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Topsalysin for benign prostatic hyperplasia

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LAY SUMMARY

Benign prostatic hyperplasia (BPH) is a medical term that is used to describe enlargement of the prostate gland. It is not a cancer and is usually not a serious threat to health if well-treated. Most males aged 50 years and above will develop BPH. As the prostate gets bigger, it can place pressure on the bladder and it may squeeze or partly block the tube that carries urine from the bladder out of the body. This often causes problems with passing urine and may also cause other complications such as recurrent urinary tract infections, blockage of the bladder outlet, and kidney failure.

Topsalysin is a new medicine that is under development for the treatment of BPH. It acts on a specific receptor on the cell surface of prostate cells leading to shrinkage of these cells. It is delivered through an injection directly into the prostate, precisely shrinking the enlarged prostate tissue without damaging neighbouring tissue and nerves. This is believed to diminish the risk of side effects. If licensed, topsalysin will offer a new treatment option for patients with BPH.

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TARGET GROUP

Benign prostatic hyperplasia (BPH)

TECHNOLOGY

DESCRIPTION

Topsalysin (PRX302), is a modified recombinant protein that has been engineered to be selectively activated by an enzyme in the prostate, leading to localized cell death and tissue disruption without damaging neighbouring tissue and nerves. Topsalysin binds to the glycosylphosphatidylinositol (GPI)-anchored receptors on the cell surface of prostate cells. Once activated by the prostate-specific antigen (PSA), topsalysin combines with other activated topsalysin molecules, forming stable transmembrane pores that induce cell death. The prostate specific activation of topsalysin by enzymatically active PSA thus limits exposure of non-prostate tissues to the drug's activity, contributing to the safety of the therapy.[1]

In the phase III clinical trial (NCT01966614), topsalysin is given as a single intraprostatic bilateral injection at a dose of 0.6 µg/g.[2]

Topsalysin does not currently have Marketing Authorisation in the EU for any indication.

Topsalysin is in phase II stage of development for the treatment of localised prostate cancer.[3]

INNOVATION and/or ADVANTAGES

Regarding the current treatment options for BPH, there is a demand for better balance between efficacy, safety and quality of life. Topsalysin is delivered through a targeted injection into the prostate, precisely ablating the prostate tissue without damaging neighbouring tissue and nerves. This method of administration limits the circulation of the drug in the body and it is believed that this limited systemic exposure to the drug, together with how the drug is activated in the body, diminishes the risk of side effects.[1] If licensed, topsalysin will offer a new treatment option for patients with BPH.

DEVELOPER

Sophiris Bio, Corp.

PATIENT GROUP

BACKGROUND

Benign prostatic hyperplasia (BPH) or benign enlarged prostate is a medical term that is used to describe enlarged prostate gland. Also known as benign prostatic hypertrophy, it is a histologic diagnosis characterized by proliferation of the cellular elements of the prostate. The prostate is a small gland, located in the pelvis, between the penis and bladder. It surrounds the urethra, the tube that carries urine from the bladder out of the body. As the prostate gets bigger, it can place pressure on the bladder and it may squeeze or partly block the urethra. This often causes problems with urination. BPH is common in men over 50 years of age. It is not a cancer and is not usually a serious threat to health.[4, 5, 6]

The cause of prostate enlargement is unknown, but it is believed to be linked to hormonal changes as men get older. The balance of hormones in the body changes as the person gets older and this may cause the prostate gland to grow.[4]

Symptoms of BPH include: difficulty starting to urinate, a frequent and/or urgent need to urinate, difficulty of fully emptying the bladder, straining to urinate, having a weak flow of urine, dribbling, nocturia (needing to get up frequently at night to urinate), and accidentally leaking urine (urinary incontinence).[4, 6]

Sometimes BPH can cause chronic bladder outlet obstruction (BOO), which may lead to urinary retention, renal insufficiency, recurrent urinary tract infections, gross haematuria (blood in the urine) and bladder calculi. End stage BOO can cause renal failure and uraemia.[6] The most important quality of life aspects reported to be most affected were sleep, anxiety and worry about the disease, mobility, leisure, daily activities, sexual activities and satisfaction with sexual relationships.[7]

CLINICAL NEED and BURDEN OF DISEASE

In the UK, 3.2 million men experience symptoms of BPH.[8] NHS England Hospital episode statistics for 2015/2016 shows that for hyperplasia of prostate (ICD 10 code: N40), there were 31,961 admissions, 33,859 finished consultant episodes (FCE), and 51,930 FCE bed days.[9]

The health burden of BPH in the UK, as measured in years of healthy life lost per 100,000 men, peaks at age 75-79. The annual years of healthy life lost per 100,000 people from BPH in UK has increased by 18.0% between 1990 and 2013, an average of 0.8% a year.[10]

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE clinical guideline. Lower urinary tract symptoms in men: management (CG97). May 2010 (updated June 2015)
- NICE interventional procedure guidance. Insertion of prostatic urethral lift implants to treat lower urinary tract symptoms secondary to benign prostatic hyperplasia (IPG475). January 2014
- NICE interventional procedure guidance. Prostate artery embolisation for benign prostatic hyperplasia (IPG453). April 2013
- NICE interventional procedure guidance. Holmium laser prostatectomy (IPG17). November 2003
- NICE diagnostic guidance. Diagnosing prostate cancer: PROGENSA PCA3 assay and Prostate Health Index (DG17). June 2015
- NICE medical technologies guidance. GreenLight XPS for treating benign prostatic hyperplasia (MTG29). June 2016
- NICE medical technologies guidance. UroLift for treating lower urinary tract symptoms of benign prostatic hyperplasia (MTG26). September 2015
- NICE medical technologies guidance. The TURis system for transurethral resection of the prostate (MTG23). February 2015

NHS ENGLAND and POLICY GUIDANCE

- NHS England. The NHS England Innovation and Technology Tariff 2017 to 2019 Technical notes. Version number: V 5.7
- NHS England. Items which should not routinely be prescribed in primary care: A Consultation on guidance for CCGs. July 2017. Version number:1

- NHS England. Clinical Commissioning Policy: Urethroplasty for benign urethral strictures in adult men. July 2016

OTHER GUIDANCE

- Wu Y, Davidian MH, DeSimone II EM. Guidelines for the Treatment of Benign Prostatic Hyperplasia. US Pharm. 2016.[11]
- American Urological Association. Management of Benign Prostatic Hyperplasia (BPH). 2010 (Reviewed and Validity Confirmed 2014)[12]
- American Urological Association Education and Research, Inc. AUA Guideline on the Management of Benign Prostatic Hyperplasia: Diagnosis and Treatment Recommendations. 2003.[13]
- European Association of Urology. Guidelines on benign prostatic hyperplasia. 2002.[14]

CURRENT TREATMENT OPTIONS

The treatment for an enlarged prostate gland will depend on the severity of the symptoms. The main treatments are lifestyle changes such as drinking less fizzy drinks and less alcohol, caffeine and artificial sweeteners. Also drinking less fluids in the evening, and frequent emptying of the bladder.[4]

Medications are offered when lifestyle changes are not helpful to reduce symptoms or are not suitable for the patient. Examples of these medications are alpha blockers, anticholinergics, 5-alpha reductase inhibitors, diuretics, and desmopressins.[4] NICE pathways recommends offering 5-alpha reductase inhibitor to men with lower urinary tract symptoms (LUTS) who have prostates estimated to be larger than 30 g or a prostate specific antigen (PSA) level greater than 1.4 ng/ml, and who are considered to be at high risk of progression (for example, older men). NICE also recommends offering a combination of an alpha blocker and a 5-alpha reductase inhibitor to men with bothersome moderate to severe LUTS and prostates estimated to be larger than 30 g or a PSA level greater than 1.4 ng/ml.[15]

Patients may need catheterisation if they have difficulty in urination due to chronic renal failure. Surgery may be an option if other treatments have not worked.[4]

EFFICACY and SAFETY	
Trial	**PLUS-1, NCT01966614; men aged 50 years and older; topsalysin vs placebo; phase III.**
Sponsor	Sophiris Bio Corp.
Status	Published in abstract.
Source of Information	Trial registry,[2] American Urology Association (abstract)[16]
Location	Ukraine, USA, Canada, Russian Federation, Australia, New Zealand.
Design	Randomised, placebo-controlled
Participants	n= 479; aged 50 years and over; males; lower urinary tract symptoms (LUTS) attributable to benign prostate hyperplasia (BPH) for ≥6 months; International Prostate Symptom Score (IPSS) ≥15; maximum urine flow (Qmax) of 5 - 15 mL/sec; prostate volume of 30 - 100 mL as determined by transrectal ultrasound (TRUS); serum PSA values <10 ng/mL; post-void residual (PVR) <= 200 mL.
Schedule	Randomised to topsalysin single intraprostatic bilateral injection at a dose of 0.6 µg/g; or placebo single intraprostatic bilateral injection of vehicle only.
Follow-up	A single treatment of topsalysin, follow-up 52 wks.
Primary Outcomes	Efficacy: international prostate symptom score (IPSS) total score change from baseline over 52 weeks.
Secondary Outcomes	• Efficacy [time frame: week 52]: - Qmax change from baseline over 52 weeks. - IPSS total score change from baseline at each individual post-baseline timepoint. - Qmax change from baseline at each individual post-baseline time point. - IPSS "responders" at each individual post-baseline time point. - Qmax "responders" at each individual post-baseline time point. - Proportion of patients who receive rescue therapy. - Time to onset of rescue therapy. - Incidence rate for episodes of urinary retention. - Transition Zone (TZ) prostate volume change from baseline as measured by transrectal ultrasound (TRUS) at each individual post-baseline time point. - Total prostate volume (PV) change from baseline as measured by TRUS at each individual post-baseline timepoint. •Safety [time frame: week 52] Treatment-emergent adverse events (TEAEs). - Episodes of acute urinary retention as determined by the independent Adjudication Panel. - Assessment of sexual function for men who are sexually active using the International Index of Erectile Function - Erectile Function (IIEF-EF) and the Male Sexual Health Questionnaire© short form for ejaculatory dysfunction (MSHQ-EjD). - Physical examinations. - Vital signs. - Electrocardiograms (ECGs).

	- Laboratory parameters, consisting of chemistry panel, complete blood count (CBC), and urinalysis. - Measurement of anti-PRX302 antibodies (APA). - Serum concentration of topsalysin only if clinically indicated by an event such as suspected systemic toxicity.
Key Results	2% of patients completed all 52 weeks. A single administration of topsalysin 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, topsalysin-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.[16]
Adverse effects (AEs)	Not reported.
Expected reporting date	Primary completion date reported as December 2015

Trial	**TRIUMPH-1, NCT00889707, ABC-123; males aged 40-80 years; topsalysin vs placebo; phase II**
Sponsor	Sophiris Bio Corp
Status	Complete.
Source of Information	Publication,[17] trial registry,[18] global data.[19]
Location	Canada
Design	Randomised, placebo-controlled
Participants	n=92; aged 40-80 years; males; LUTS attributable to BPH for at least 6 months prior to dosing; untreated, intolerant or refractory to α-blockers; should not have received the medication for at least 2 weeks prior to screening and 4 weeks prior to dosing; no presence of prostate cancer; untreated, intolerant or intolerant to 5-α reductase inhibitors and must be off medication for at least 6 months prior to dosing; IPSS of 15 or higher; prostate volume at screening estimated at 30 to 100 mL as determined by TRUS.
Schedule	Randomised to topsalysin administered at a volume equivalent to 20% of PV and at a fixed concentration of 3.0 µg/ml for a fixed dose of 0.6 µg/gm prostate t; or placebo administered at the same volume of 20%. Vehicle treatment consisted of injection of only the diluent (2% human serum albumin) at the same 20% of prostate volume
Follow-up	Follow-up 1 year.
Primary Outcomes	Change in International Prostate Symptom Scale (IPSS) of Lower Urinary Tract Symptoms From Baseline to 3 Months (Total Score at 3 Months Minus Total Score at Baseline) [Time Frame: 3 months post-treatment]

Secondary Outcomes	Change in Maximum Urinary Flow Rate (Qmax) From Baseline to 3 Months (Qmax at 3 Months Minus Qmax at Baseline) [Time Frame: 3 months after treatment]
Key Results	Topsalysin treatment resulted in an approximate 9-point reduction in I-PSS and 3 ml per second increase in peak urine flow that were statistically significant changes from baseline compared to vehicle. Efficacy was sustained for 12 months. Early withdrawal for other benign prostatic hyperplasia treatment was more common for patients in the vehicle group. Relative to vehicle, topsalysin apparent toxicity was mild, transient, and limited to local discomfort/pain and irritative urinary symptoms occurring in the first few days, with no effect on erectile function.[17]
Adverse effects (AEs)	Adverse effects attributable to topsalysin were generally mild and transient, beginning within the first few days after treatment and resolving without sequelae. More than 10% of the subjects in the treatment group had haematuria, dysuria, pollakiuria, micturition urgency, and perineal pain.[17]
Expected reporting date	-

ESTIMATED COST and IMPACT

COST

The cost of topsalysin is not yet known.

IMPACT – SPECULATIVE

IMPACT ON PATIENTS AND CARERS

☐ Reduced mortality/increased length of survival

☒ Reduced symptoms or disability

☐ Other

☐ No impact identified

IMPACT ON HEALTH and SOCIAL CARE SERVICES

☐ Increased use of existing services

☒ Decreased use of existing services

☐ Re-organisation of existing services

☒ Need for new services: possibility of the need for health professional to administer topsalysin injection.

☐ Other

☐ None identified

IMPACT ON COSTS and OTHER RESOURCE USE

☐ Increased drug treatment costs

☐ Reduced drug treatment costs

☒ Other increase in costs: possibility of the need for health professional to administer topsalysin injection.

☐ Other reduction in costs

☐ Other

☐ None identified

OTHER ISSUES

☐ Clinical uncertainty or other research question identified

☒ None identified

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