Zacks Small-Cap Research

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Sophiris Bio, Inc.

(SPHS-NASDAQ)

SPHS: Dosing of Patients in Phase 2b Trial of Topsalysin in Prostate Cancer to Initiate Soon…

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

Current Price (05/18/17)	$2.43
Valuation	**$6.00**

OUTLOOK

On May 15, 2017, Sophiris Bio, Inc. (SPHS) announced financial results for the first quarter of 2017 and provided a business update. The company announced that dosing of patients in the Phase 2b trial of topsalysin would begin as soon as final regulatory clearance is obtained for the diluent, which is expected this month. The trial is anticipated to enroll 40 patients who will be treated with topsalysin through MRI-assisted intraprostatic injection. Targeted biopsies will be performed six months following treatment, and we anticipate this data being available in the first quarter of 2018 for all patients. The protocol allows for an additional treatment with topsalysin if a patient has no treatment-related serious adverse events along with a clinical response from the first dose, but still has the presence of a clinically significant lesion. The final biopsy data from all patients who receive a second dose will be available in the fourth quarter of 2018.

SUMMARY DATA

52-Week High	**$5.95**
52-Week Low	**$0.83**
One-Year Return (%)	**176.14**
Beta	**1.59**
Average Daily Volume (sh)	**246,923**
Shares Outstanding (mil)	**30**
Market Capitalization ($mil)	**$73**
Short Interest Ratio (days)	**N/A**
Institutional Ownership (%)	**6**
Insider Ownership (%)	**1**
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)
2016	0.0 A	0.0 A	0.0 A	0.0 A	0.0 A
2017	0.0 A	0.0 E	0.0 E	0.0 E	0.0 E
2018					0.0 E
2019					0.0 E

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

	Q1 (Mar)	Q2 (Jun)	Q3 (Sep)	Q4 (Dec)	Year (Dec)
2016	-$0.13 A	-$0.21 A	-$0.17 A	-$0.02 A	-$0.49 A
2017	-$0.09 A	-$0.08 E	-$0.08 E	-$0.08 E	-$0.34 E
2018					-$0.33 E
2019					-$0.35 E

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WHAT'S NEW

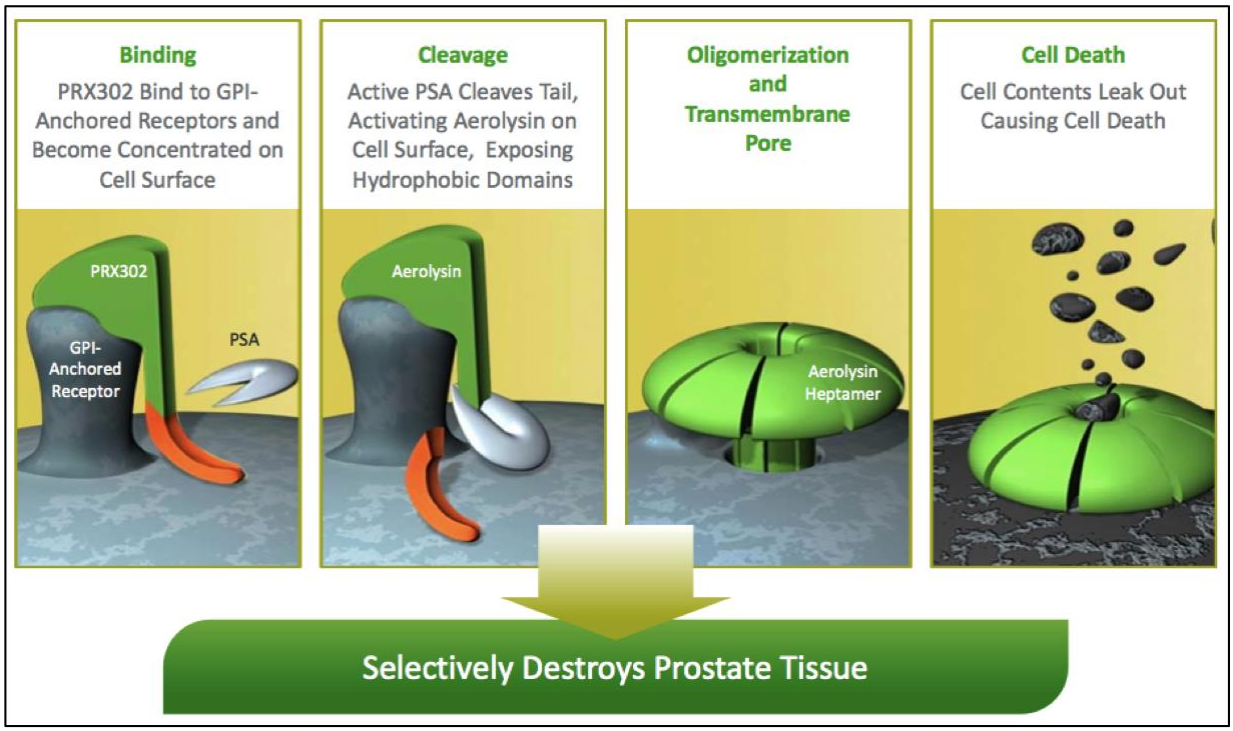
Business Update

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, topsalysin (PRX302), 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.

Topsalysin (PRX302)

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). A schematic showing the mechanism of action for topsalysin is shown in the following figure.



Source: Sophiris Bio, Inc.

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.

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.

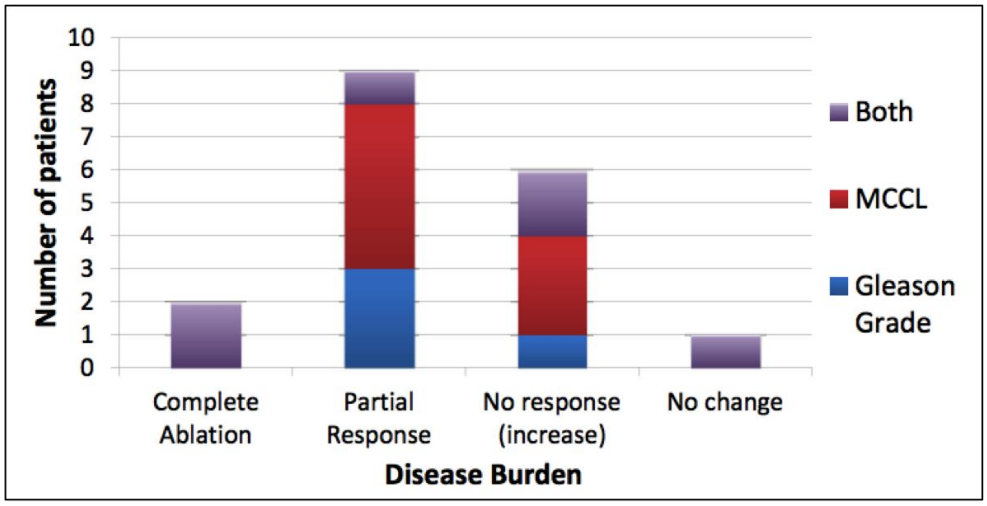
The disease is quite rare in men less than 40 years of age, and is still uncommon in men younger than 50. Sixty percent of cases are in men aged 65 or older and the average age of diagnosis is 66. Prevalence rates are significantly higher in African-Americans than in White or Hispanic populations, although 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.

Topsalysin in Localized Prostate Cancer

Treating prostate cancer with topsalysin 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.

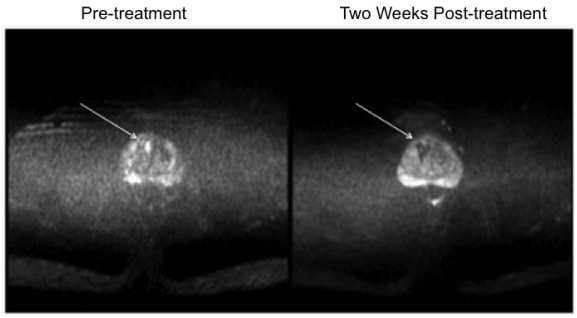
Thus far topsalysin has been tested in a proof-of-concept clinical study in patients with localized low-to-intermediate risk prostate cancer (NCT02499848). It was a single center, open label, six month study in 18 men that were administered topsalysin to treat a single, histologically proven, clinically 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. Recently, the company announced that two of the patients who were classified as “non-responders” should have been classified as “partial responders”, thus 11/18 patients showed at least some reduction in tumor due to treatment with topsalysin. The results are all summarized in the following graph.



Source: Shanmugabavan *et al*., 2017

On May 15, 2017, the company announced that data from the Phase 2a study was presented at the 112th American Urological Association Meeting. The poster included an example of a radiological response seen at two weeks (below left) as well as secondary outcomes focused on sexual and urinary function, which showed good preservation of pre-treatment function (below left).



Source: Bass *et al*., 2017

Score	Mean at Baseline (SD)	Mean at 24 Wks (SD)	Mean Change from Baseline (SD)
IPSS	8.9 (6.28)	7.3 (6.63)	-1.6 (2.4)
ULCA EPIC Urinary Domain	87.6 (13.07)	88.1 (12.7)	0.5 (9.63)
IIEF	50.5 (20.98)	50.6 (18.86)	0.1 (17.47)

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

- Topsalysin was administered at a dose of 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 topsalysin/g of tumor while for those that did not respond most received < 500 µg topsalysin/g of tumor.

- The delivery of topsalysin will be optimized in future trials by using a spring needle 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 topsalysin 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 topsalysin. Based on the data obtained thus far, we believe that topsalysin 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).

Dosing in Phase 2b Trial Set to Begin

Sophiris has initiated a Phase 2b clinical trial of topsalysin in patients with localized clinically significant low to intermediate risk prostate cancer (NCT03081481). The trial is expected to enroll 40 patients and is taking place at sites in both the U.S. and U.K. Patient dosing is expected to begin as soon as final regulatory clearance is obtained for the diluent, which is expected this month. Six months following treatment with topsalysin, a targeted biopsy will be performed of the treated area. All biopsy data should be available from the 40 patients in the first quarter of 2018. The study includes an option to re-treat the targeted lesion with a second dose of topsalysin, followed by a second targeted biopsy six months following the second dose. In order to receive a second dose, a patient cannot have experienced a significant adverse event attributable to topsalysin or the dosing procedure and the patient will need to have had a clinical response from the first dose but still have a clinically significant lesion. Final biopsy data from all patients who receive a second dose of topsalysin will be available by the fourth quarter of 2018.

Financial Update

On May 15, 2017, Sophiris announced financial results for the first quarter of 2017. As expected, the company did not report any revenues during the quarter. Net loss for the first quarter of 2017 was $2.6 million, or $0.09 per share. R&D expenses were $1.2 million for the first quarter of 2017, compared to $0.9 million during the first quarter of 2016. The increase was due to costs associated with the Phase 2b trial of topsalysin in prostate cancer along with increased manufacturing costs. G&A expenses were $1.4 million for the first quarter of 2017 compared to $1.2

million for the first quarter of 2016. The increase was due to non-cash stock-based compensation expense. Sophiris exited the first quarter of 2017 with approximately $25.7 million in cash, cash equivalents, and marketable securities. We believe this will be sufficient to fund operations to the end of 2018. As of May 10, 2017, Sophiris had approximately 30.1 million common shares outstanding and when factoring options and warrants a fully diluted share count of approximately 38.6 million.

Valuation

We value Sophiris using a probability adjusted discounted cash flow that takes into account potential future revenues from the sale of topsalysin in both BPH and prostate cancer. For both BPH and prostate cancer, we anticipate the company ultimately entering into collaboration before commercialization of topsalysin. For modeling purposes, we are estimating a second Phase 3 study starting in BPH in 2018 and approval in 2022. For prostate cancer, we estimate a Phase 3 program completing by 2021 and approval in 2022.

Prostate cancer likely represents the greatest value proposition for the company, as topsalysin 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 2017 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 topsalysin 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 topsalysin 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 topsalysin in BPH to be $46 million.

Combining the values for topsalysin 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 $223 million. Dividing this number by the fully diluted share count of approximately 38.6 million shares leads to a valuation of approximately $6, and we note considerable upside is possible to this valuation with continued clinical success of topsalysin in the company's Phase 2b trial in prostate cancer.

PROJECTED FINANCIALS

Sophiris Bio, Inc.
Income Statement

Sophiris Bio, Inc.	2016 A	Q1 A	Q2 E	Q3 E	Q4 E	2017 E	2018 E	2019 E
Topsalysin BPH	$0	$0	$0	$0	$0	$0	$0	$0
YOY Growth	-	-	-	-	-	-		
Topsalysin 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	$3.5	$1.2	$1.2	$1.2	$1.2	$4.8	$5.0	$7.5
General & Administrative	$6.8	$1.4	$1.3	$1.3	$1.3	$5.3	$6.0	$6.0
Other Expenses	$0	$0	$0	$0	$0	$0	$0	$0
Operating Income	($10.3)	($2.6)	($2.5)	($2.5)	($2.5)	($10.1)	($11.0)	($13.5)
Operating Margin	-	-	-	-	-	-		
Non-Operating Expenses (Net)	($0.9)	($0.0)	($0.1)	($0.1)	($0.1)	($0.3)	($0.5)	($0.5)
Pre-Tax Income	($11.2)	($2.6)	($2.6)	($2.6)	($2.6)	($10.4)	($11.5)	($14.0)
Income Taxes Paid	$0	$0	$0	$0	$0	$0	$0	$0
Tax Rate	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*
Net Income	**($11.2)**	**($2.6)**	**($2.6)**	**($2.6)**	**($2.6)**	**($10.4)**	**($11.5)**	**($14.0)**
Net Margin	-	-	-	-	-	-		
Reported EPS	**($0.49)**	**($0.09)**	**($0.08)**	**($0.08)**	**($0.08)**	**($0.34)**	**($0.33)**	**($0.35)**
YOY Growth	-	-	-	-	-	-		
Basic Shares Outstanding	23.0	30.1	30.8	31.0	31.5	30.9	35.0	40.0

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

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