Zacks Small-Cap Research

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Sophiris Bio, Inc.

(SPHS-NASDAQ)

SPHS: Initiating on Sophiris Bio, Inc.; Developing Novel Treatments for Urologic Conditions…

Based on our probability adjusted DCF model that takes into account potential future revenues from PRX302 in both BPH and prostate cancer, SPHS is valued at $6/share. This model is highly dependent upon the clinical success of PRX302 and will be adjusted accordingly based upon future clinical results.

Current Price (09/12/16)	$2.70
Valuation	**$6.00**

INITIATION

Sophiris Bio, Inc. (SPHS) is focused on the development of topsalysin (PRX302) for the treatment of lower urinary tract symptoms of benign prostatic hyperplasia (BPH) and localized low to intermediate risk prostate cancer. Topsalysin is a genetically modified protein that is delivered directly to the prostate via ultrasound-guided injection. The protein is selectively activated by enzymatically active prostate specific antigen (PSA), which is present only in the prostate, and leads to localized cell death without damage to neighboring tissues or nerves. The company has successfully completed one Phase 3 study in BPH and is currently evaluating strategic options for the advancement of the compound in that indication. A Phase 2 study in prostate cancer has been completed and the company recently raised funds to conduct a Phase 2b study in that indication.

SUMMARY DATA

52-Week High	**$5.95**
52-Week Low	**$0.73**
One-Year Return (%)	**217.65**
Beta	**1.78**
Average Daily Volume (sh)	**2,965,477**
Shares Outstanding (mil)	**29**
Market Capitalization ($mil)	**$79**
Short Interest Ratio (days)	**N/A**
Institutional Ownership (%)	**5**
Insider Ownership (%)	**6**
Annual Cash Dividend	**$0.00**
Dividend Yield (%)	**0.00**
5-Yr. Historical Growth Rates	
Sales (%)	**N/A**
Earnings Per Share (%)	**N/A**
Dividend (%)	**N/A**
P/E using TTM EPS	**N/A**
P/E using 2016 Estimate	**N/A**
P/E using 2017 Estimate	**N/A**
Risk Level	**N/A,**
Type of Stock	**N/A**
Industry	**Med-Biomed/Gene**

ZACKS ESTIMATES

Revenue
(In millions of $)

	Q1 (Mar)	Q2 (Jun)	Q3 (Sep)	Q4 (Dec)	Year (Dec)
2015	0.0 A	0.0 A	0.0 A	0.0 A	0.0 A
2016	0.0 A	0.0 A	0.0 E	0.0 E	0.0 E
2017					0.0 E
2018					0.0 E

Earnings per Share
(EPS is operating earnings before non-recurring items)

	Q1 (Mar)	Q2 (Jun)	Q3 (Sep)	Q4 (Dec)	Year (Dec)
2015	-$0.26 A	-$0.22 A	-$0.22 A	-$0.14 A	-$0.84 A
2016	-$0.13 A	-$0.21 A	-$0.09 E	-$0.08 E	-$0.47 E
2017					-$0.37 E
2018					-$0.45 E

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WHAT'S NEW

Initiating Coverage

We are initiating coverage of Sophiris Bio, Inc. with a valuation of $6/share. Sophiris is a biopharmaceutical company developing treatments for urological diseases. The company's technology is focused on PRX302 (topsalysin), a biologic treatment for benign prostatic hyperplasia (BPH) and low to intermediate risk localized prostate cancer. Topsalysin is a genetically modified version of proaerolysin, a protein secreted by the *Aeromonas* genus of Gram-negative, anaerobic bacteria. Proaerolysin is activated to aerolysin and forms a heptameric oligomer that inserts into the cell membrane forming a transmembrane pore. Loss of small molecules and ions through the channels eventually leads to cell death.

Proaerolysin is activated through cleavage of a specific amino acid sequence by furin proteases that are found throughout the body. In order to target the molecule to the prostate for use as a potential therapeutic agent, the furin cleavage sequence was replaced with a prostate specific antigen (PSA)-selective cleavage sequence. PSA is a protease produced by the prostate gland, where enzymatically active PSA is found, both in normal and malignant prostate tissue. PSA found in the bloodstream is deactivated by protease inhibitors and therefore cannot activate topsalysin. The PSA-activated enzyme, topsalysin, is injected directly into the prostate to further localize the therapeutic effect.

Sophiris' technology has a number of advantages over currently available treatments for both BPH and localized prostate cancer, including:

- **A safe, localized mechanism of action**: PRX302 is injected directly into the prostate, and only activated by PSA, which is expressed and enzymatically active only in the prostate, thus there is little danger of off-target effects. PRX302 has been tested in over 400 patients with a good safety and tolerability profile.

- **Treatment with PRX302 for BPH is simple and effective**: PRX302 for the treatment of BPH can be administered in a doctor's office through a few localized injections. For BPH, PRX302 showed a statistically significant and clinically meaningful improvement in the symptoms of moderate to severe BPH over 12 months following a single treatment in a Phase 3 clinical trial.

- **Potentially effective treatment for localized prostate cancer with fewer side effects**: Typically, men with localized clinically significant low to intermediate risk prostate cancer that warrants treatment can either choose radiation or radical prostatectomy. Both radiation and prostatectomy can have considerable side effects including significant bleeding, impotence, and incontinence. Thus far, in 18 patients with localized prostate cancer treated with PRX302, two patients had complete elimination of the tumor while seven others had a partial response with no patients reporting sexual or other serious side effects.

The company recently completed a public offering of 6.5 million shares of common stock that raised gross proceeds of $26 million. The company now has sufficient funds to conduct a Phase 2b clinical trial in localized prostate cancer that should begin before the end of 2016, with topline results likely to be reported before the end of 2017. For BPH, we anticipate the company entering into a collaboration before a second Phase 3 clinical trial commences.

INVESTMENT THESIS

Sophiris Bio, Inc. (SPHS) is developing treatments for lower urinary tract symptoms of benign prostatic hyperplasia (BPH) and localized clinically significant low to intermediate risk prostate cancer. The company's lead candidate, PRX302 (topsalysin), is a genetically engineered recombinant protein that is activated through enzymatic cleavage by prostate specific antigen (PSA), which is produced in large quantities by the prostate gland. Once activated, topsalysin combines with other topsalysin molecules to form stable transmembrane pores and initiate cell death. The compound has been successfully tested in one Phase 3 clinical trial for BPH and a Phase 2a clinical trial for localized prostate cancer.

PRX302 (Topsalysin)

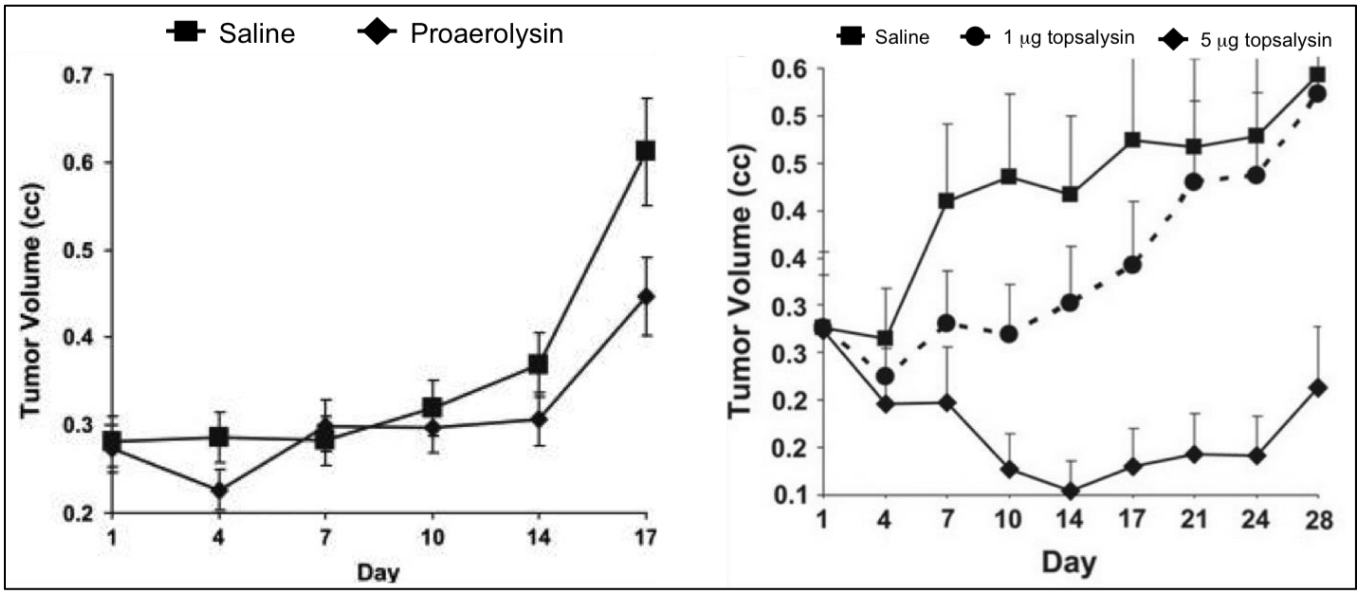
Proaerolysin is an inactive precursor protein secreted by the *Aeromonas* genus of Gram-negative, anaerobic bacteria (Buckley, 1992). Once released by the bacterium, proaerolysin binds to the surface of target cells, where it is cleaved by furin-like proteases to produce aerolysin (Abrami *et al*., 1998). Activation of aerolysin results in the formation of a heptameric oligomer that inserts into the cell membrane forming a transmembrane pore. Loss of small molecules and ions through the channels eventually leads to cell death.

The specific cleavage of proaerolysin is due to the presence of the furin cleavage sequence KVRRAR located within the protein. Furin is a ubiquitous protease that is produced by most cell types, thus native proaerolysin can be activated throughout the body. In order to target the molecule to the prostate for use as a potential therapeutic agent, the furin cleavage sequence was replaced with a prostate specific antigen (PSA)-selective cleavage sequence HSSKLQ (Denmeade *et al*., 1997). PSA is a protease produced by the prostate gland, and while it is found in the bloodstream, the vast majority of circulating PSA is bound by protease inhibitors and thus is enzymatically inactive (Christensson *et al*., 1990). Enzymatically active PSA is found almost exclusively in normal and malignant prostate tissue (Olsson *et al*., 2005). Prostate targeted drugs using a PSA-specific cleavage sequence have also been developed using doxorubicin and thapsigargin, the latter of which is being developed by Inspyr Therapeutics, Inc. (NSPX). A schematic showing the mechanism of action for topsalysin (PRX302) is shown in the following figure.



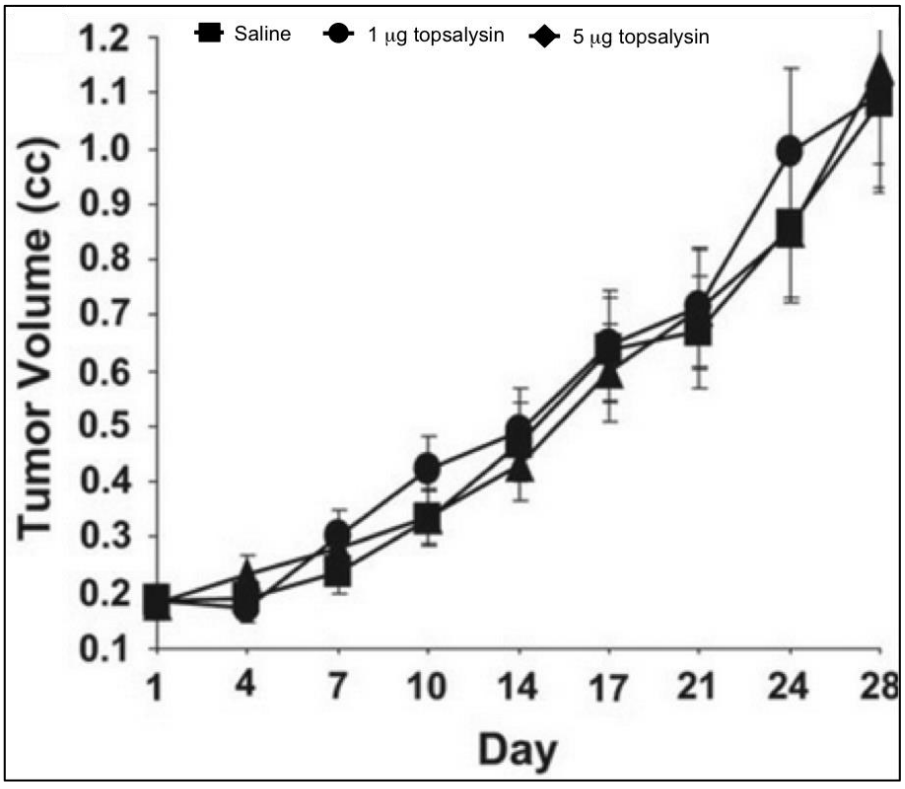
Source: Sophiris Bio, Inc.

The activity of topsalysin in comparison to aerolysin is shown in the following figure. In both experiments, mice were injected with LNCaP cells, which are prostate cancer cells that express PSA. Once the tumors got to a certain size, single injections of saline, proaerolysin, or different concentrations of topsalysin were injected directly into the tumor. As the following graphs show, single injections of saline or proaerolysin did not have any anti-cancer effect while a single injection of 5 µg topsalysin caused tumor regression.



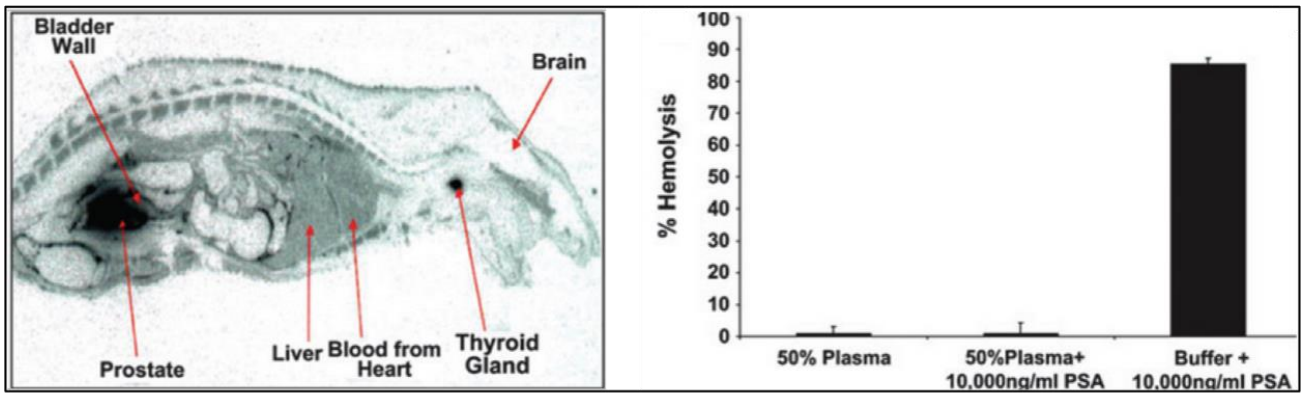
Adapted from: Williams *et al*., 2007

The specificity of topsalysin is shown in the following figure. In that experiment, mice were injected with TSU tumor cells, which are a human bladder cancer cell line. Treatment with saline or topsalysin did not have any effect on the growth of the tumors. Topsalysin was not effective against TSU cells due to the fact that those cells do not express PSA.



Adapted from: Williams *et al*., 2007

In order to determine the biodistribution of topsalysin following injection into the prostate, ^{125}I-topsalysin was prepared and injected into the right prostatic ventral lobe of Sprague-Dawley rats (the prostate in rats is not encapsulated unlike in men). Results showed that the majority of the radioactivity was confined to the prostate, with the remaining radioactivity found in the thyroid gland. A representative whole-body autoradiograph is shown in the below left figure. While those results were encouraging, it would still be possible for some topsalysin to leak from the tissue into the bloodstream. To determine if topsalysin could be activated in the bloodstream by plasma proteases, topsalysin was incubated in a 2% red blood cell (RBC) solution with 50% human plasma with or without 10,000 ng/mL of enzymatically active human PSA. The results show that incubation of topsolysin with PSA in serum-free buffer resulted in close to 90% lysis of RBCs, while less than 5% lysis of RBCs occurred when topsolysin was incubated in human plasma containing PSA. These data are supportive of topsolysin being a safe treatment with activity limited only to the prostate.



Source: Williams *et al*., 2007

Indication I: Benign Prostatic Hyperplasia

Benign Prostatic Hyperplasia (BPH) is growth of the prostate gland as a result of unregulated proliferation of connective tissue, smooth muscle, and glandular epithelial cells (Auffenberg *et al*., 2009). The increase in cell growth leads to an increase in prostate volume and the formation of nodules in the periurethral zone. As the nodules increase in size, they can lead to compression of the urethra, resulting in increased resistance to urine flow from the bladder. While an increase in PSA expression is sometimes seen in those with BPH, the condition is not associated with an increased risk of cancer.

BPH can lead to various lower urinary tract symptoms (LUTS), a term used to describe a wide range of symptoms related to the bladder, prostate, and urethra. LUTS are grouped into voiding or storage symptoms, and include

- ✓ A longer than usual wait for urination to begin
- ✓ A weak urine stream
- ✓ Straining to urinate
- ✓ Involuntary interruption in urination
- ✓ Frequent urination
- ✓ An urgent feeling to urinate
- ✓ Waking at night two or more times to urinate

Androgens are known to be required for the development of BPH. As men age, the level of testosterone in the body typically decreases, however the level of dihydrotestosterone (DHT) and androgen receptor remain high due to the presence of 5α-reductase within the prostate (McConnell *et al*., 1995). DHT promotes cell growth through mitogenic activation of growth factors in both epithelial and stromal cells.

BPH is considered a normal part of aging in men, with an estimated 50% of men demonstrating histopathological BPH by the age of 60 and 90% of men by age 85. Up to 14 million men in the U.S. and 30 million men worldwide have symptoms of BPH (NIDDK).

Diagnosis of BPH is made based on a history of LUTS, a digital rectal exam (DRE), and the ruling out of other etiologies, since other diseases can cause the symptoms of BPH. Additional screening tools include the use of the American Urological Association Symptom Index (AUA-SI) or the International Prostate Symptom Score (IPSS). The IPSS is an eight question written screening tool with seven symptom questions (scored 1 to 5) and one quality-

of-life question (scored 1 to 6). The total score from the seven symptom questions is categorized as follows:

- 1-7: Mild BPH
- 8-19: Moderate BPH
- 20-35: Severe BPH

Treatment options that offer at least a three point improvement in IPSS are considered clinically meaningful by urologists. The IPSS is the primary clinical endpoint that has been utilized for the approval of products that are used for treating the symptoms of BPH.

Current Treatment Options for BPH

Patients with mild or moderate BPH who are not bothered by their symptoms and are not experiencing complications due to the condition are typically managed with a strategy of watchful waiting and re-evaluated yearly or as their symptoms get worse. Pharmacologic therapy is currently being employed by approximately three million men suffering from BPH, while there are approximately 200,000 surgical procedures performed for BPH each year. A summary of the current treatment options for BPH is below:

Alpha-1-receptor blockade: Many of the symptoms of LUTS associated with BPH are believed to be due to smooth-muscle tension in the prostate, urethra, and bladder neck, which is mediated by alpha-1-adrenergic receptors. In those regions, the alpha-1a subtype is the most prominent. Examples of drugs in this class include tamsulosin (Flomax®) and silodosin (Rapaflo®), which generated worldwide revenues of $477 million and $410 million, respectively, in 2015 (EvaluatePharma). Side effects reported for alpha-1-receptor blockers include dizziness and low blood pressure.

5-Alpha reductase inhibitors: The discovery that DHT deficiency can lead to a hypoplastic prostate, through a lack of 5-alpha reductase activity, led to use of 5-alpha reductase inhibitors for treating BPH. These drugs appear to be most effective in those with larger prostates. Examples of drugs in this class include dutasteride (Avodart®) and finasteride (Proscar®/Propecia®), which generated worldwide revenues of $1 billion and $225 million, respectively, in 2015 (EvaluatePharma). These drugs have been associated with an increased risk of being diagnosed with a more serious form of prostate cancer.

Combination therapy: The Medical Therapy of Prostatic Symptoms (MTOPS) trial showed that combination therapy with an alpha-1-receptor blocker and a 5-alpha-reductase inhibitor reduced the risk of progression and produced a greater improvement in IPSS than monotherapy, however it is recommended only for those with moderate-to-severe BPH (Madersbacher *et al*., 2007)

Transurethral Resection of the Prostate (TURP): This procedure is reserved for those who have BOO secondary to BPH along with serious conditions such as recurrent gross hematuria, urinary tract infections, and renal insufficiency secondary to obstruction. TURP involves placing a working sheath up the urethra with an attached wire loop and is performed under general anesthesia. An electric current run through the wire is used to shave away prostatic tissue. Side effects include the potential for significant bleeding, structuring of the urethra, impotence, and retrograde ejaculation.

Minimally Invasive Surgical Treatment: Due to the serious side effects of TURP, a number of different minimally invasive therapies have been developed. Most of these procedures involve the use of heat, which is delivered in the form of laser energy, microwaves, radiofrequency energy, high-intensity ultrasound waves, and high-voltage electrical energy. As with TURP, these procedures are usually performed using a working sheath placed in the urethra. While these procedures are less invasive than TURP, they are still associated with a number of similar side effects including the need for catheterization and a risk of bleeding.

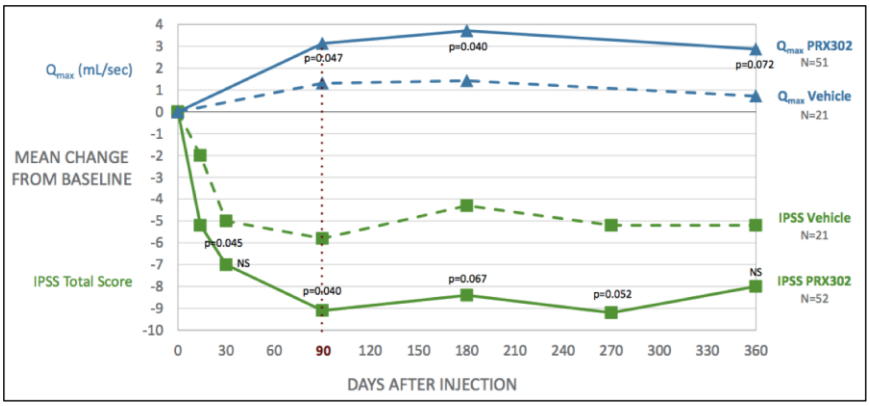
PRX302 for Treating BPH

PRX302 is administered to patients through an ultrasound-guided series of injections into the prostate that takes approximately four minutes to complete. The procedure can be completed during a short office visit and is currently being developed as a one-time use procedure. PRX302 is designed to be safe, simple, convenient, and provide rapid, sustained relief of BPH symptoms. It has been tested thus far in five clinical trials involving 365 BPH patients.

TRIUMPH Study (PRX302-2-03): This was a Phase 2b randomized, double blind, placebo controlled study of a transperineal intraprostatic injection of 0.6 µg PRX302/g of prostate. The trial enrolled 61 men to be treated with PRX302 and 31 men to be treated with placebo. The primary endpoint of the trial was the change from baseline in

IPSS at three months with secondary endpoints examining change in Qmax (maximum urine flow).

The following graph shows the change from baseline in both IPSS and Qmax, showing that treatment with PRX302 resulted in a statistically significant reduction in IPSS (-9.1 vs. -5.8; *P*=0.040) and a statistically significant increase in Qmax (3.1 vs. 1.3; *P*=0.047) at three months following treatment.

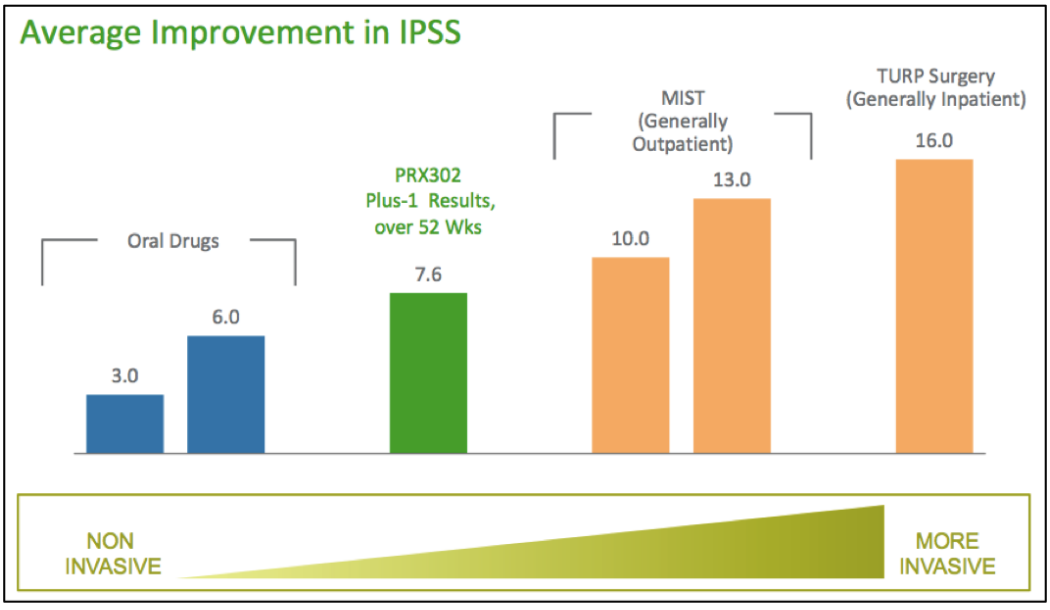


Source: Sophiris Bio, Inc.

Importantly, there were no adverse events reported in regards to erectile function (something that is commonly seen with other treatments for BPH) or any drug-related Grade 3 or 4 adverse events. In addition, there were more withdrawals from the trial in the placebo cohort than the PRX302-treated cohort (16.1% vs. 3.3%).

Plus-1 Study (PRX302-3-01): This was a Phase 3 randomized, double blind, placebo controlled study of a transperineal intraprostatic injection of 0.6 µg PRX302/g of prostate. The trial enrolled 239 men to be treated with PRX302 and 240 men to be treated with placebo. The primary endpoint of the trial was the change from baseline in IPSS at 52 weeks with secondary endpoints examining change in Qmax (maximum urine flow) at 6, 12, 18, 26, 32, 39, and 52 weeks along with the change in IPSS at each of those same time points.

Results from the Phase 3 study showed that injection of PRX302 resulted in a statistically significant improvement in IPSS total score from baseline over 52 weeks (7.60 vs. 6.58; *P*=0.043). A secondary analysis of IPSS total score showed a maximal effect at week 18 between PRX302-treated and placebo-treated patients (8.31 vs. 6.89; *P*=0.012). The change from baseline in Qmax over 52 weeks showed a statistical trend with overall improvement of 1.77 mL/sec (*P*=0.055). In the quality of life portion of the IPSS questionnaire, treatment with PRX302 resulted in a statistically significant change from baseline for every post-baseline visit beginning at week 18 (reaching *P*=0.004). As shown in the following figure, the average change from baseline of -7.6 points puts PRX302 in between oral therapies and surgical procedures in terms of efficacy.

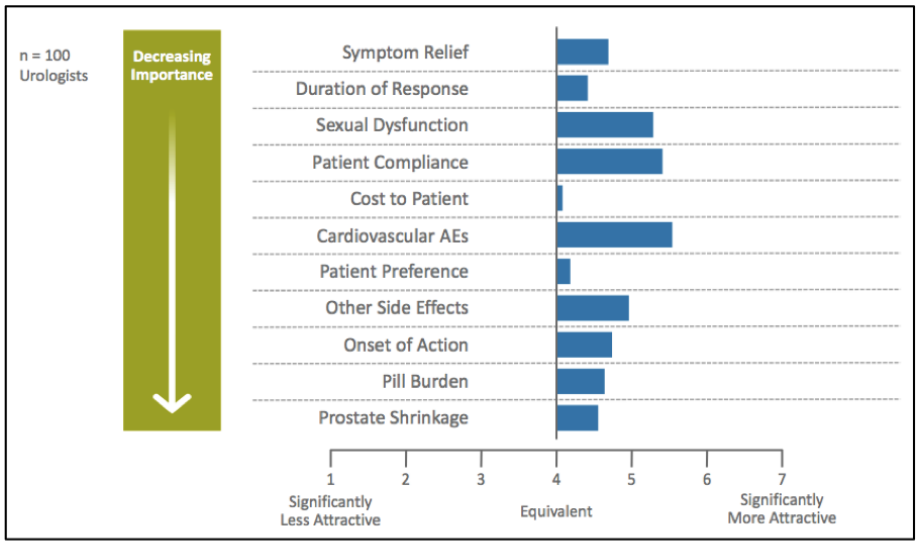


Source: Sophiris Bio, Inc.

Just as with the Phase 2b study, adverse events were typically mild or moderate, occurred on the day of the injection, and were transient with a median duration of less than a day. There were also no indications of any adverse sexual or cardiovascular side effects.

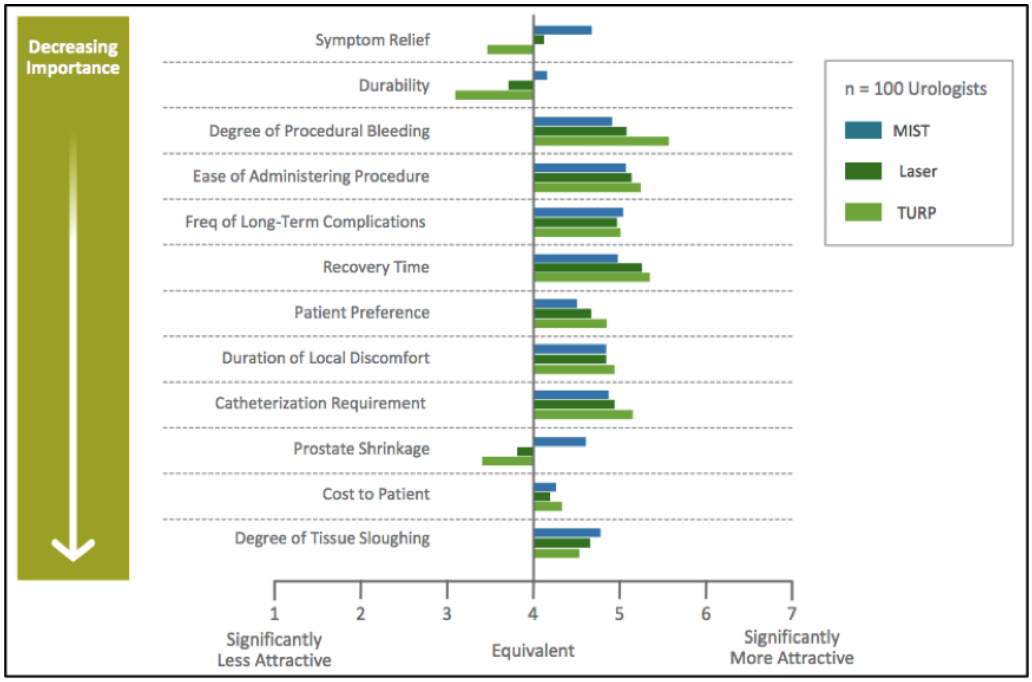
PRX302 Viewed Favorably by Urologists

In 2012, Sophiris conducted market research with 100 urologists that showed PRX302 compared favorably to both oral therapies and surgical procedures for treating BPH. The following figure shows how PRX302 was thought to be more attractive than oral therapy for a wide range of issues.



Source: Sophiris Bio, Inc.

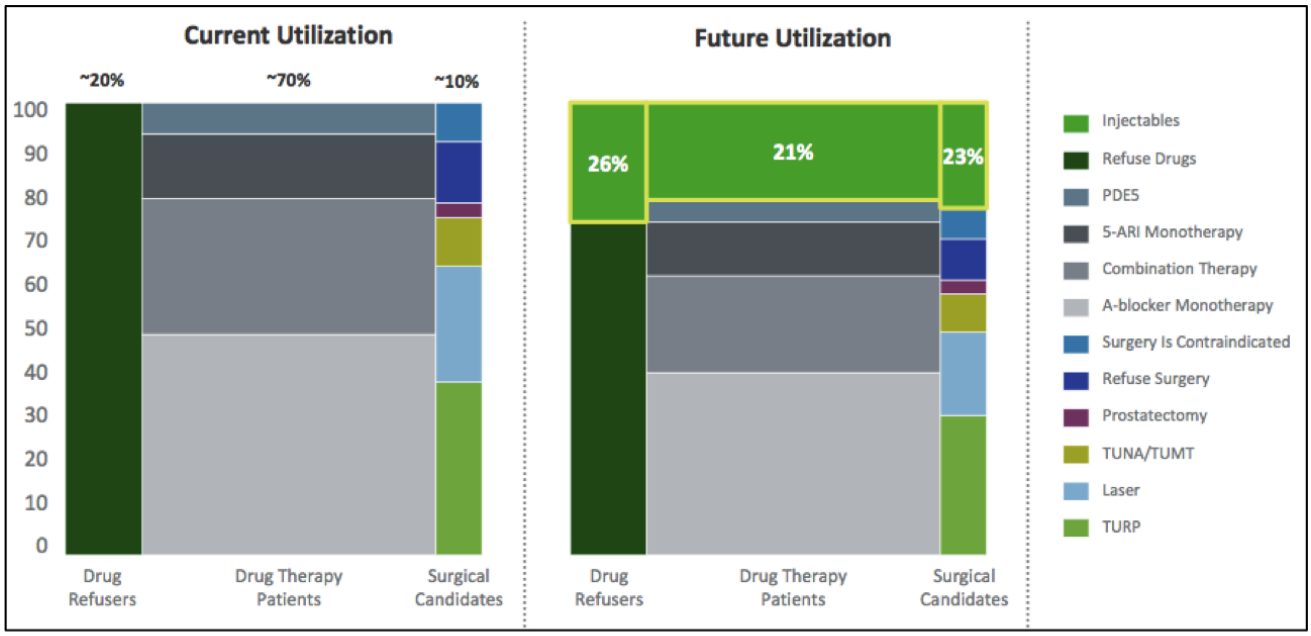
The results were similar when PRX302 was compared to different surgical options for treating BPH.



Source: Sophiris Bio, Inc.

In regards for how urologists currently treat their patients and how PRX320 would fit into their armamentarium, the results from Sophiris' market analysis indicate that PRX320 could potentially have sizeable uptake and be utilized to treat patients that currently refuse pharmacologic therapy, those on drug therapy, and those that could be treated

with surgery.



Source: Sophiris Bio, Inc.

Development Plan for PRX302 in BPH

Sophiris is currently evaluating options to advance PRX302 further in development for the treatment of BPH. A second Phase 3 clinical trial will be required in order to apply for approval with the FDA, which will cost a significant amount of money (we estimate approximately $35 million). While the company is currently uncertain about how exactly the second Phase 3 trial will be funded, it is likely that a non-dilutive partnership or royalty agreement will be utilized and that a second Phase 3 trial would not be initiated until such arrangement was procured.

Indication #2: Localized Prostate Cancer

Prostate cancer is the most common non-cutaneous cancer diagnosed in men. It is typically a slow growing cancer, although it still accounts for approximately 10% of all cancer related deaths in men. Currently, most of the cases of prostate cancer are found through routine screening of prostate specific antigen (PSA) level, although some cases are also identified as an incidental pathological finding when tissue is removed during transurethral resection to manage obstructive prostatic symptoms. Almost 95% of all prostate cancers are adenocarcinomas (American Cancer Society), meaning that it arises from epithelial tissue that has glandular origin.

The American Cancer Society estimates that approximately 180,890 men will be diagnosed with prostate cancer in 2016, while approximately 26,120 men will die from the disease (SEER database). Approximately 80% of those diagnosed will have localized disease. Half of those will have low-risk disease that is unlikely to ever spread outside of the prostate, however the other half of those with localized disease will have intermediate- or high-risk disease that is more suited to treatment.

The disease is quite rare in men less than 40 years of age, and is still uncommon in men younger than 50. Sixty percent of cases are in men aged 65 or older and the average age of diagnosis is 66. Prevalence rates are significantly higher in African-Americans than in White or Hispanic populations, although the exact reasons for this are unclear (Hoffman *et al*., 2001). In addition to age and race, other risk factors include geography, as most cases occur in North American, Northwestern Europe, Australia, and the Caribbean Islands, and genetics, as prostate cancer appears to run in some families.

Prostate Cancer Screening

There are currently two screening tests available to detect prostate cancer: the digital rectal exam (DRE) and the prostate specific antigen (PSA) test. There is controversy surrounding their use because, while they do detect cancer earlier, it is unclear at this point whether regular screening using these two tests saves lives. This is because some prostate cancers are slow growing, and many times a patient that has prostate cancer is more likely to die

from another cause before they die from prostate cancer due to advanced age or other comorbid conditions.

PSA: Prostate-specific antigen is an enzyme produced by normal prostate cells. The highest amounts of PSA are found in seminal fluid, however some PSA escapes the prostate and can be found in the blood. Increased levels of PSA are associated with prostate cancer. (Stamey *et al*., 1987). The PSA test became commercially available in 1986 and has been utilized to assess response to prostate cancer therapy, determine tumor progression, and screen for prostate cancer. Two large studies on prostate cancer screening were published in 2009: The Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial and The European Randomized Study of Screening for Prostate Cancer (ERSPC). The PLCO study randomized 76,693 men age 55 to 74 to either annual screening with PSA and DRE or usual care (Andriole *et al*., 2009) while the ERSPC study randomized 182,000 men to usual care or DRE and PSA screening every four years (Schroder *et al*., 2009). The PLCO study found approximately 17% more cancers in the screening group, however there was no difference in cancer-related deaths between the groups. The ERSPC study found 39% more cancers in the screening group along with a 20-31% reduction in prostate cancer death in the screening arm compared to control. Both studies found that men with a very low PSA level (0-1.0 ng/mL) are at a low risk of developing a clinically significant prostate cancer within the next few years.

Current screening guidelines from the American Cancer Society notes that testing for PSA may reduce the likelihood of dying from prostate cancer, however there are serious risks associated with the test in regards to treating prostate cancer that would not have caused ill effects if left undetected (Wolf *et al*., 2010).

The National Comprehensive Cancer Network (NCCN) has issued updated guidelines in regards to PSA testing:

- Obtain PSA testing in healthy men aged 45 to 70 years and older.
- For men aged 45-49 years with serum PSA levels below 0.7 ng/mL, retest at age 50 years.
- For men aged 45-49 years with serum PSA levels above 0.7 ng/mL, and those aged 50-59 years with serum PSA levels above 0.9 ng/mL, retesting may be performed every 1-2 years.
- Follow-up testing should be performed every 1-2 years for all men with PSA levels above 1.0 ng/mL.
- After age 70 years, PSA testing should be individualized, and indications for biopsy should be carefully evaluated.
- Refer patients for a prostate tissue biopsy when their serum PSA levels exceed 3.0 ng/mL.

Current Treatment Options for Prostate Cancer

Based on the fact that prostate cancers can be either slow or fast growing, along with the fact that it is typically diagnosed in older men, the American Urological Association has published guidelines for the initial evaluation and treatment of prostate cancer that takes into account the following two factors (Thompson *et al*., 2007):

- The patient's overall life expectancy (as determined by age and comorbidities) and overall health status
- The biologic characteristics of the tumor, together with its predicted aggressiveness and behavior

When a biopsy of the prostate is performed the results are usually given in the form of a Gleason score, which is a scoring system that assigns a number from 2-10 to describe how abnormal the prostate cells appear. A score of 2-4 means the cells still look like normal cells and pose little danger of spreading quickly. A score of 8-10 indicates that the cells are abnormal and likely to be aggressive. A score of 5-7 indicates intermediate risk. Treatment options will depend on the Gleason score, the patients' PSA score, and the tumor stage.

The following treatment options are currently available for localized prostate cancer:

Active Surveillance: The physician monitors the course of the disease and intervenes with treatment if the disease begins to progress. This is being utilized more often for patients with low-risk disease, which includes a T1-2a stage, PSA < 10 ng/mL., and a Gleason score <6. No randomized studies have been conducted to determine the optimal management of men on active surveillance, however monitoring of PSA every 3 months with repeat biopsies every one to two years is typically performed.

Radiation Therapy: This therapy may be delivered in the form of external-beam radiation therapy (EBRT) or brachytherapy (insertion of radioactive seeds into the prostate). EBRT includes 3-dimensional conformal radiation therapy (3D-CRT) and intensity-modulated radiation therapy (IMRT).

Radical Prostatectomy: This is removal of the entire prostate gland and is typically utilized in patients with locally advanced disease (stage T3). Androgen deprivation therapy is typically used in conjunction with

prostatectomy when the patient's disease has spread to local lymph nodes.

PRX302 in Localized Prostate Cancer

Treating prostate cancer with PRX302 is possible due to the high levels of enzymatically active PSA that surround prostate lesions. In addition, MRI imaging can be combined with real-time 3D ultrasound in order to target the treatment specifically to a histologically proven, clinically significant lesion, thus sparing surrounding healthy prostate tissue and offering a more favorable safety profile.

Thus far PRX302 has been tested in a proof-of-concept clinical study in patients with localized low-to-intermediate risk prostate cancer (NCT02499848). It was a single center, open label, six month study in 18 men that were administered PRX302 to treat a single, histologically proven, clinically significant lesion. Patients needed to have a Gleason score of 7 and ≤ 10 mm Maximum Cancer Core Length (MCCL) or a Gleason score of 6 and > 3 mm MCCL. The primary outcome of the study was safety and tolerability over six months with secondary outcomes examining histological and MRI evidence of tumor control over six months.

The company released biopsy results from the 18 patients in June 2016. The data showed that two men experienced complete ablation of their targeted tumor with no evidence of tumor remaining at six months, seven men experienced a partial response, defined as either a reduction in the MCCL or a reduction in Gleason pattern, and nine patients had no response to treatment.

Two very important findings from the study in relation to dosing and administration of PRX302 were identified that could lead to greater efficacy in future clinical trials:

- In the BPH clinical trials, PRX302 was administered at a dose of 0.6 µg/g of prostate tissue while in the prostate cancer trial it was administered at 5 µg/g of prostate tissue. One of the key findings from the prostate cancer trial was that dosing should be performed based on the size of the tumor, not the prostate. An analysis of treatment response based on the size of the tumor for the Phase 2a trial showed that most of the responders in the study received > 500 µg PRX302/g of tumor while for those that did not respond most received < 500 µg PRX302/g of tumor.

- The delivery of PRX302 will be optimized in future trials by attaching the injection needle to an infusion pump such that the drug can be administered slowly, thus allowing it to diffuse into the tumor cells and surrounding regions. The company reported that some of the patients in the Phase 2a study had tumors that were very dense, and when the drug was injected it was not able to properly saturate the tumor. By decreasing the rate at which the drug is injected, the company believes that PRX302 will be more likely to stay in the tumor microenvironment and fully penetrate the tumor tissue.

The fact that two patients saw a complete response in the proof-of-concept clinical trial is very encouraging, as the study was only designed to allow for a greater understanding of the optimal dose and delivery method for PRX302. Based on the data obtained thus far, we believe that PRX302 could offer men with low-to-intermediate risk prostate cancer the potential to have their lesion ablated, or at least decreased to a size that warrants active surveillance as opposed to radical treatment (e.g., radical prostatectomy).

Development Plan for PRX302 in Prostate Cancer

Sophiris will follow up on the results of the Phase 2a clinical trial of PRX302 in prostate cancer with a Phase 2b study involving approximately 40 patients with localized clinically significant low to intermediate risk prostate cancer that should begin before the end of 2016. As mentioned above, the dose of PRX302 is likely to be based on the size of the tumor, and will likely be on the order of 1000 µg PRX302/g of tumor. Administration of the drug will be performed with an infusion pump to decrease the rate of injection and standardize the treatment delivery across clinical sites. We anticipate topline results to be released before the end of 2017. We believe this trial will cost approximately $4 to $6 million.

Financials and Capital Structure

As of June 30, 2016, Sophiris had approximately $8.3 million in cash and cash equivalents. On August 22, 2016 the company announced a public offering of common stock and warrants that resulted in gross proceeds of approximately $26.0 million. We believe the company has cash to fund operations into 2018. As of June 30, 2016, the company had $4.6 million in principal outstanding from a $6.0 million loan and security agreement with Oxford Finance, LLC that was entered into on June 30, 2014.

As of August 2, 2016, the company had approximately 22.6 million common shares outstanding, which includes the approximately 3.57 million shares that were sold in connection with the public offering that closed on May 11, 2016. Following the public offering that closed on August 26, 2016, we estimate that the company now has approximately 29.1 million common shares outstanding. There are approximately 2.0 million stock options outstanding with a weighted average exercise price of $4.07 along with approximately 5.5 million warrants, although 0.6 million of these have an exercise price of $22.56.

Risks to Consider

The company is currently deciding the best path forward to continue development of PRX302 in BPH: Sophiris has engaged Oppenheimer and Co. as its financial advisor to evaluate strategic alternatives to advance PRX302 in clinical testing. Conducting an additional Phase 3 clinical trial in BPH, which is necessary for filing a Biologics Licensing Application (BLA) with the FDA, will cost approximately $35 million. Sophiris has indicated that the most likely path forward in BPH is through a non-dilutive, royalty-based collaboration, however no collaboration currently exists and a decision on the best path forward has not been made thus far.

There is significant competition in the treatment of BPH and prostate cancer: PRX302 will compete will numerous BPH therapeutics, which include both surgical and pharmaceutical treatment options. For prostate cancer, PRX302 will compete with surgical treatment options and radiation treatment. Even if the FDA eventually approves PRX302, there is no guarantee that doctors and/or patients will be willing to use it.

The terms of the senior debt facility require meeting certain operating covenants: The company entered into a $6 million senior secured loan with Oxford Finance LLC in June 2014. The loan is secured by a lien covering all of the company's assets and intellectual property. Any event that Oxford believes results in a material adverse change could result in a declaration of default and have a materially adverse effect on the company.

MANAGEMENT PROFILES

Randall E. Woods – President and Chief Executive Officer

Randall Woods joined Sophiris as Chief Executive Officer in August 2012 and brings with him 40 years of biotech and pharmaceutical leadership experience. Prior to joining Sophiris, Mr. Woods was President and CEO of Sequel Pharmaceuticals, a spin-out of NovaCardia developing a potential treatment for atrial fibrillation. Mr. Woods was previously the President and CEO of NovaCardia, a pharmaceutical company focused on cardiovascular diseases until its acquisition by Merck & Co for $350 million in 2007. Prior to NovaCardia, Mr. Woods was President and CEO of Corvas International, a publicly held biopharmaceutical company focused on cardiovascular disease and cancer until its acquisition by Dendreon in 2003. Before joining Corvas, he served as President of Boehringer Mannheim's U.S. Pharmaceutical operations, and spent 20 years at Eli Lilly & Company in various sales and marketing positions. Mr. Woods is a past Chairman for the Advisory Board of UC San Diego's Sulpizio Family Cardiovascular Center and is a past Chairman of the Board of Directors for BIOCOM, a life science industry association in Southern California. Mr. Woods serves on the Board of Arena Pharmaceuticals and is Chairman of the Board for Sorbent Therapeutics. He received his B.S. in Biology and Chemistry from Ball State University and an MBA in Marketing from Western Michigan University.

Alison Hulme, PhD – Chief Operating Officer

Dr. Hulme has been Chief Operating Officer and Head of Research and Development at Sophiris since April 2011, and she brings over 20 years of drug development experience to the company. From January 2005 to October 2009, Dr. Hulme served as Executive Vice President of Autoimmune, Tysabri, Global Development and Head of Autoimmune and Tysabri Franchise at Elan Corporation, plc (also known as Elan Pharmaceuticals), a neuroscience-focused biotechnology company. She served as Executive Vice President and head of global development at Elan Pharmaceuticals from October 1995 to January 2005. Previously, Dr. Hulme held several positions in clinical research at Glaxo Wellcome Pharmaceuticals and served as lecturer at Luton University. Dr. Hulme holds a first class honors Degree in Science from Luton University and a Ph.D. from Cranfield Institute of Technology.

Peter T. Slover – Chief Financial Officer

Mr. Slover has been Chief Financial Officer at Sophiris since January 2013. He previously served as Head of Finance and Principal Accounting Officer from April 2012 to January 2013. From April 2004 to April 2012, Mr. Slover held a variety of significant management positions at Anadys Pharmaceuticals, Inc., a public biotechnology company, including Vice President, Finance and Operations, a position that he held from July 2009 to April 2012, Senior Director, Finance and Corporate Controller, Senior Manager, Financial Reporting and Internal Controls and Manager of Financial Reporting. Prior to joining Anadys, Mr. Slover was an auditor at KPMG LLP, where he spent seven years in public accounting. Mr. Slover is a Certified Public Accountant in the State of California. He received a B.S. degree in Business Administration from Shippensburg University.

VALUATION

We are initiating coverage of Sophiris Bio, Inc. (SPHS) with a $6.00 valuation. Sophiris is a biopharmaceutical company developing treatments for urological diseases. The company's technology is focused on PRX302 (topsalysin), a biologic treatment for benign prostatic hyperplasia (BPH) and clinically significant low to intermediate risk localized prostate cancer.

PRX302

PRX302 (topsalysin) is a genetically modified form of proaerolysin, a bacterial protein that binds to the surface of target cells, forming a transmembrane complex that opens pores in the cell surface and allows for the release of small molecules and ions critical for cell function. PRX302 is a prodrug that is activated through cleavage by prostate specific antigen (PSA), a protease produced by the prostate gland. Protease inhibitors inactivate PSA in the bloodstream, thus enzymatically active PSA is only found in normal and malignant prostate tissue. This specificity of PSA activity allows for the targeting of drugs to the prostate, with limited systemic side effects. PRX302 is further targeted through administration to patients through an ultrasound-guided series of injections into the prostate.

PRX302 in BPH

A randomized, double blind, placebo controlled Phase 3 clinical trial was performed in 479 men suffering from BPH randomized 1:1 to receive PRX302 or placebo. Results from the study showed that injection of PRX302 resulted in a statistically significant improvement in IPSS total score from baseline over 52 weeks (7.60 vs. 6.58; *P*=0.043). A secondary analysis of IPSS total score showed a maximal effect at week 18 between PRX302-treated and placebo-treated patients (8.31 vs. 6.89; *P*=0.012).

Sophiris is currently evaluating options to advance PRX302 further in development for the treatment of BPH. A second Phase 3 clinical trial will be required in order to apply for approval with the FDA, which will cost a significant amount of money (we estimate approximately $35 million). While the company is currently uncertain about how exactly the second Phase 3 trial will be funded, it is likely that a non-dilutive partnership or royalty agreement will be utilized and that a second Phase 3 trial would not be initiated until such arrangement was procured.

PRX302 in Prostate Cancer

PRX302 was studied in a single center, open label, six month study in 18 men with a single, histologically proven, clinically significant prostate tumor. Patients needed to have a Gleason score of 7 and ≤ 10 mm Maximum Cancer Core Length (MCCL) or a Gleason score of 6 and > 3 mm MCCL. The primary outcome of the study was safety and tolerability over six months with secondary outcomes examining histological and MRI evidence of tumor control over six months.

Results from the study showed that two men experienced complete ablation of their targeted tumor with no evidence of tumor remaining at six months, seven men experienced a partial response, defined as either a reduction in the MCCL or a reduction in Gleason pattern, and nine patients had no response to treatment. The fact that two patients saw a complete response in the proof-of-concept clinical trial is very encouraging, as the study was only designed to allow for a greater understanding of the optimal dose and delivery method for PRX302. Based on the data obtained thus far, we believe that PRX302 could offer men with low-to-intermediate risk prostate cancer the potential to have their lesion ablated, or at least decreased to a size that warrants active surveillance as opposed to radical treatment (e.g., radical prostatectomy).

Valuation

We value Sophiris using a probability adjusted discounted cash flow that takes into account potential future revenues from the sale of PRX302 in both BPH and prostate cancer. For both BPH and prostate cancer, we anticipate the company ultimately entering into collaboration before commercialization of PRX302. For modeling purposes, we are estimating a second Phase 3 study starting in BPH in 2018 and approval in 2021. For prostate cancer, we estimate the upcoming Phase 2b trial concluding by the end of 2017, a Phase 3 program completing by 2020 and approval in 2021.

Prostate cancer likely represents the greatest value proposition for the company, as PRX302 is highly differentiated from other therapies currently available and under development and the company generated very promising data from the proof-of-concept study that included two complete responses. We estimate approximately 180,000 men will develop prostate cancer in 2016 and that approximately 80% of those will have localized disease, 50% of which will require treatment for a total target population of approximately 72,000. We believe that PRX302 could attain 20% market share and have peak revenues of approximately $950 million in the U.S. and $850 million in the E.U. Using a 15% royalty rate, a 13% discount rate, and a 40% chance of approval, we estimate the net present value for PRX302 in prostate cancer to be $178 million.

For BPH, we model for a low market share for the approximately 4 million men who receive treatment for BPH and peak revenues of approximately $300 million. Using a 15% royalty rate, a 13% discount rate, and a 60% chance of approval, we estimate the net present value for PRX302 in BPH to be $46 million.

Combining the values for PRX302 in prostate cancer and BPH along with the company's current cash total and expected additional capital requirement of $30 million, we arrive at a net present value for the company of $219 million. Dividing this number by the fully diluted share count of approximately 36 million shares leads to a valuation of $6, and we note considerable upside is possible to this valuation with continued clinical success of PRX302 in the company's upcoming Phase 2b trial in prostate cancer.

PROJECTED FINANCIALS

Sophiris Bio, Inc.
Income Statement

Sophiris Bio, Inc.	2015 A	Q1 A	Q2 A	Q3 E	Q4 E	2016 E	2017 E	2018 E
PRX302 BPH	$0	$0	$0	$0	$0	$0	$0	$0
YOY Growth	-	-	-	-	-	-	-	
PRX302 Prostate Cancer	$0	$0	$0	$0	$0	$0	$0	$0
YOY Growth	-	-	-	-	-	-	-	
Grants & Collaborative Revenue	$0	$0	$0	$0	$0	$0	$0	$0
YOY Growth	-	-	-	-	-	-	-	
Total Revenues	**$0**	**$0**	**$0**	**$0**	**$0**	**$0**	**$0**	**$0**
YOY Growth	-	-	-	-	-	-	-	
Cost of Sales	$0	$0	$0	$0	$0	$0	$0	$0
Product Gross Margin	-	-	-	-	-	-	-	
Research & Development	$9.9	$0.9	$1.0	$1.0	$1.0	$3.9	$5.0	$8.0
General & Administrative	$3.6	$1.2	$1.4	$1.2	$1.2	$4.9	$5.5	$6.0
Other Expenses	$0	$0	$0	$0	$0	$0	$0	$0
Operating Income	($13.5)	($2.1)	($2.3)	($2.2)	($2.2)	($8.8)	($10.5)	($14.0)
Operating Margin	-	-	-	-	-	-	-	
Non-Operating Expenses (Net)	($0.7)	($0.1)	($1.8)	($0.1)	($0.1)	($2.1)	($0.5)	($0.5)
Pre-Tax Income	($14.2)	($2.2)	($4.1)	($2.3)	($2.3)	($10.9)	($11.0)	($14.5)
Income Taxes Paid	$0	$0	$0	$0	$0	$0	$0	$0
Tax Rate	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*
Net Income	**($14.2)**	**($2.2)**	**($4.1)**	**($2.3)**	**($2.3)**	**($10.9)**	**($11.0)**	**($14.5)**
Net Margin	-	-	-	-	-	-	-	
Reported EPS	**($0.84)**	**($0.13)**	**($0.21)**	**($0.09)**	**($0.08)**	**($0.47)**	**($0.37)**	**($0.45)**
YOY Growth	-	-	-	-	-	-	-	
Basic Shares Outstanding	16.9	17.2	19.3	27.0	29.0	23.1	30.0	32.0

Source: Zacks Investment Research, Inc. *David Bautz, PhD*

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