Zacks Small-Cap Research

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Can-Fite Biopharma Ltd. (CANF - NYSE)

CANF: Preparing for Phase 3 Clinical Trials for CF101 in Rheumatoid Arthritis and Psoriasis…

Current Recommendation	**Hold**
Prior Recommendation	N/A
Date of Last Change	04/14/2015
Current Price (09/01/15)	$1.77
Target Price	**$3.00**

INITIATION

On August 27, 2015 Can-Fite Biopharma Ltd. released financial results for the six months ending June 30, 2015. During the second quarter, the company had a net loss of $1.7 million, or $0.07 per share. The company ended the second quarter of 2015 with $7.7 million in cash and cash equivalents.

The company is currently focused on preparing a Phase 3 clinical trial protocol for CF101 in the treatment of psoriasis, discussing with EU regulators the path forward for CF101 in rheumatoid arthritis, the ongoing Phase 2 clinical trial of CF102 in patients with liver cancer, and the preparation of an investigational new drug (IND) application for CF602 for the treatment of erectile dysfunction.

SUMMARY DATA

52-Week High	**$5.54**
52-Week Low	**$1.61**
One-Year Return (%)	**-54.38**
Beta	**4.07**
Average Daily Volume (sh)	**31,434**
Shares Outstanding (mil)	**11**
Market Capitalization ($mil)	**$19**
Short Interest Ratio (days)	**1.88**
Institutional Ownership (%)	**4**
Insider Ownership (%)	**N/A**
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 2015 Estimate	**N/A**
P/E using 2016 Estimate	**N/A**

Risk Level	**Above Average**
Type of Stock	**Small-Growth**
Industry	**Med-Biomed/Gene**

ZACKS ESTIMATES

Revenue

(In millions of $)

	Q1 (Mar)	Q2 (Jun)	Q3 (Sep)	Q4 (Dec)	Year (Dec)
2014	0 A	0 A	0 A	0 A	0 A
2015	0 A	0 A	0 E	0 E	0 E
2016					0 E
2017					0 E

Earnings per Share

(EPS is operating earnings before non-recurring items)

	Q1 (Mar)	Q2 (Jun)	Q3 (Sep)	Q4 (Dec)	Year (Dec)
2014	-$0.11 A	-$0.10 A	-$0.06 A	-$0.10 A	-$0.37 E
2015	-$0.02 A	-$0.07 A	-$0.05 E	-$0.06 E	-$0.20 E
2016					-$0.35 E
2017					-$0.33 E

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WHAT'S NEW

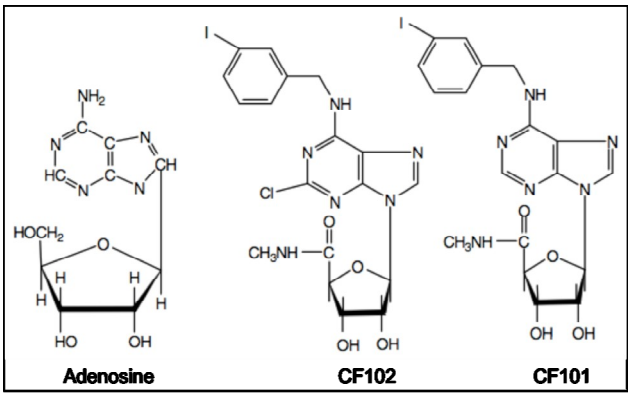
Financial Update

On August 27, 2015, Can-Fite Biopharma Ltd. (NYSE: CANF) announced financial results for the second quarter and first six months of 2015. The company reported negligible revenues for the quarter. R&D expenses for the second quarter of 2015 were $0.94 million, compared to $1.4 million for the same period in 2014. This decrease was attributable to the completion of the Phase 2/3 psoriasis clinical trial during the first quarter of 2015. G&A expenses for the second quarter of 2015 were $0.62 million, compared to $0.73 million in 2014. Net loss for the quarter was $1.7 million, compared to $1.8 million for the corresponding quarter in 2014. The decrease in net loss was mostly attributable to decrease operating expenses.

The company exited the second quarter of 2015 with approximately $7.75 million on cash and cash equivalents, compared to $9.58 million on Dec. 31, 2014. The decrease in cash was due to operating expenses offset by an upfront payment of $1.36 million received from Cipher Pharmaceuticals (NASDAQ: CPHR). The company burned approximately $1.8 million in the first six months of 2015 and received $1.36 million from Cipher, thus the pro-forma burn rate was approximately $3.2 million. We anticipate a similar burn rate for the second half of 2015.

Update on CF101 and CF102

Can-Fite is developing CF101 for the treatment of psoriasis and rheumatoid arthritis (RA), and CF102 for the treatment of hepatocellular carcinoma (HCC). The compounds are derivatives of adenosine, and are prepared in a simple four-step chemical process. Doses of 0.1 mg, 1.0 mg, 2.0 mg, and 4.0 mg have been tested in human clinical trials thus far.



Source: Fishman *et al.*, 2002

Each molecule is a selective agonist for the A_3AR receptor, as shown by the K_i values in the following table for each compound for the different ARs.

A_3AR Agonist	A_1	A_{2a}	A_{2b}	A_3
CF101 (IB-MECA)	51	2,900	11,000	1.8
CF102 (Cl-IB-MECA)	220	5,360	>100,000	1.4

K_i values (nM), *Adapted from*: Jacobson *et al.*, 2006

Both compounds have been evaluated in a number of preclinical and clinical studies. No safety issues related to toxicology have been reported thus far from studying the compounds in mice, rats, and dogs. Phase 1 clinical testing in humans showed CF101 to have linear pharmacokinetic parameters in doses up to 10 mg. Single oral doses up to 5 mg and repeated doses up to 4 mg every 12 hours were safe and well tolerated. Increased heart rate was noted after a single 10 mg dose. A dose-related increase in heart rate was noted on day 1 of the multiple dose study; however, by day 7 this effect was no longer present. Importantly, no increase in QT interval was noted with the increased heart rate. Based upon the Phase 1 studies, 4 mg twice a day was selected as the highest dose for Phase 2 studies.

Currently, the company is focused on three main areas with CF101 and CF102:

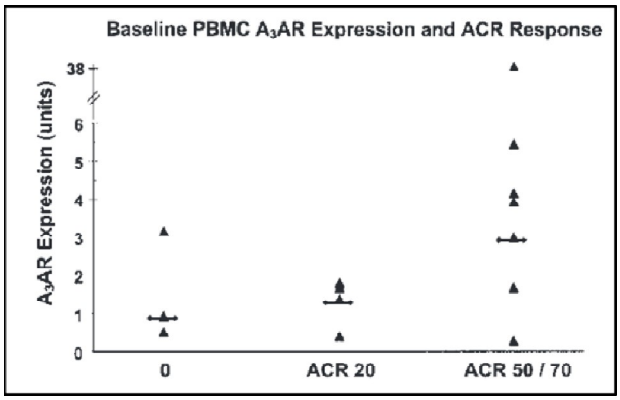
1) Developing the Phase 3 clinical trial protocol for CF101 in psoriasis.
2) Discussing the Phase 3 clinical trial plan for RA with regulators in the EU in order to clarify the path forward.
3) Continuing to enroll patients in the Phase 2 clinical trial of CF102 in patients with liver cancer

Proposed Generic Name for CF101 is Piclidenoson

On July 29, 2015, Can-Fite announced that the World Health Organization's International Nonproprietary Name (INN) group has accepted the proposed name "piclidenoson" for the company's lead asset, CF101. INNs are utilized to distinguish pharmaceutical substances as each is a globally recognized unique name that allows for the clear identification, safe prescribing, and clear communication about drug substances worldwide.

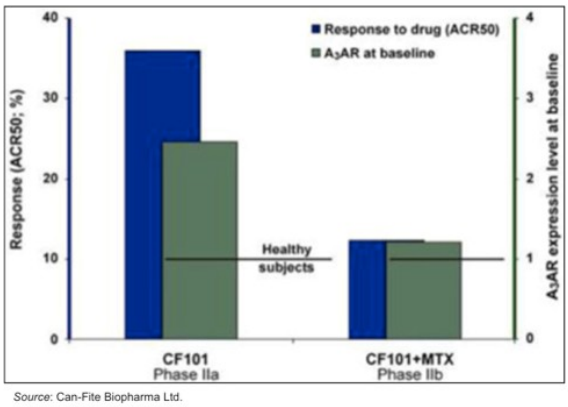
Update on CF101 in Rheumatoid Arthritis

CF101 was initially tested in a Phase 2a clinical trial evaluating three different doses in 74 RA patients: 0.1 mg, 1.0 mg, and 4.0 mg (Silverman *et al*., 2008). Of the 74 patients who were randomized into the study, 50 finished the trial with 24 patients withdrawing due to lack of efficacy (n=16), noncompliance (n=2), adverse events (n=3), or consent withdrawn (n=3). The primary outcome of the study was ACR20 after 12 weeks of treatment, which was 42.9%, 55.6%, and 41.7% of patients in the 0.1 mg, 1.0 mg, and 4.0 mg cohorts, respectively; however, these results were not statistically significant. Most adverse events reported were mild with the most common being headache, nausea, and rash. Interestingly, there seemed to be a correlation between A_3AR expression in PBMCs and response to treatment, as shown in the following figure, suggesting that A_3AR level could be utilized as a biomarker to select those patients most likely to respond to treatment.



***Source*: Silverman *et al*., 2008**

The company followed up the Phase 2a trial by conducting two separate Phase 2b trials of CF101 in combination with MTX in 230 patients and 252 patients. Both studies failed to show a statistically significant improvement in ACR20 in CF101 treated patients compared to placebo. Analysis of A_3AR expression revealed a possible reason for the failure of both studies: the patients in the Phase 2b studies all showed a low level of A_3AR expression, as shown in the following figure.

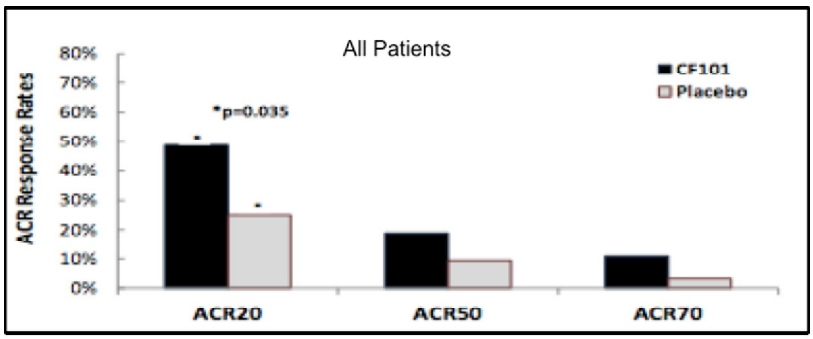


Source: Can-Fite Biopharma Ltd.

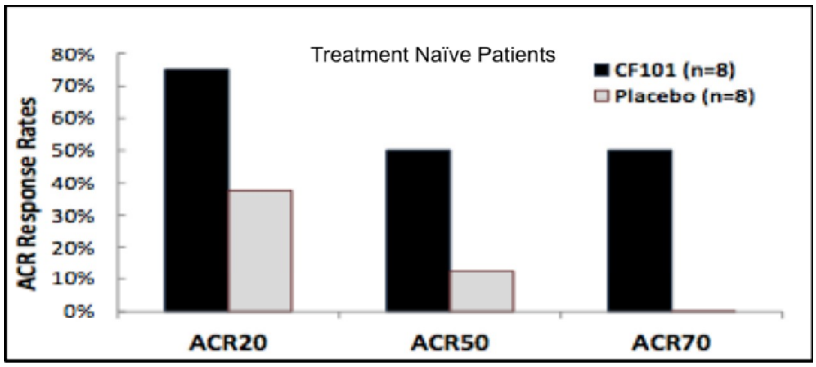
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The results from the Phase 2b trials were unexpected based upon data showing that RA patients have increased A_3AR expression compared to healthy controls (Madi *et al*., 2007). Due to the unsuccessful results using CF101 in combination with MTX, the company performed another Phase 2b study using CF101 as a monotherapy (Stoilov *et al*., 2014).

This was a multicenter, randomized, double blind, placebo controlled study comparing 1 mg CF101 to placebo (NCT01034306). The primary endpoint of the study was ACR20 after 12 weeks of treatment. Importantly, patients were enrolled into the study based on A_3AR expression level, defined as 1.5-fold over a predetermined normal population standard. Seventy percent of screened patients were found to have high levels of A_3AR. A total of 79 patients were randomized into the trial with 71 (90%) completing the 12 weeks of treatment. There was a statistically significant difference in ACR20 between CF101 (49%) and placebo (25%) treated patients (P = 0.04). ACR50 (19% vs. 9%) and ACR70 (11% vs. 3%) responses were not significant but both favored CF101 treatment. Interestingly, in a subpopulation of treatment-naïve patients (n=8 for both treated and placebo groups), the response to CF101 was much higher compared to the response of the whole population, with ACR20 of 75% and ACR50 and ACR75 of 50%.



Source: Stoilov *et al*., 2014



Source: Stoilov *et al*., 2014

While the results seen with treatment-naïve patients are encouraging, it must be kept in mind that they were obtained from a very small number of patients (n=8). However, given the fact that treatment with CF101 was able to result in 75% of patients attaining ACR20 at 12 weeks puts it in the same company as the top-selling RA therapeutics.

Opportunity in RA

At the end of 2014, Can-Fite announced the completion of the study design for the RA Phase 3 clinical trial. It will be a multicenter, randomized, double blind, placebo controlled parallel group study that will investigate the efficacy of CF101 dosed at 2 mg and 3 mg twice a day compared to placebo for 12 weeks. Approximately 300 patients will be enrolled and the study is likely to be initiated in the first half of 2016. The doses selected for this trial fall in between the 1 mg and 4 mg doses that were utilized in the Phase 2a trial that resulted in ACR20 at 12 weeks of 56% and 42%, respectively. The company is hoping to hit the peak of the bell-shaped dose response curve with either the 2 mg or 3 mg dose.

While the opportunity for CF101 in RA is quite large, we feel that there is a difficult path forward for CF101 as a stand-alone therapy. In CF101's favor, those patients with high A_3AR expression level (who are easily identified)

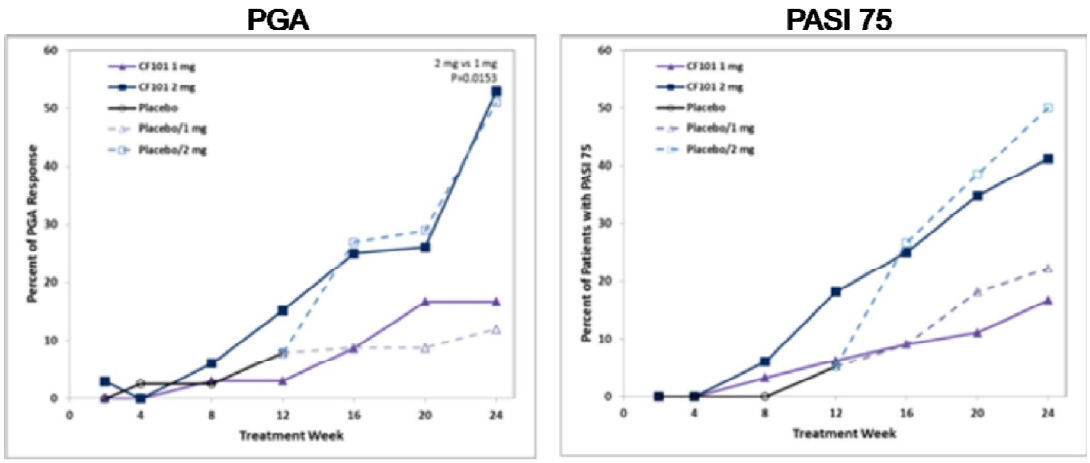
appear to respond best to treatment, treatment-naïve patients exhibited a strong response to treatment (ACR20 of 75%), CF101 is orally administered, and CF101 appears to have a very benign safety profile. The factors working against CF101 are that the RA market is highly competitive, most currently available therapeutics offer better efficacy that is achieved in a shorter period of time, and there is now an orally available therapy (Xeljanz®) that is just as efficacious as the biologic treatments.

At this point, what intrigues us most about the opportunity for CF101 in RA are 1) the drug appears to be quite safe, thus based on the differentiated mechanism of action there could be an opportunity for CF101 to be used in conjunction with other therapeutics, and 2) the market is so large that even garnering a tiny piece of it could be quite lucrative. Unfortunately, using CF101 as a combo therapy is not going to be tested in the upcoming Phase 3 clinical trial, thus we will not be able to gain any insight into whether this could be a possible path forward. It appears as if Can-Fite is planning to go forward with CF101 as a stand-alone treatment for RA. Given the fact that it is a $22 billion market means that even getting 1% peak market share represents a potential $200 million opportunity.

Update on CF101 in Psoriasis

Can-Fite originally initiated a Phase 2/3 clinical trial of CF101 in patients with moderate to severe psoriasis in 2011 (NCT01265667). The study enrolled 103 patients into one of three arms: 1 mg of CF101; 2 mg of CF101; or placebo. After 12 weeks of treatment, those in the placebo arm were randomized to receive either 1 or 2 mg of CF101 and the study continued for an additional 24 weeks.

An interim analysis was performed after 24 weeks of treatment, with the results showing a clear difference between patients in the 2 mg cohort and those receiving placebo. Importantly, there was a marked improvement in patients who were randomized to the 2 mg cohort following the first 12 weeks on placebo in both PGA and PASI75, as shown in the following figure.



Source: Can-Fite Biopharma Ltd.

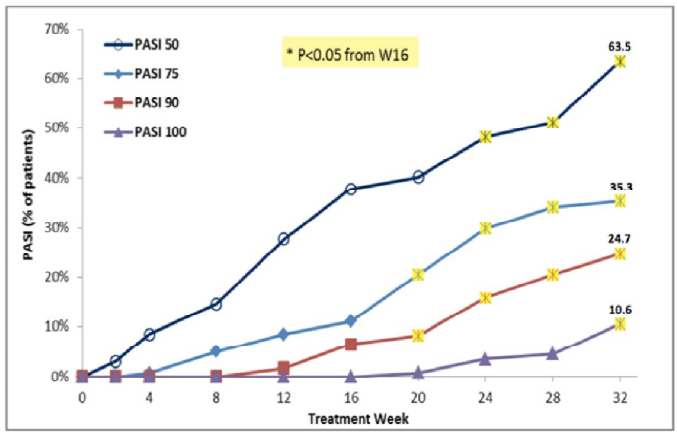
However, on March 30, 2015 Can-Fite announced topline results from the Phase 2/3 study showing that treatment with CF101 did not achieve the study's primary endpoint, which was evaluation of PASI75 after 12 weeks of treatment. The proportion of patients treated with CF101 who achieved PASI75 was 8.5% compared to 6.9% in the placebo group. With respect to PGA, 6.4% of patients treated with CF101 achieved a score of 0 or 1 compared to 3.4% of placebo patients.

We were quite surprised by the results when they were announced given the clear efficacy signal shown in the interim analysis. The PASI75 for CF101 treated patients appeared to be approximately 18% at the 12-week mark based on the graph shown above. This data was from 31 patients treated with CF101. The second cohort of patients totaled 112 and we calculate that they would have had a PASI75 of approximately 5.9% in order to average out to the final reported result of 8.5%. It is quite strange that there was such a dramatic decrease in efficacy between the two cohorts, and we still can't say for sure what might have occurred.

Further Analysis Reveals Positive Data From Phase 2/3 Study

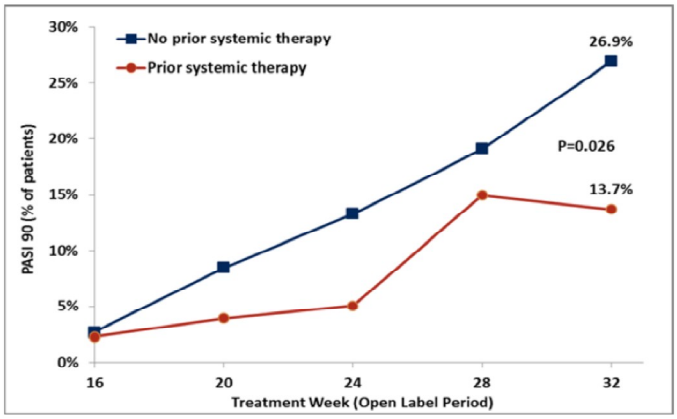
On April 27, 2015, Can-Fite announced favorable data from further analysis of the Phase 2/3 study. Specifically, after 32 weeks of treatment, 35.3% of patients treated with CF101 achieved PASI75 with a mean percent

improvement in PASI score of 57%. This means that, on average, patients who were treated with CF101 saw a 57% reduction in their psoriatic lesions. In addition, 24.7% and 10.6% of patients achieved PASI90 and PASI100, respectively, at week 32. PASI100 indicates a complete clearance of psoriatic lesions. Historically, patients treated with placebo achieve PASI90 or PASI100 only 1-2% of the time.



***Source*: Can-Fite Biopharma, Ltd.**

A subset analysis was performed examining patients who had previous systemic therapy compared to those who were systemic therapy naïve. PASI90 at week 32 was achieved in 26.9% of patients who had received no prior systemic therapy compared to 13.7% of patients who had received prior systemic therapy. The company believes that this data allows for the opportunity to develop CF101 as a first-line therapy in previously untreated patients with moderate-to-severe psoriasis who do not wish to be treated with currently available systemic therapies (e.g., monoclonal antibodies) due to safety concerns or due to an aversion to injections.



***Source*: Can-Fite Biopharma Ltd.**

Celgene's Otezla® is likely to be the main competitor for CF101 in psoriasis patients as it is 1) an oral medication like CF101 and 2) the data between the two compounds seems to be fairly comparable. The following table compares the data seen with CF101 in the Phase 2/3 study and Otezla®/placebo from the Phase 2 "Core Study" (NCT00773734).

We chose to use Otezla® data from that study for comparison due to 1) the comparable number of patients between the two studies; 2) Celgene reported PASI90 data from that study; and 3) the extension part of that study allows for direct comparison of time points between CF101 and Otezla®.

	2 mg CF101	30 mg Otezla®[a]	30 mg Otezla®[a] Extension Study	Placebo[a]
No. Patients	103	88	58	88
PASI Improvement From Baseline	Wk 32: 57.1%	Wk 16: 53.2% Wk 24: 56.8%	Wk 32: 72.7% Wk 40: 71.1% Wk 52: 65.3%	Wk 16: 20.3% Wk 24: -
PASI75	Wk 16: ~10% Wk 32: 35.3%	Wk 16: 40.9% Wk 24: 39.8%	Wk 32: 46.6% Wk 40: 34.5% Wk 52: 36.2%	Wk 16: 5.7% Wk 24: -
PASI90	Wk 16: ~7% Wk 32: 24.7%	Wk 16: 11.4% Wk 24: 14.8%	Wk 32: 19.0% Wk 40: 17.2% Wk 52: 13.8%	Wk 16: 1.1% Wk 24: -
PASI100	Wk 16: 0% Wk 32: 10.6%	Not recorded	Not recorded	Not recorded

[a]Data from Phase 2 "Core Study" (NCT00773734)
Source: Zacks SCR

There are a couple of takeaways from the preceding chart:

→ **CF101 has a slow onset**: It takes approximately four months longer to see the same efficacy from CF101 as is seen from Otezla®, as judged by the percent improvement in PASI from baseline and PASI75.

→ **But is efficacious**: Patient's continue to improve over time with CF101 but there appears to be a "plateau" effect with Otezla®, with some outcomes decreasing with time after peaking for Otezla® treated patients. For example, 47% of Otezla® treated patients achieved PASI75 at week 32, but this decreased to 36% by week 52. The same effect was seen for PASI90.

→ **And has a durable response:** CF101 appears to generate a higher PASI90: 25% of CF101 treated patients experienced PASI90 at week 32 (with that increasing linearly from week 12) compared to 19% of Otezla® treated patients at week 32 (with the percentage of Otezla treated patients experiencing PASI90 decreasing at week 40 and 52).

…How CF101 May Fit Into Psoriasis Treatment Landscape…

We've previously discussed how important it is for investors to understand just how many treatment options are available for patients with psoriasis, how many more therapeutics are likely to be approved in the very near future, and how CF101 could possibly find its niche in a highly competitive market.

The following table lists the medications that are currently available as well as those that we have identified that are under development, along with their clinical efficacy for the treatment of psoriasis:

Drug	Company	Biological Target	Time Point	Efficacy	Development	Dosage
Oral Therapeutics						
Otezla® (apremilast)	Celgene	PDE4	16 wks	PASI75 33%	Approved	30 mg BID
Xeljanz® (tofacitinib)	Pfizer	JAK1/3	16 wks	PASI75 59%	sNDA; PDUFA Oct. 2015	10 mg BID
CF101	Can-Fite	A_3AR	32 wks	PASI75 33%	Phase 3	2 mg BID
Injected Therapeutics						
Enbrel® (etanercept)	Amgen	TNF-α	12 wks	PASI75 49%	Approved	50 mg BIW
Humira® (adalimumab)	Abbvie	TNF-α	12 wks	PASI75 71%	Approved	40 mg every other week
Remicade® (infliximab)	Janssen	TNF-α	10 wks 10 wks	PASI75 80% PASI90 57%	Approved	5 mg/kg every 2 months
Stelara® (ustekinumab)	Janssen	IL-12/IL-23	12 wks	PASI75 67%	Approved	45 mg every 3 months
Cosentyx® (secukinumab)	Novartis	IL-17a	12 wks 12 wks	PASI75 82% PASI90 59%	Approved	300 mg every 4 weeks
Tildrakizumab	Merck/Sun Pharma	IL-23	16 wks	PASI75 74%	Phase 3; Data in 2015	200 mg every 4 weeks
Guselkumab	Janssen	IL-23	16 wks	PASI75 81%	Phase 3; Data in 2015	100 mg every 8 weeks
Ixekizumab	Eli Lilly	IL-17	12 wks	PASI75 78-90%	NDA in 2015	80 mg every 4 weeks
Brodalumab	AZN/Valeant	IL-17 receptor	12 wks	PASI75 86% PASI100 44%	NDA in 2015	210 mg every 2 weeks
Cimzia® (certolizumab pegol)	UCB/Dermira	TNF-α	12 wks	PASI75 75%	Phase 3 complete in 2017	200 or 400 mg every 2 weeks

Source: Company Data / Zacks SCR

Just recently, Amgen announced that it was withdrawing from a partnership with AstraZeneca for the development of brodalumab based on events of suicidal ideation and suicide in clinical trials. On September 1, 2015, AstraZeneca announced that it signed a collaboration agreement with Valeant Pharmaceuticals (VRX) whereby Valeant would be responsible for continued development and commercialization of brodalumab. Valeant plans to file a BLA in the fourth quarter of 2015, however given the bad publicity the drug has received it will likely not be a top-seller in the psoriasis market. Brodalumab is unique in targeting the IL-17 receptor, thus we doubt that other psoriasis treatments or drugs in development will show the same adverse effect. In addition, CF101 was not going to be able to compete with brodalumab due to inferior efficacy, thus the impact on the potential market size for CF101 is likely to be minimal.

We continue to believe that CF101 is going to have a very difficult time competing for any patient that would consider an injectable treatment. CF101 does appear to be efficacious in treating psoriasis; however, it takes approximately twice as long as the other currently available oral psoriasis medication (Otezla®) to achieve the same efficacy, and it is only about half as efficacious as Pfizer's Xeljanz®, which is likely to be approved for treating psoriasis in October 2015. This would seem to negate the advantage that CF101 has as a psoriasis treatment in being orally dosed.

However, one area where CF101 may have an advantage in terms of efficacy is with helping patients achieve PASI90, where head to head comparisons show more patients achieved PASI90 on CF101 than on Otezla®. If these results hold up in a larger Phase 3 trial, this could be a major selling point for CF101 as it attempts to gain market share in a highly competitive landscape. Another area that CF101 appears to have a large advantage is in regards to side effects. The following chart shows that there was a much higher rate of adverse events in patients treated with Otezla® compared to patients treated with CF101.

	2 mg CF101	30 mg Otezla®[a]	Placebo[a]
Any Adverse Event (AE)	25.5%	61.4%	38.6%
Infection AE	6.9%	15.9%	4.6%
Withdrawel due to AE	0%	11%	6%

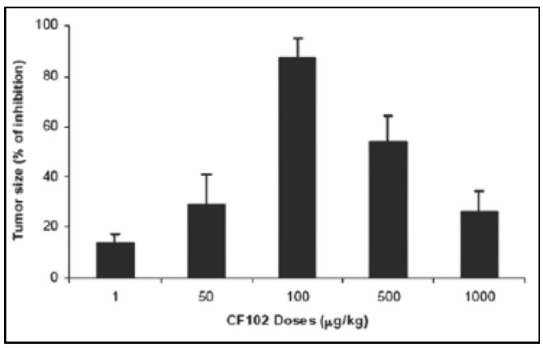
[a]Data from Phase 2 "Core Study" (NCT00773734)

Source: Zacks SCR

At this point, we are uncertain of how CF101 would be accepted by physicians and patients given the increased length of time necessary to achieve clinically similar results to Otezla® (or inferior results to soon to be available Xeljanz®), even with the strong safety record. We can imagine one path forward for CF101 as a psoriasis treatment may be as a "maintenance" therapy that is given to patients after beginning treatment with an injectable therapy. For instance, a patient could be treated with Amgen's Enbrel® for 12 weeks, and if they achieved a desirable clinical response they could then switch to CF101 to avoid the risk of severe side effects that long-term treatment with anti-TNF-α agents can produce. However, until Can-Fite releases details of the Phase 3 clinical plan for CF101 in psoriasis, we are unsure of how the company plans to position the drug.

Update on CF102 in Hepatocellular Carcinoma

Preclinical results showed that A_3AR is highly expressed in HCC tissue compared to adjacent healthy tissue, thus justifying the use of an A_3AR inhibitor as a therapeutic agent in HCC (Bar-Yehuda *et al*., 2008). This increased level of A_3AR was also noted in PBMCs from HCC patients that the tumor tissues were derived from. Treatment of HCC with CF102 in an orthotopic rat model resulted in growth inhibition and a bell shaped dose-dependent inhibitory effect, as shown in the following figure.



***Source*: Bar-Yehuda *et al*., 2008**

The preclinical results seen with CF102 were followed up by a Phase 1/2 trial in HCC patients. The open label, dose escalation study was undertaken in 18 HCC patients to test the safety, tolerability, and pharmacokinetics of CF102 at doses of 1 mg, 5 mg, and 25 mg twice a day. The compound exhibited good bioavailability and had linear pharmacokinetics. Median overall survival for all 18 patients was 7.8 months. In a subpopulation of patients (n=5) who were Child-Pugh B (liver disease staging system indicative of significant liver disease; discussed further below), median overall survival was 8.1 months. This compares to historical median overall survival rates in this patient subpopulation of approximately 4 months (Pressiani *et al*., 2013). Interestingly, one of the patients who presented with skin metastases showed complete metastasis regression during the three months of treatment with CF102.

Can-Fite Targeting HCC Patients with Child-Pugh B Liver Disease

The Child-Turcotte score was originally proposed over 50 years ago as a way to predict the outcome after liver surgery in patients with cirrhosis (Child, 1964). It included two continuous variables (bilirubin and albumin) and three discrete variables (ascites, encephalopathy, nutritional status). A modified version named Child-Pugh was published approximately 10 years later that included one alteration, the replacement of nutritional status with prothrombin time (Pugh *et al*., 1974). Each of the five categories is assigned a score of 1, 2, or 3 and the final score then corresponds to a Child-Pugh grade A (5 to 6 points), B (7 to 9 points) or C (10 to 15 points).

	1 point	2 points	3 points
Total bilirubin (µmol/L)	<34	34-50	>50
Serum albumin (g/L)	>35	28-35	<28
Prothrombin time (s)	<1.7	1.71-2.30	>2.30
Ascites	None	Mild	Moderate to Severe
Hepatic encephalopathy	None	Grade I-II (or suppressed with medication)	Grade III-IV (or refractory)

	Class A	Class B	Class C
Total points	5-6	7-9	10-15

Source: 2minutemedicine.com/Zacks SCR

Numerous studies have shown that the Child-Pugh score is an independent prognostic marker in a wide range of diseases, including alcoholic cirrhosis, hepatitis C related cirrhosis, ruptured esophageal varices, and primary biliary cirrhosis. In patients with HCC, Child-Pugh score is correlated with overall survival, as patients with Child-Pugh A consistently show increased survival over those with Child-Pugh B or C (Cabibbo *et al*., 2012).

Clinical experience with patients who are Child-Pugh B is somewhat limited. Nexavar® (sorafenib), the only currently approved systemic therapeutic for HCC, was approved on the basis of two randomized, double blind, placebo controlled clinical trials that showed an increased median overall survival of approximately 3 months for patients treated with Nexavar® compared to placebo (Llovet *et al*., 2008; Cheng *et al*., 2009). However, those trials were mostly restricted to patients who were Child-Pugh A (≥95%). Treating patients who were Child-Pugh B with Nexavar® has consistently shown decreased median overall survival compared to those who were Child-Pugh A (Hollebecque *et al*., 2011; Marrero *et al*., 2013).

Can-Fite is targeting HCC patients who have failed sorafenib therapy and are Child-Pugh B, and we have thus far been unable to locate any clinical trials that have specifically examined this patient population. There have been a number of recent clinical failures in second-line HCC therapy with a focus on Child-Pugh A, including:

- **Brivanib**: This is a dual tyrosine kinase inhibitor that potently inhibits vascular endothelial growth factor receptors (VEGFR)-1, 2, and 3 as well as fibroblast growth factor receptor (FGFR). In the BRISK-PS study it was tested in 395 HCC patients who had either progressed on/after or were intolerant to sorafenib therapy, with patients randomized 2:1 to receive brivanib or placebo (Llovet *et al*., 2013). 92% of patients were Child-Pugh A. Results showed no difference in overall survival between brivanib and placebo (9.4 months vs. 8.2 months, $P = 0.3307$). Exploratory endpoints showed a median time to progression of 4.2 months for brivanib and 2.7 months for placebo ($P < 0.001$) and an overall response rate of 10% for brivanib and 2% for placebo.

- **Everolimus (Afinitor™)**: This is an mTOR inhibitor that has been approved for the treatment of renal cell carcinoma. In the EVOLVE-1 trial it was tested in 546 HCC patients who had progressed on/after or were intolerant to sorafenib therapy, with patients randomized 2:1 to receive everolimus or placebo (Zhu *et al*., 2014). 97% of patients were Child-Pugh A. Results showed no significant different in overall survival between everolimus or placebo (7.6 months vs. 7.3 months, *P* = 0.68). Median time to progression for everolimus was 3.0 months and for placebo was 2.6 months.

HCC patients are a very difficult group to treat based on the usual advanced stage of the disease when it is diagnosed and the underlying liver damage that typically accompanies the condition. Patients with Child-Pugh B cirrhosis are even more difficult to treat, which is exemplified by the fact that most pharmaceutical companies won't even test a drug in that cohort. Can-Fite's strategy to test CF102 in HCC patients who are Child-Pugh B and have failed sorafenib is very risky, however the reward could be immense if the strategy pays off, as there is no current treatment option for these patients.

Opportunity in HCC

Can-Fite has initiated a multi-center, randomized, double blind, placebo controlled, Phase 2 trial of CF102 in patients with advanced HCC and Child-Pugh B cirrhosis (NCT02128958). A total of 78 patients are expected to be randomized 2:1 to receive 25 mg of CF102 or placebo twice a day for consecutive 28-day cycles. The study is currently enrolling patients in Israel and Europe. The primary outcome of the study is overall survival, which will not be evaluated until after 75 deaths have occurred. The first patient was dosed in December 2014 and we anticipate data from the study in mid-2016. Can-Fite recently announced that CF102 was granted Orphan Drug Status by the U.S. Food and Drug Administration (FDA) for the treatment of advanced HCC.

There are a large number of other medications currently in development for the treatment of HCC, including antiangiogenic agents, mTOR inhibitors, and growth factor receptor inhibitors. However, with only one drug approved for treating HCC, there is ample opportunity for other therapies that show efficacy in treating the disease. Can-Fite has chosen to focus on HCC patients who also have Child-Pugh B cirrhosis, which is indicative of more advanced liver disease, as CF102 showed somewhat better efficacy in treating those patients in the Phase 1/2 trial and did not appear to have toxic effects on the liver. With a benign side effect profile and positive proof-of-concept data, CF102 has the potential to stand out as a therapy for this hard-to-treat patient population.

Update on CF602 in Sexual Dysfunction

CF602 is an allosteric modulator that enhances the affinity of the natural ligand, adenosine, to the A_3AR. The compound has been tested in an experimental animal model of diabetic rats, which similar to diabetic patients, suffer from sexual dysfunction. Erectile dysfunction (ED) was assessed by monitoring the ratio between intra-cavernosal pressure (ICP) and mean arterial pressure (MAP) as a physiological index of erectile function. The ICP/MAP for the CF602 treated group improved by 118% over the placebo group.

In additional preclinical studies, CF602 was administered to diabetic rats for a period of 1 and 5 days. Treatment with CF602 resulted in a 188% ($P<0.01$) and 250% ($P<0.001$) increase in penial intra-cavernosal pressure (ICP) after 1 and 5 days of treatment, respectively, compared to placebo. Importantly, CF602 had no effect on blood pressure in that model, indicating that it could potentially be used in conjunction with currently available ED medications. Lastly, treatment with CF602 was shown to reverse smooth muscle and endothelial damage in a dose dependent manner, leading to the improvement in ED. The company is currently finishing up IND-enabling studies such that an IND can be filed with the FDA and clinical studies with CF602 can begin in 2016.

Conclusion and Recommendation

We value Can-Fite using a risk-adjusted discounted cash flow model that takes into account the potential for CF101 in RA and psoriasis and CF102 in HCC. For all indications, we estimate that Can-Fite will sign partnership agreements that will generate royalty income based on revenues of each product, with a 15% royalty assumed for each indication.

Our model has been adjusted based on the fact that at this point the greatest risk for CF101 is not whether it will be approved for psoriasis and RA (we peg them both at 50% probability) but that there will be no uptake for the drug when/if it is approved. Given the immense competition in both the RA and psoriasis market, we forecast peak market share of approximately 1% in both indications. We believe the RA market is currently an approximately $22 billion opportunity while the psoriasis market is worth approximately $10 billion. Upside to our model is likely if Can-

Fite can forge a partnership that would increase the probability of using CF101 as a combo therapy with another therapeutic in RA and/or psoriasis, thus increasing its potential peak market share.

For CF102 in HCC, we assign a very low probability of approval (15%) based on the fact that cohort of patients is incredibly difficult to treat and there have been numerous clinical trial failures with other drugs in the past few years. Positive results from the Phase 2 trial next year would cause our probability of approval to increase significantly.

Upcoming milestones for the company include the finalization of the psoriasis Phase 3 clinical trial protocol in the second half of 2015, the initiation of the CF101 Phase 3 clinical trial in RA in the first half of 2016, and the data from the CF102 clinical trial in HCC in mid-2016. We believe the shares are worth $3 and we are maintaining a 'Hold' rating on the stock, noting that this could change were the company to enter into a strategic partnership to increase the potential opportunity for CF101.

PROJECTED FINANCIALS

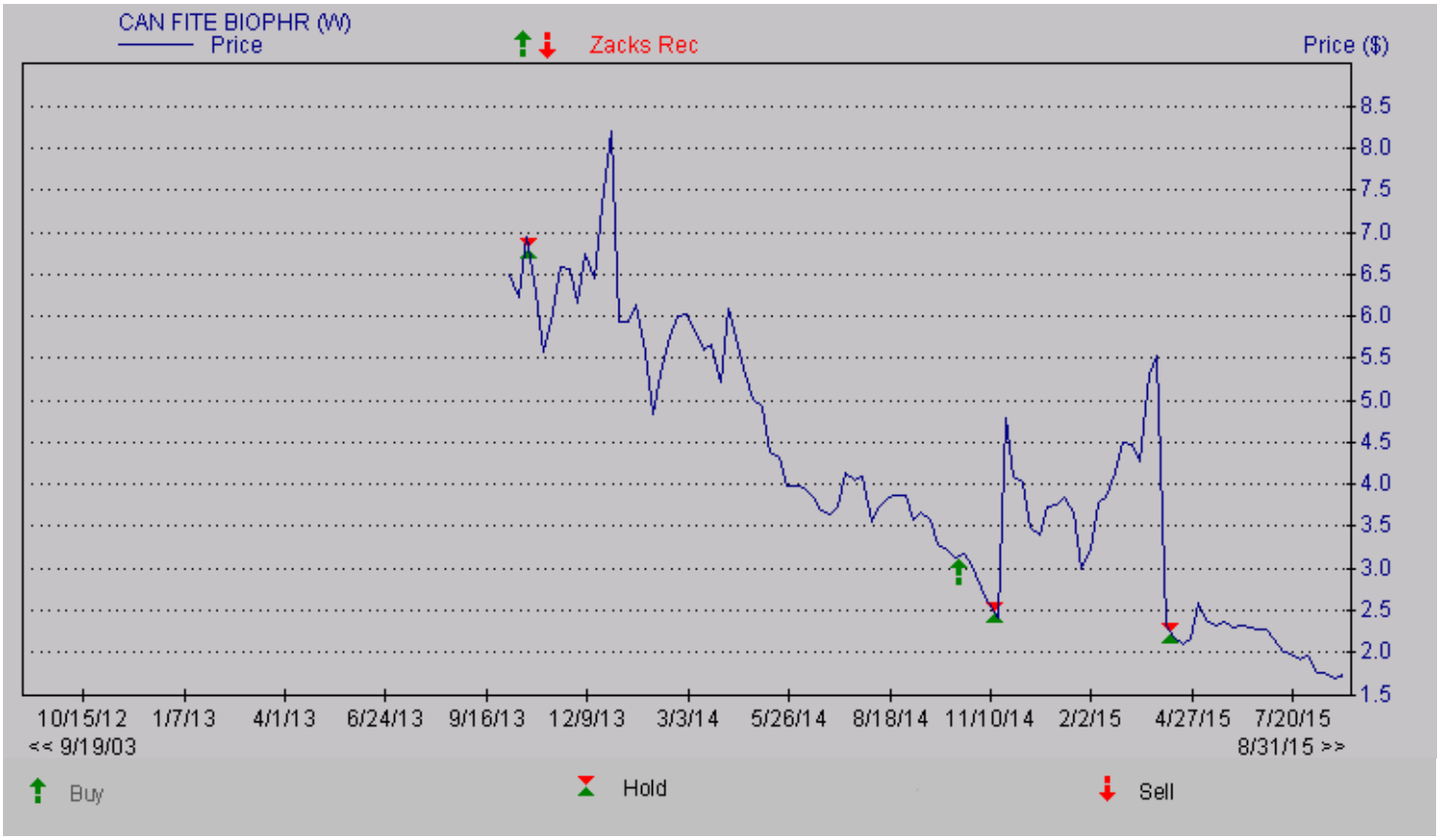
Can-Fite Biopharma Ltd.
Income Statement

Can-Fite Biopharma Ltd.	2014 A	Q1 A	Q2 A	Q3 E	Q4 E	2015 E	2016 E
CF101 (Psoriasis)	$0	$0	$0	$0	$0	$0	$0
YOY Growth	-	-	-	-	-	-	-
CF101 (RA)	$0	$0	$0	$0	$0	$0	$0
YOY Growth	-	-	-	-	-	-	-
CF101 (Glaucoma)	$0	$0	$0	$0	$0	$0	$0
YOY Growth	-	-	-	-	-	-	-
CF102 (HCC)	$0	$0	$0	$0	$0	$0	$0
YOY Growth	-	-	-	-	-	-	-
Grants & Collaborative Revenue	$0	$0	$0	$0	$0	$0	$0
YOY Growth	-	-	-	-	-	-	-
Total Revenues	**$0**	**$0**	**$0**	**$0**	**$0**	**$0**	**$0**
YOY Growth	-	-	-	-	-	-	-
Cost of Sales	$0	$0	$0	$0	$0	$0	$0
Product Gross Margin	-	-	-	-	-	-	-
Research & Development	$4.2	$0.6	$0.9	$0.7	$0.8	$3.0	$6.0
General & Administrative	$3.0	$0.6	$0.6	$0.9	$1.0	$3.1	$5.0
Other Expenses	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.5
Operating Income	($7.1)	($1.2)	($1.5)	($1.6)	($1.8)	($6.1)	($11.5)
Operating Margin	-	-	-	-	-	-	-
Non-Operating Expenses (Net)	$0.6	$0.8	($0.2)	$0.3	$0.3	$1.2	($0.1)
Pre-Tax Income	($6.6)	($0.4)	($1.7)	($1.3)	($1.5)	($4.9)	($11.6)
Income Taxes Paid	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0
Tax Rate	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*
Net Income	**($6.6)**	**($0.4)**	**($1.7)**	**($1.3)**	**($1.5)**	**($4.9)**	**($11.6)**
Net Margin	-	-	-	-	-	-	-
Reported EPS	**($0.37)**	**($0.02)**	**($0.07)**	**($0.05)**	**($0.06)**	**($0.20)**	**($0.35)**
YOY Growth	-	-	-	-	-	-	-
Basic Shares Outstanding	17.546	21.850	23.280	25.000	27.000	24.283	33.000

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

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