

PRX302 is a transperineally administered, PSA-activated protoxin that produces symptomatic relief in men with moderate to severe BPH

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Introduction

- PRX302 is a modified bacterial protoxin (proaerolysin) in which the native furin-cleavage site¹ has been modified to be proteolytically cleaved by prostate specific antigen (PSA)^{2,3}. Cleavage by PSA releases the C-terminal inhibitory peptide and generates the active toxin. This fragment forms heptamers and the resulting complex inserts into the cell membrane to form 1.5 nm pores that induce ion leakage, loss of membrane integrity, and cell death. Thus, PSA will activate PRX302 in a tissue localized manner and targeting is limited to the prostate.
- In a Phase I study, transperineal administration of PRX302 at varying concentrations to men with symptomatic BPH was well tolerated and provided symptomatic relief, as evidenced by sustained decreases in IPSS and QoL scores.
- In a Phase II study, PRX302 was administered at a fixed concentration and increasing volumes such that total volume injected was 10%, 20% or 30% of total prostate volume. The PRX302 was well tolerated and provided symptomatic relief with greatest effect observed in patients receiving higher volume (≥1 mL per deposit)
- Combined results from the Phase I and Phase II studies are presented here with patient follow-up to one year

Objective

The objective of these studies was to evaluate the safety and efficacy of a single treatment of PRX302 when injected into the prostate via the transperineal route in patients with moderate to severe BPH and to determine optimal dosing for further clinical studies.

Mode of Action



Engineered Proaerolysin binds to a receptor on cell surface. The protease activity of PSA cleaves the tail, forming the activated toxin, Aerolysin

Aerolysin assembles into a heptameric structure that inserts in the cell membrane, forming a pore. Cell contents leak out causing cell death (apoptosis).

Methods

- The Phase I study was a dose escalation (0.075µg/mL to 14µg/mL) safety study and the Phase II study a volume-escalation (10%, 20% and 30% of prostate volume) safety/efficacy study with a fixed PRX302 concentration of 3µg/mL
- The Phase I study enrolled 15 patients in 5 cohorts of 3 patients and the Phase II study enrolled 18 patients in 3 cohorts of 6 patients each. All patients were injected with PRX302 transperineally into the prostate under transrectal ultrasound (TRUS) guidance
- Each lobe was treated with a single injection. With each injection, deposits were made in the transition zone along the urethral length
- Before and after treatment, patients were evaluated for International Prostate Symptoms Scores (IPSS), Quality of Life (QoL) indicators, International Index of Erectile Function (IIEF) score and Prostate Volume. PSA serum values were also measured. Adverse effects (AE) were graded according to the Common Terminology Criteria Adverse Event (CTCAE) scale, v3.0, and causality between AE and treatment was assessed by the Investigator
- All patients have completed evaluation time points before treatment, and also at day 30, 90, 180, 270 and 360.

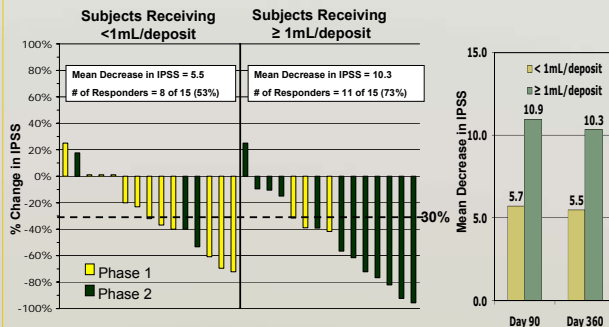
Patients

- Mean age Phase I: 64.5 years (range 52 – 82)
Phase II: 66.1 years (range 49 – 80)
- Mean prostate size: Phase I: 45.3 cm³ (range 30 – 81)
Phase II: 49.2 cm³ (range 30 – 74)
- All patients are Caucasian
- In Phase I previous therapies were limited to alpha-blockers with minimum 4 week washout prior to dosing and/or 5-alpha-reductase inhibitors (5-ARI) with 6 months washout. Phase II allowed prior alpha-blockers but excluded patients with prior 5-ARIs
- Subjects required to have significant lower urinary tract symptoms (LUTS) attributable to BPH (i.e. frequency, nocturia, urgency, weak urine stream, hesitancy, intermittency, or post-void dribbling) for ≥ 6 months with:
 - IPSS ≥ 12
 - QoL ≤ 3
 - Q_{max} ≤ 15 mL/sec
- Phase I: 33% of patients on the study were treatment naive with no prior therapy for BPH symptoms
- Phase II: 56% of patients on the study were treatment naive with no prior therapy for BPH symptoms

Results

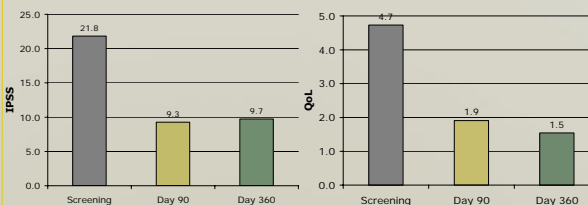
International Prostate Symptoms Scores (IPSS)

Change in IPSS in Individual Patients at day 360 post-injection (Phase I & 2)



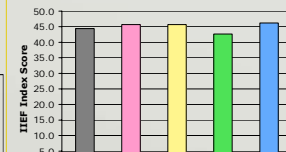
PRX302 produced a sustained ≥ 30% improvement in IPSS in the majority of patients at Day 360. A 30% improvement in IPSS is indicative of clinically relevant response. Most of the patients (11/15) receiving ≥1mL/deposit were responders. Overall patients in each study receiving ≥ 1mL per deposit had improvements in IPSS of 10.9 points at day 90 and 10.3 points at day 360. These studies confirm the importance of volume in the efficacy of PRX302

Phase II Results in Patients Receiving ≥ 1mL/deposit



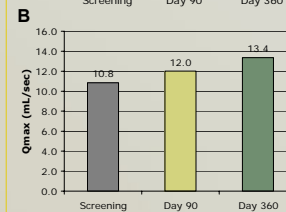
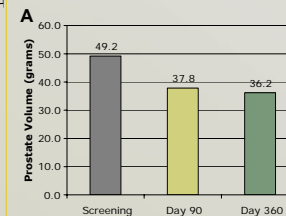
In the Phase II volume escalation study, evaluable patients receiving ≥ 1 mL per deposit (n=11) had ~12 point improvement in IPSS at day 90, which was sustained at day 360. QoL scores in these patients also improved by 2.8 points (~60% improvement) at day 90 and was sustained at day 360.

Erectile Function Phase II (all patients)



PRX302 did not impact erectile function in any of the cohorts in both the Phase I (data not shown) or Phase II study

Prostate Volume and Qmax Phase II (all patients)



Prostate volume measurements by TRUS at screening and Day 90 and 360 post-treatment, showed an ~30% decrease in prostate volume, in a majority of subjects following treatment (Figure A). Qmax improved by an average of 2.6 mL/sec (Figure B).

Adverse Events

- All AEs in both Phase I and II trials were mild to moderate in severity (Grade I-II)
- AEs were transient and most resolved within a few days without intervention
- The majority of AEs were localized to the urinary tract.
- No treatment related systemic manifestations have been observed
- No treatment related SAEs or Grade 3 or higher AEs were observed to date in either trial
- Only one patient out of 33 total patients treated required urinary catheter for less than 24 hr post treatment

Conclusions

- PRX302 is a novel and promising, first-in-class, disease modifying agent for the treatment of BPH
- PRX302 is well tolerated in BPH patients at injection volumes equivalent to up to 30% of prostate size
- A volume per deposit of ≥ 1 mL was associated with improved efficacy
- IPSS and Quality of Life scores improved significantly (p<0.01) out to at least 360 days following a single treatment
- Patients receiving the optimum dose (≥ 1mL per deposit) in the Phase II study had an average of 12 point improvement in IPSS at day 360 post dosing
- 73% of the patients receiving the optimum dose were treatment responders (>30% drop in IPSS)
- Improvement in symptom scores were attributed to decrease in the Irritative (42%) as well as Obstructive (57%) scores
- PRX302 does not adversely impact sexual function
- PRX302 is easy to administer in a 10-15 minute outpatient based setting

References

- Abrami, L, et al (1998) The pore-forming toxin proaerolysin is activated by furin. J Biol Chem. 273, 32656-32661.
- Williams SA, et al. (2007) A prostate-specific antigen-activated channel-forming toxin as therapy for prostatic disease. J Natl Cancer Inst. 99, 376-385.
- Singh, R, et al. (2007) Recombinant prostate-specific antigen proaerolysin shows selective prostate sensitivity and cell cytotoxicity. Anticancer Drugs 18, 809-816.