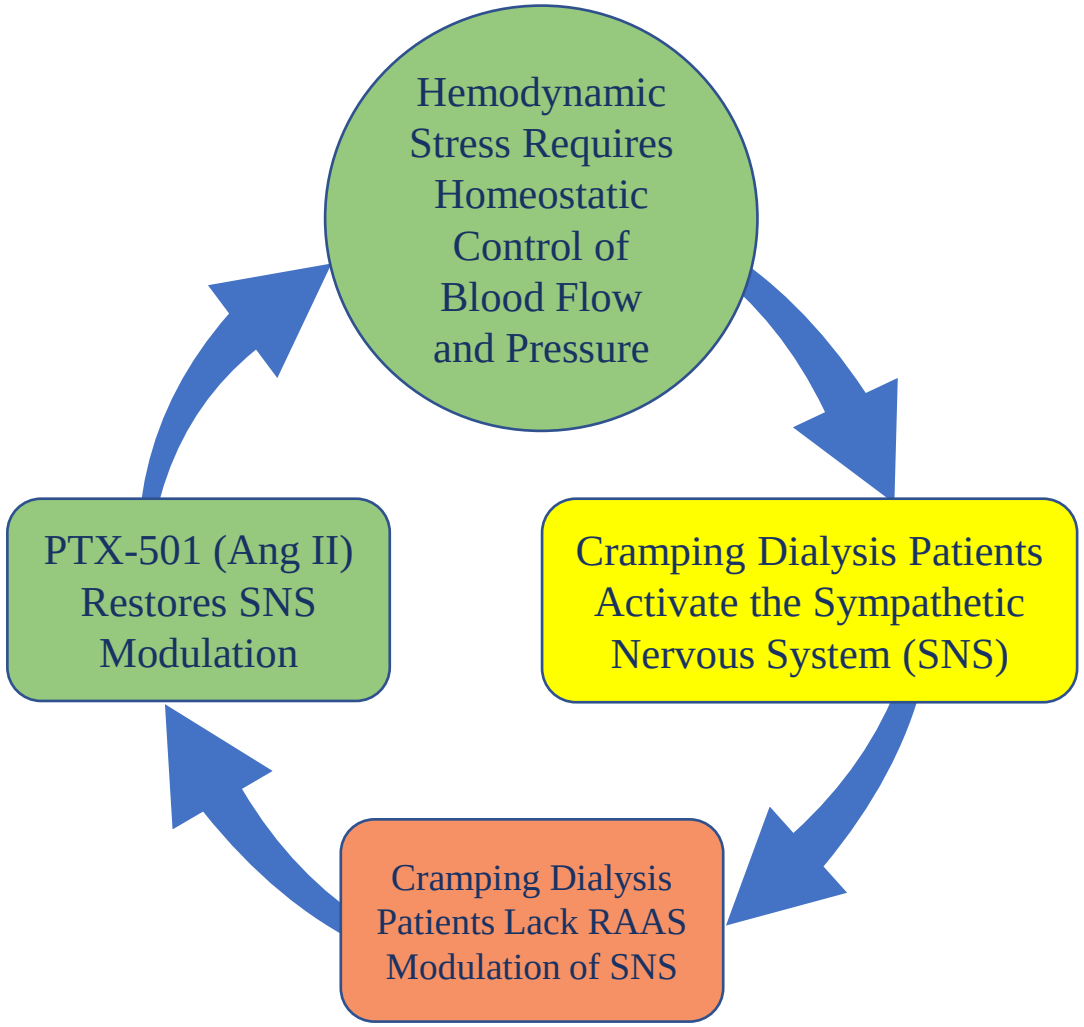
Source: Atkinson AJ. Elucidation of the pathophysiology of intradialytic muscle cramps: pharmacokinetics applied to translational research. Transl Clin Pharmacol. 2019 Dec;27(4):119-122.

Standard of Care

- No approved drugs for this use, and of the ones used off-label, none have a convincing rationale to support their use.
- Prophylactic therapies:
  - Quinine
  - Nifedipine
  - Creatine
  - Shakuyaku-kanzo-to (Shao-Yao-Gan-Cao-Tang)
- Quinine's risk/reward ratio fails to warrant its use except in some patients with malaria.
- No integrated pharmacologic rationale has been proposed for the other prophylactic therapies.
- Currently available intradialytic cramp therapy is limited to:
  - Saline
  - Mannitol
  - Hypertonic glucose
- Although these minimize the dialysis-associated reduction in plasma volume, they undesirably increase solute load.
- Consequently, there is a need for a treatment that can prevent painful muscle cramps that occur during dialysis.

Angiotensin II

- Angiotensin II is part of the renin–angiotensin–aldosterone system (RAAS), a complex system responsible for, among other things, regulating blood pressure.
- The RAAS system can be activated when there is a loss of blood volume or a drop in blood pressure (such as in hemorrhage, dehydration or dialysis), but the RAAS is deficient in hemodialysis patients.
- PTX-501 is a formulation of angiotensin II, an 8 amino acid, endogenous peptide.



Evidence of Angiotensin II for Muscle Cramps

Animal and human data support the use of Ang II to decrease muscle cramps:

- Evidence that catecholamines are linked to cramps
  - Blocking catecholamines with prazosin improves muscle cramps in patients undergoing dialysis (Sidhom et al.)
- Patients who cramp frequently have a blunted RAAS response (Kaplan et al.)
- Evidence that Ang II will ameliorate cramps
  - Blocking Ang II with an ACE inhibitor (captopril) worsens muscle cramps in dialysis patients (Piergies et al.)
  - Dialysis patients treated concurrently with RAAS blocking drugs are statistically more likely to experience cramps than patients not treated with these agents (Punji et al.)
  - Normal RAAS response during dialysis of animals with intact kidneys is sufficient to block capillary derecruitment (Bowsher et al.)
- Administration of Ang II decreases the need for catecholamines (Khanna et al.)
- Administration of norepinephrine decreases capillary muscle recruitment and Ang II increases muscle capillary recruitment (Jarhult).

PTX-501

- PTX-501 is a formulation of angiotensin II, an 8 amino acid, endogenous peptide.
- The active pharmaceutical ingredient (API) can be made by several peptide manufacturers.
- The drug product is aseptically filled liquid in a vial.
- Cost of goods is ~$24 per vial.
- Selling price flexibility.

PTX-501 Market Size

- We have discovered the cause of muscle cramping during dialysis.
- Not all patients that undergo dialysis experience cramps, but those that do experience cramps either frequently or in every procedure. Hence, they will need the product for life.

	2026
Dialysis sessions	98,490,903
Number of dialysis sessions terminated early due to cramping [1]	1,210,569
Dialysis sessions not terminated but need PTX-501 (3x terminated)	3,666,619
Total	4,888,825
Price [3]	$150
Market size	$733,323,702

Sources: 1) Rocco MV, Burkart JM. Prevalence of missed treatments and early sign-offs in hemodialysis patients. J Am Soc Nephrol. 1993 Nov;4(5):1178-83. 2) Company estimate.
3) https://www.cms.gov/medicare/payment/prospective-payment-systems/end-stage-renal-disease-esrd/esrd-pps-transitional-drug-add-payment-adjustment

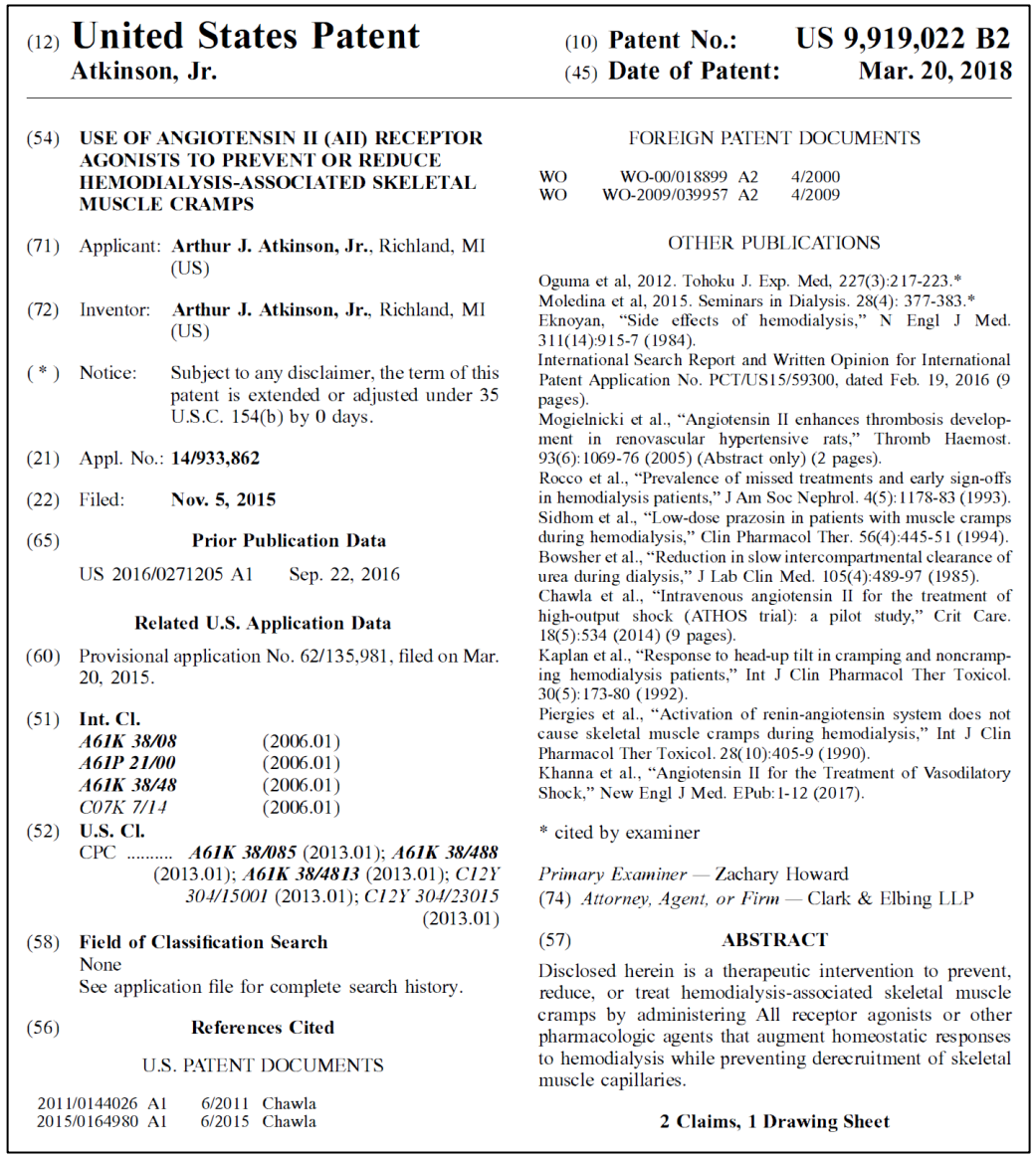
PTX-501 Revenue Projections

- Number of procedures in need of pain relief due to muscle cramps
  - 4,888,825 million in 2028
  - Growth rate: 3.5% per year
- Price point
  - $150, 3.5% price growth

	2028	2029	2030	2031	2032	2033	2034	2035	2036	2037
Number of Applicable Procedures	3,241,980	3,355,449	3,472,890	3,594,441	3,720,246	3,850,455	3,985,221	4,124,703	4,124,703	4,124,703
Market Penetration	5.0%	10.0%	20.0%	40.0%	60.0%	75.0%	84.4%	89.4%	189.40%	289.40%
Dialysis Sessions	162,099	335,545	694,578	1,437,776	2,232,148	2,887,841	3,362,530	3,689,032	7,812,187	11,936,890
Price	$161	$166	$172	$178	$184	$191	$198	$204	$151	$152
Revenue	$6,078,713	$12,582,934	$26,046,675	$53,916,615	$83,705,535	$115,513,650	$179,334,945	$247,482,180	$311,415,077	$376,172,914

Intellectual Property & Exclusivity

- Regulatory path is via 505(b)(2)
- 3 years of regulatory exclusivity
- Patent expires in 2035
  - A method of preventing, reducing, or treating cramping during hemodialysis, said method comprising administering to a subject an effective amount of angiotensin II
  - The method of claim 1, wherein the effective amount of angiotensin II is between 0.1 and 250 ng/kg of body weight of the subject
- Additional IP to be filed based on clinical study results already received



(12) **United States Patent**
Atkinson, Jr.

(10) **Patent No.: US 9,919,022 B2**
(45) **Date of Patent: Mar. 20, 2018**

(54) **USE OF ANGIOTENSIN II (AII) RECEPTOR AGONISTS TO PREVENT OR REDUCE HEMODIALYSIS-ASSOCIATED SKELETAL MUSCLE CRAMPS**

(71) Applicant: **Arthur J. Atkinson, Jr.**, Richland, MI (US)

(72) Inventor: **Arthur J. Atkinson, Jr.**, Richland, MI (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **14/933,862**

(22) Filed: **Nov. 5, 2015**

(65) **Prior Publication Data**

US 2016/0271205 A1 Sep. 22, 2016

Related U.S. Application Data

(60) Provisional application No. 62/135,981, filed on Mar. 20, 2015.

(51) **Int. Cl.**

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A61P 21/00	(2006.01)
A61K 38/48	(2006.01)
C07K 7/14	(2006.01)

(52) **U.S. Cl.**
CPC ***A61K 38/085*** (2013.01); ***A61K 38/488*** (2013.01); ***A61K 38/4813*** (2013.01); *C12Y 304/15001* (2013.01); *C12Y 304/23015* (2013.01)

(58) **Field of Classification Search**
None
See application file for complete search history.

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Primary Examiner — Zachary Howard
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(57) **ABSTRACT**

Disclosed herein is a therapeutic intervention to prevent, reduce, or treat hemodialysis-associated skeletal muscle cramps by administering All receptor agonists or other pharmacologic agents that augment homeostatic responses to hemodialysis while preventing derecruitment of skeletal muscle capillaries.

2 Claims, 1 Drawing Sheet

Summary of PTX-501

- Experienced management: successful FDA approvals and startup exits
- Large and growing market for initial product and follow-on products
- No non-clinical work needed to enter clinic
- Simple clinical study design
  - Endpoint is achieved on the day of treatment
  - Patient can act as own control
- IP issued for PTX-501
- Reimbursement for PTX-501 eligible for ESRD PPS TDAPA [1]
- Exit opportunities at the end of each phase

1) The Transitional Drug Add-On Payment Adjustment (TDAPA) supports payment and patient access to new therapies introduced to the End-Stage Renal Disease (ESRD) Prospective Payment System (PPS).

Founding Team

James Wilkie, Founder & CEO

- 39 years of experience in the life science industry developing both drugs and devices.
- Founder and CEO of Lowell Therapeutics – acquired by AcelRx Pharmaceuticals in 2022.
- VP La Jolla Pharmaceutical Co. who launched angiotensin II in 2018 for use in the ICU. Acquired by Innoviva in 2022.
- COO of Pluromed, Inc., acquired by Sanofi in 2012.
- Director of Engineering at MedChem Products, Inc., acquired by Bard in 1995, spun out Surgical Sealants, Inc.
- B.S. in Engineering from the University of Massachusetts in 1985.

Lakhmir Chawla, MD, Founder

- Led the development and FDA approval of angiotensin II, an ICU drug with 14 issued patents and $40 million in revenue in 2024.
- Received the International Vicenza Award for Critical Care Nephrology in June 2015, which recognizes individuals who have made seminal clinical research advancements that have significantly improved the care of critically ill patients with AKI and have been adopted worldwide. Dr. Chawla was selected as the recipient of the Vicenza Award for his contributions to the development of the renal angina model, the development and standardization of the furosemide stress test, the link between AKI and chronic kidney disease (CKD), and the use of angiotensin II in the treatment of high-output shock.
- Internationally renowned expert in the field of AKI and is an active investigator in the fields of inflammation and AKI, AKI biomarkers, AKI risk prediction, chronic kidney disease caused by AKI and AKI therapeutics.
- Department of Critical Care, University of California San Diego, San Diego, California

Founding Team

Arthur Atkinson, MD, Founder (1938-2024)

Dr. Atkinson received his A.B. degree in Chemistry from Harvard College in 1959 and his M.D. from Cornell University Medical College in 1963. While at Northwestern, he and his colleagues set up the first laboratory devoted to drug monitoring, conducted the first clinical investigations to develop the acetylated metabolite of procainamide as an antiarrhythmic drug, carried out the first PK studies with stable isotope-labeled drugs, and completed basic research that elucidated the physiologic basis of some multicompartmental models of drug distribution. In 1994, Dr. Atkinson was appointed Corporate VP for Clinical Development and Medical Affairs at Upjohn. Following the Upjohn-Pharmacia merger, he joined the Center for Drug Development Science at Georgetown University as an Adjunct Professor of Pharmacology. From 1975 to 1979, Dr. Atkinson served as a member of the Pharmacology/Toxicology Program Committee of the National Institute of General Medical Sciences (NIGMS), and from 1984 to 1986, chaired the Pharmacological Sciences Program Committee for that institute. In 1997, he returned to NIH as a Special Expert Consultant in Clinical Pharmacology for NIGMS. He was appointed Senior Advisor in Clinical Pharmacology to the Director of the NIH Clinical Center where he directed the ClinPRAT postdoctoral training program and the Clinical Center course on *Principles of Clinical Pharmacology*. Dr. Atkinson is a Master of the American College of Physicians (MACP) and has been President of the Chicago Society of Internal Medicine, President of the American Board of Clinical Pharmacology, and President of the American Society for Clinical Pharmacology and Therapeutics. He serves as an Emeritus Associate Editor of *Clinical Pharmacology and Therapeutics* and Emeritus Editor of *Translational and Clinical Pharmacology*. He has served as an editor for all four editions of the *Principles of Clinical Pharmacology* textbook, which in the fourth edition was re-named *Atkinson's Principles of Clinical Pharmacology.* He received the Harry Gold Award from ASPET, the Oscar Hunter Award from ASCPT, and the Award in Excellence from the PhRMA Foundation.

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