AUA Late-Breaking Abstract 16-8385: Prospective, Randomized, Double Blind, Vehicle Controlled, Multinational, Phase 3 Clinical Trial of the Pore Forming Protein PRX302 for Targeted Treatment of Symptomatic Benign Prostatic Hyperplasia (The PLUS 1 Trial)

Claus Roehrborn, UT Southwestern Med Ctr, Dallas, TX; Reg Bruskewitz, U of Wisconsin, Madison, WI; Richard Yocum, Sophiris, La Jolla, CA; Allison Hulme, Sophiris, La Jolla, CA; Marc Gittelman, So Florida Med Res, Aventura, FL

ABSTRACT

INTRODUCTION AND OBJECTIVE: Patients with lower urinary tract symptoms (LUTS) due to benign prostatic hyperplasia (BPH) desire treatment options besides medications, which have side effects and lack of sustainability, and more invasive surgical interventions, which also have side effects and complications. PRX302 (topsalysin) is a genetically modified pore-forming protein (aerolysin) activated intraprostatically only by enzymatically active PSA, and thus a specific, highly-targeted, localized approach to lysing cells in the prostate transition zone.

METHODS: 479 patients from 75 sites in 6 countries with International Prostate Symptom Score (IPSS) ≥15, peak urine flow (Qmax) 5-15 mL/s, and prostate volume (PV) 30-100 mL were randomized 1:1 to a single transrectal intraprostatic injection of PRX302 vs. placebo (vehicle) and then monitored for 52 weeks. BPH medications were washed out and prohibited on study. Injection was 20% of PV and 0.6 µg PRX302/g PV.

RESULTS: 92% of patients completed all 52 weeks. A single administration of PRX302 provided 7.6 points mean improvement in LUTS that was statistically significantly superior to vehicle-only injection, sustained through the Week 52 end of monitoring. This IPSS primary endpoint efficacy was supported by secondary endpoints, including positive findings for Qmax and two patient-rated disease-specific quality of life instruments.

Relative to vehicle, PRX302-apparent toxicity was in general mild, transient, limited to irritative urinary symptoms (dysuria 20%, pollakiuria 10%, urinary retention 4%), local discomfort/pain (perineal pain 9%), and general constitutional symptoms (fever 8%, chills 2%), occurring primarily on the day of injection, with no adverse effect on sexual function.

CONCLUSIONS: A single intraprostatic administration of PRX302 as a short, office-based procedure was well tolerated and produced clinically meaningful and sustained improvement in BPH LUTS over the 52 weeks of follow-up. Additional studies are planned.

MATERIALS & METHODS

Objectives: Confirm the efficacy and safety of PRX302 in reducing lower urinary tract symptoms (LUTS) in patients with benign prostatic hyperplasia (BPH).

Study Drug: PRX302 (topsalysin) is a modified recombinant version of the native pore-forming protein proaerolysin. As a prodrug, after activation only by enzymatically-active PSA (found only within prostate tissue), PRX302 creates a transmembrane pore leading to cell lysis and death. PRX302 is prepared in a diluent of recombinant human serum albumin (rHSA) in phosphate buffered saline.

Study Design:

- Blinded 1:1 randomization to PRX302 0.6 µg/g prostate vs. "placebo" of vehicle-only (no PRX302, visually indistinguishable)
- Pre-injection enema and prophylactic antibiotics (oral & parenteral); local anesthesia optional at Investigator's discretion
- Single transrectal intraprostatic bilateral injection of volume = 20% of total prostate volume (PV), followed by 52 weeks of monitoring
- IDMC evaluated safety after every 100 patients

Major Inclusion Criteria: Men ≥50 yrs, BPH LUTS for ≥6 months, IPSS total score ≥15, Peak urine flow (Qmax) 5-15 mL/sec, PV 30-100 mL, serum PSA<4 or 4-10 ng/mL if biopsy excluded cancer, & PVR ≤200 mL.

Major Exclusion Criteria: Other causes for LUTS, conditions confounding assessment of safety/tolerability, meds affecting LUTS (washouts ≥4 weeks for α-blocker & ≥6 months for 5-ARI), inability to void ≥125 mL, prior prostate surgery, MIST or intraprostatic injection (except Botox if >1 year) for BPH.

Primary Endpoint: IPSS total change from baseline using a restricted maximum likelihood based repeated measures linear mixed model analysis for all post-baseline timepoints over the 52-week study duration.

MATERIALS & METHODS

Secondary Endpoints: Qmax and other IPSS analyses, BPH rescue therapy, acute urinary retention (AUR), transition zone & total prostate volumes. Descriptive-only parameters of disease-specific quality of life questionnaires, PSA, PSA density, CRP, PVR, and % voided volume.
Safety: AEs, AUR, IIEF-EF and MSHQ-EjD questionnaires, physical exams, vital signs, ECGs, labs, and serum PRX302 & antibodies.
Analyses: All analyses shown include all patients treated and are ANCOVA using last observation carried forward (LOCF).

ENROLLMENT & DISPOSITION

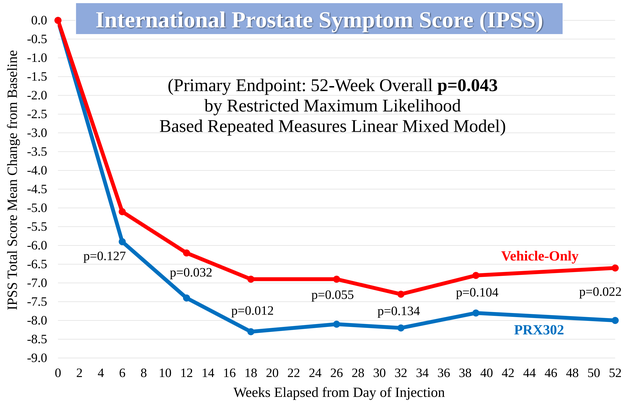
- 75 study centers in 6 countries randomized & dosed 479 patients, from US (252 patients), Ukraine (112), Russia (92), New Zealand (11), Canada (7), & Australia (5), between Oct 2013 and Sep 2014.
- Treatment groups well-balanced for all baseline characteristics.
- Study completion rate was high: 91.2% for PRX302 vs. 92.5% vehicle; median duration on study 365 days for both treatment groups.
- BPH rescue therapy opted by 2.1% (5 patients) in each treatment group.

Baseline Patient Characteristic (mean)	PRX302 (N=239)	Vehicle-Only (N=240)
Age (years)	64.4	64.9
IPSS Total Score	21.6	21.6
Peak Urine Flow Rate (Qmax) (mL/sec)	9.5	9.5
Global Question 1 (GQ1) Score (Additional "bother" question used to validate IPSS)*	2.4	2.4
Global Question 2 (GQ2) Score (8th Question on IPSS)*	4.5	4.6
Total Prostate Volume (PV) (mL)	50.1	48.0
Serum Prostate-Specific Antigen (PSA) (ng/mL)	2.05	2.01
Post-Void Residual (PVR) (mL)	68	64

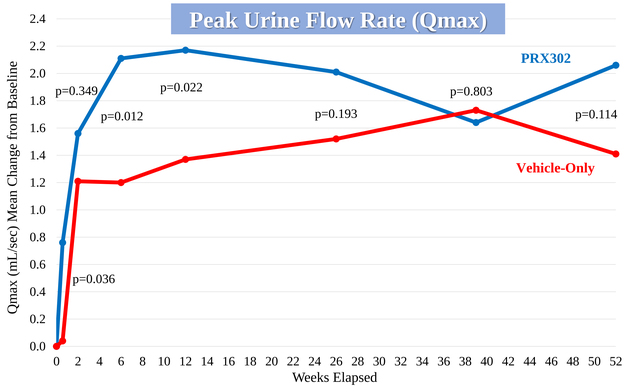
EFFICACY

- The protocol-defined primary efficacy endpoint was met: Overall 7.60 points improvement for PRX302 vs. 6.58 for vehicle-only (p=0.043)
- The PRX302 peak effect on IPSS (8.31 points at Week 18) was 97% preserved at the Week 52 timepoint (8.04 points)
- The PRX302 effect was greater than vehicle-only at all timepoints for both obstructive & irritative IPSS domains, with greater effect on obstructive
- The PRX302 effect on IPSS was superior to vehicle-only in all subgroup analyses: Geographic region (North America vs. Rest of World), IPSS (≤19 vs. ≥20), prior BPH therapy (yes vs. no), total PV (<50 vs. ≥50 mL), concurrent PDE-5 inhibitor use (yes vs. no), & age (<65 vs. ≥65 yrs)
- The PRX302 overall effect on Qmax, 1.77 mL/sec improvement for PRX302 vs. 1.23 for vehicle-only, narrowly missed significance (p=0.055)
- Transition zone & total prostate volumes changed little by end of study, without apparent PRX302 treatment effect on these volumes or on PSA
- The cell-lytic effect of PRX302 was evidenced by transient rises in both markers: Serum CRP (3.6-fold for PRX302 vs. 1.9-fold for vehicle-only) & serum PSA (7.7-fold for PRX302 vs. 3.9-fold for vehicle-only)

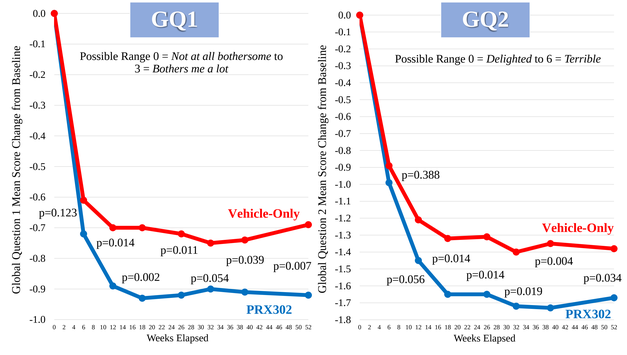
International Prostate Symptom Score (IPSS)



Peak Urine Flow Rate (Qmax)



Disease-Specific Quality of Life Patient Questionnaires (Global Questions 1 & 2)



SAFETY

- No premature withdrawals due to AE or other safety concern.
- No deaths or life-threatening SAEs.
- No treatment-related events of sepsis, hypersensitivity, or erectile or ejaculatory dysfunction. No PRX302-related cardiovascular toxicity.
- AEs most likely attributable to PRX302 based on comparative incidence may be categorized as irritative symptoms (MedDRA terms Dysuria [20.1%], Pollakiuria [9.6%], & Urinary Retention [4.2%]), localized pain/discomfort (Perineal pain [8.8%]), & general constitutional symptoms (Pyrexia [8.8%] & Chills [2.1%]), of which the longest median times for AE resolution were 1.6 days (Urinary retention) & 1.1 days (Dysuria); the other 5 AEs had median durations <1 day.

MedDRA Preferred Term (Reported Terms) AEs Observed in ≥5% in Either Treatment Group Over 52 Weeks of Study	PRX302 (N=239) n (%)	Vehicle-Only (N=240) n (%)
Dysuria (dysuria, pain or burning on urination)	48 (20.1)	20 (8.3)
Haematuria (37.5% gross or macroscopic)	45 (18.8)	36 (15.0)
Pollakiuria (urinary frequency, pollakiuria)	23 (9.6)	14 (5.8)
Perineal pain (perineal pain or burning)	21 (8.8)	13 (5.4)
Pyrexia (fever, hyperthermia)	21 (8.8)	10 (4.2)
Urine flow decreased (weak stream, flow decreased)	5 (2.1)	13 (5.4)
Headache (headache, intermittent headache)	3 (1.3)	12 (5.0)

SUMMARY & CONCLUSIONS

A single administration of PRX302 provided moderate-severe BPH patients a clinically meaningful magnitude of improvement in LUTS that was:

- Statistically significantly superior to vehicle-only injection
- Sustained without meaningful decline over the entire 52 weeks of monitoring
- Supported by the patient's own self-assessments on 2 disease-specific quality of life questionnaires
- Well-tolerated with most PRX302-related side effects generally mild-moderate, confined to the first couple of days, localized to the area of injection, transient, and anticipated based on the PRX302 mechanism of action of cell lysis causing inflammation within the prostate
- Superior in magnitude (7.6 points overall) on average than documented in pivotal trials of daily oral medications approved for BPH

LITERATURE

*Barry MJ, *et al.* The American Urological Association symptom index for benign prostatic hyperplasia. Measurement Committee of the American Urological Association. *J Urol* 1992;148:1549-57.

Denmeade SR, *et al.* Phase 1 & 2 studies demonstrate the safety & efficacy of intraprostatic injection of PRX302 for the targeted treatment of lower urinary tract symptoms secondary to benign prostatic hyperplasia. *Eur Urol* 2011;59:747-54.

Elhilali MM, *et al.* Prospective, randomized, double-blind, vehicle controlled, multicenter Phase IIb clinical trial of the pore forming protein PRX302 for targeted treatment of symptomatic benign prostatic hyperplasia. *J Urol* 2013; 189(4):1421-6.

*O'Leary MP, *et al.* Correlation of the International Prostate Symptom Score bother question with the Benign Prostatic Hyperplasia Impact Index in a clinical practice setting. *BJU International* 2008;101(12):1531-5.

FUNDING This study was sponsored and fully funded by Sophiris Bio Corp, 1258 Prospect Street, La Jolla, CA, USA 92037. For more information, contact richard@sophiris.com.