Zacks Small-Cap Research

November 9, 2015
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Can-Fite Biopharma Ltd. (CANF - NYSE)

CANF: Upgrading to Buy based on multiple achievements and attractive valuation----Buy

Current Recommendation	**Buy**
Prior Recommendation	Hold
Date of Last Change	11/08/2015
Current Price (11/06/15)	$3.17
Target Price	**$7.50**

We upgrade Can-Fite shares to Buy from previous Hold with a new price target of $7.50 per ADS.

Can-Fite's lead compounds, CF101 and CF102, are first-in-class agonists of the A_3AR receptor and have shown activity in a number of indications including rheumatoid arthritis (RA), psoriasis, and cancer. The company is set to initiate a Phase III trial with CF101 in RA in 2015 and a Phase III in psoriasis in 2016. A Phase II trial of CF102 in patients with HCC is ongoing. New positive data from Phase II/III of CF101 for psoriasis has increased the probability of success in advanced study.

Based on the multiple achievements and the attractive valuation, we upgrade Can-Fite shares to Buy.

SUMMARY DATA

52-Week High	**$5.54**
52-Week Low	**$1.61**
One-Year Return (%)	**22.39**
Beta	**0.50**
Average Daily Volume (sh)	**1,534,958**
Shares Outstanding (mil)	**14**
Market Capitalization ($mil)	**$45**
Short Interest Ratio (days)	**0.12**
Institutional Ownership (%)	**N/A**
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 ADS
(Adjusted after non-recurring items)

	Q1 (Mar)	Q2 (Jun)	Q3 (Sep)	Q4 (Dec)	Year (Dec)
2014	-$0.22 A	-$0.21 A	-$0.12 A	-$0.20 A	-$0.75 A
2015	-$0.03 A	-$0.15 A	-$0.11 E	-$0.12 E	-$0.42 E
2016					-$0.60 E
2017					-$0.75 E

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WHAT'S NEW

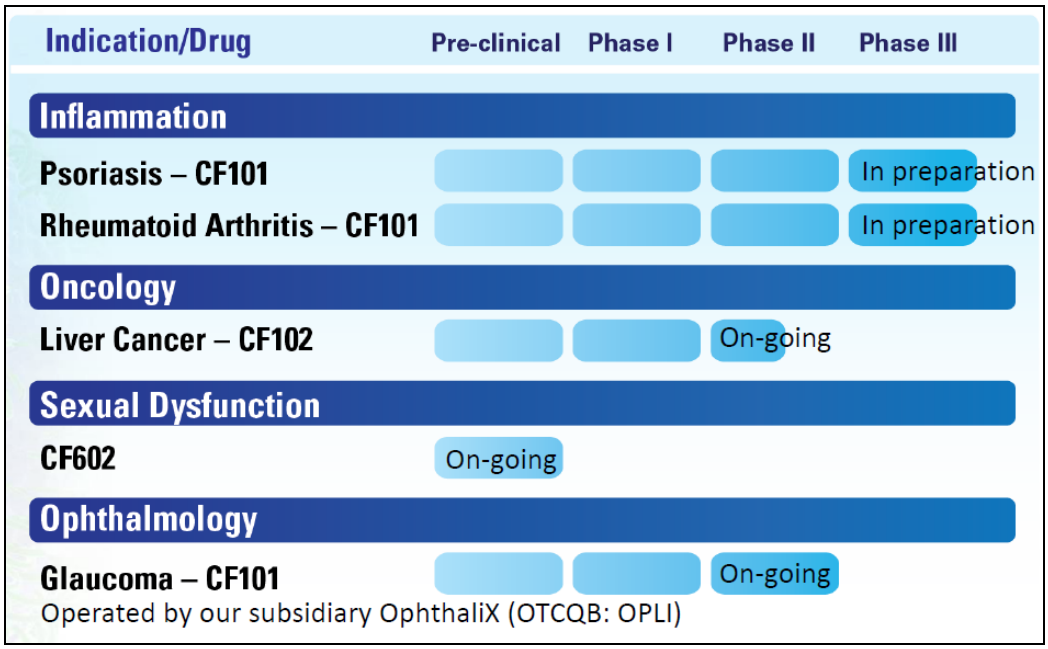
We are Upgrading CANF shares to Buy from Neutral

We are upgrading Can-Fite Biopharma Ltd. (CANF) shares to **Buy** from previous Neutral. Our new 12-month price target is **$7.50 per share**. Our call is based on the multiple achievements the company has made in the past 6 months and the compelling valuation.

For those who are not familiar with Can-Fite, the company is a biopharmaceutical company focused on the development of **orally** available small molecule therapeutic products for the treatment of autoimmune-inflammatory, oncological, and ophthalmic diseases. The company has three lead candidate products: CF101, CF102, and CF602.

Can-Fite is developing **CF101** for rheumatoid arthritis (RA), psoriasis and glaucoma. The company recently completed a **Phase IIb** study of CF101 for the treatment of **RA** and will be initiating a Phase III clinical trial in RA later in 2015. A **Phase II/III** trial of CF101 for **psoriasis** was also completed recently and the company plans to move forward with a **Phase III** trial in 2016. A **Phase II** trial of CF101 for the treatment of glaucoma is ongoing.

Can-Fite is currently evaluating **CF102** in a **Phase II** study in hepatocellular carcinoma (HCC) patients. **CF602** is in pre-clinical development as a treatment for sexual dysfunction.



All of the company's products target the A3 Adenosine Receptor **(A_3AR),** which is overexpressed in a number of cancer cells as well as the peripheral blood mononuclear cells (PBMCs) of patients with various inflammatory conditions including rheumatoid arthritis, psoriasis, and Crohn's disease. However, the A_3AR is expressed in very low levels in normal tissue, thus making it a compelling target for pharmaceutical intervention as the receptor affects pathological and normal cells differently. While specific A_3AR agonists, such as CF101 and CF102, and allosteric modulators, such as CF602, appear to inhibit growth and induce apoptosis of cancer and inflammatory cells, normal cells are refractory, or unresponsive to the effects of these drugs. To date, the A_3AR agonists have had a positive safety profile as a result of this differential effect.

Attractive Valuation

Can-Fite is a **late stage** development biopharmaceutical company focused on the development of orally available small molecule therapeutic products for the treatment of autoimmune-inflammatory, oncological, and ophthalmic diseases. The company has three lead candidates in each category: **CF101** for autoimmune disease (RA and Psoriasis), **CF102** for liver cancer, and **CF602** for glaucoma.

The most advanced candidate is CF101. Can-Fite has completed a couple of Phase II studies of CF101 for **RA** with the most recent one achieving statistically significance based on the A_3AR expression level as an enrollment criteria. The company plans to initiate a **Phase III** trial of CF101 for RA late this year using the same enrollment criteria.

For **psoriasis**, Can-Fite also completed a Phase II and a Phase II/III study of CF101. The Phase II study achieved statistically significant results, but the Phase II/III failed its initial primary endpoint (PASI75 in 12 weeks). However, further analysis indicated that CF101 achieved multiple statistically significant results (PASI50, 75, 90, 100 in 32 weeks). We think the cumulative and linear improvement in CF101's efficacy over a longer period of time is a very significant finding for Can-Fite and the psoriasis treatment market. Based on the new data and the favorable safe profile, Can-Fite intends to continue the development of CF101 for the treatment of psoriasis and has initiated work on the design of the next **advanced–stage** clinical trial protocol.

We are especially encouraged by the fact that CF101 has the potential as a **first-line systemic therapy** for patients with moderate-severe psoriasis and for patients who do not want to be treated with the current systemic drugs due to safety issues. Currently there is no universally accepted first-line systemic therapy for patients diagnosed with psoriasis, and therefore CF101, an orally bioavailable drug with an excellent safety profile can be positioned for this unmet need.

For **CF102**, Can-Fite is conducting a **global Phase II** trial as a second line treatment for advanced HCC in subjects with **Child-Pugh B** cirrhosis who failed Nexavar (sorafenib) as a first line treatment. Top line data from this Phase II trial are expected to be available in mid-2016. Can-Fite's strategy to test CF102 in HCC patients who are Child-Pugh B and have failed sorafenib is very risky, however it is warranted based on the positive preclinical data and Phase I/II data showing the drug to be both safe and effective in that cohort. The reward could be immense if the strategy pays off, as there is no current treatment option for advanced liver cancer patients.

Can Fite is also developing CF101 for glaucoma with a **Phase II** trial ongoing.

The big change since our previous report comes from the company's Phase II/III trial of CF101 for psoriasis. Initial results failed the primary endpoint (PASI75 in 12 weeks). However, further analysis of the data indicated that CF101 achieved multiple positive results including PASI50, 75, 90, and 100 in 32 weeks. Moreover, the PASI 90 subset analysis further suggests a higher and significant (p=0.026) CF101 response rate of 26.9% among patients previously **untreated** with systemic psoriasis therapy compared to patients pre-treated with systemic drugs. Based on the new data, we believe CF101 has the increased probability to succeed in the newly planned advanced Phase III trial which will begin in early 2016.

Based on the new updates, we think current market price does not reflect the intrinsic value of Can-Fite anymore.

For RA, we estimate the company will initiate the Phase III trial in late 2015, file an NDA in 2017, and receive approval in late 2018 or early 2019. For psoriasis, we estimate the company will initiate the Phase III trial in early 2016, file an NDA in late 2017 or early 2018, and get approval in late 2018 or early 2019.

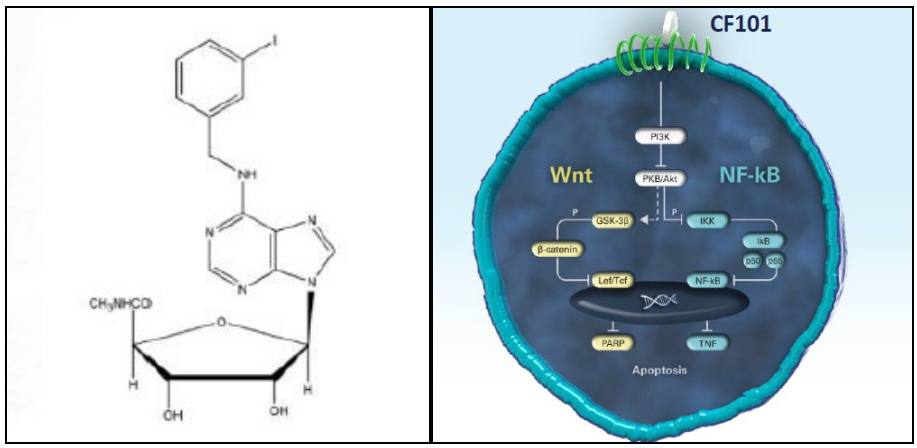
For CF102, we estimate that upon completion of the Phase II trial a Phase III trial will be initiated in 2017, with an NDA filing in 2019 and approval in 2020. There is a very slim chance that the data from the Phase II trial will be good enough to request approval, however we do not see this as likely enough to include in our model.

Based on our long term financial model, Can-Fite will achieve profitability in 2010 with an earnings of $0.77 per ADS based on total revenue of $85 million. We believe a P/E multiple of 35 x is appropriate for the valuation of the company. Based on this relative valuation metric, we come up with a new price target of $7.5 per ADS using 25% discount rate for 5 years. Our price target values the company at $105 million based on 14 million ADS outstanding. This is still conservative in our view.

But keep in mind **the risks**. Our valuation assumes the final approval of the company's three lead clinical programs including RA, psoriasis and liver cancer. Any clinical/regulatory failure or delay will have a significant negative impact on the company's shares. Cash burn is also on our close watch list. As the company moves its clinical programs into advanced stage, R&D expenses will soar. Current cash balance can only last into 2017. The company will need to tap the capital market for further financing before it become cash flow positive in 2020. Any equity related financing will dilute existing shareholder base and will have negative impact on share price. But overall, the company has a favorable risk/award profile for investors with a long term investment horizon.

CF101 for the Treatment of RA

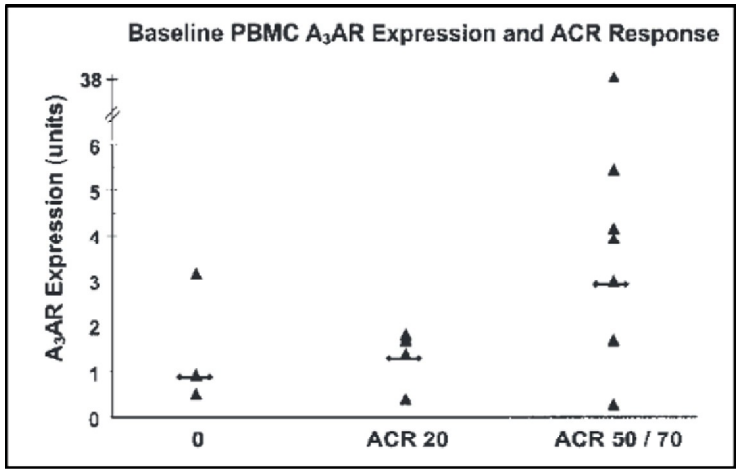
CF101 is a highly specific A_3AR agonist. It is a water insoluble and orally bioavailable nucleoside derivative.



The first indication of CF101 Can-Fite is developing is for the treatment of rheumatoid arthritis **(RA).** The compound has been evaluated in approximately 1,410 patients in multiple Phase I and Phase II clinical trials and has had a very limited side effect profile.

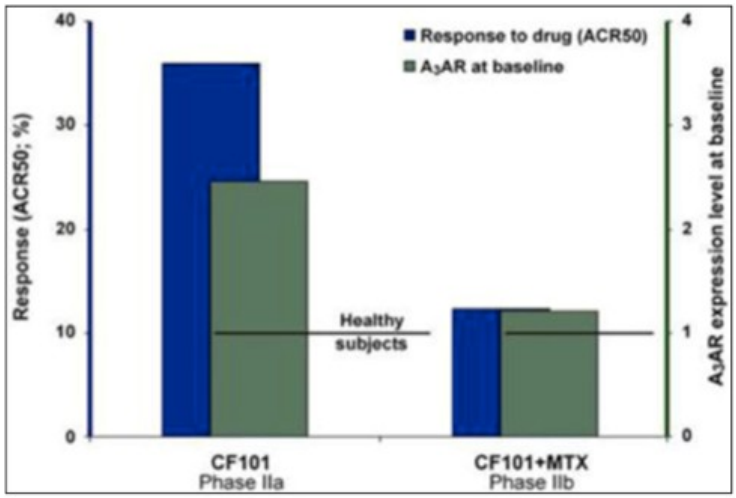
In a completed **Phase IIa** trial, CF101 was evaluated in three different doses in 74 RA patients: 0.1 mg, 1.0 mg, and 4.0 mg (Silverman *et al*., 2008). Of the 74 patients who were randomized into the study, 50 finished the trial with 24 patients withdrawing due to lack of efficacy (n=16), noncompliance (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** compared to placebo. CF101 was generally well tolerated, with mild headache (4.1%), nausea (2.7%), and rash (2.7%) being the most common treatment-related adverse events.

However, 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**

Can-Fite followed up the Phase IIa trial by conducting two separate **Phase IIb** trials of CF101 in combination with MTX in 230 patients and 252 patients respectively. 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 IIb** studies all showed a low level of A_3AR expression, as shown in the following figure.



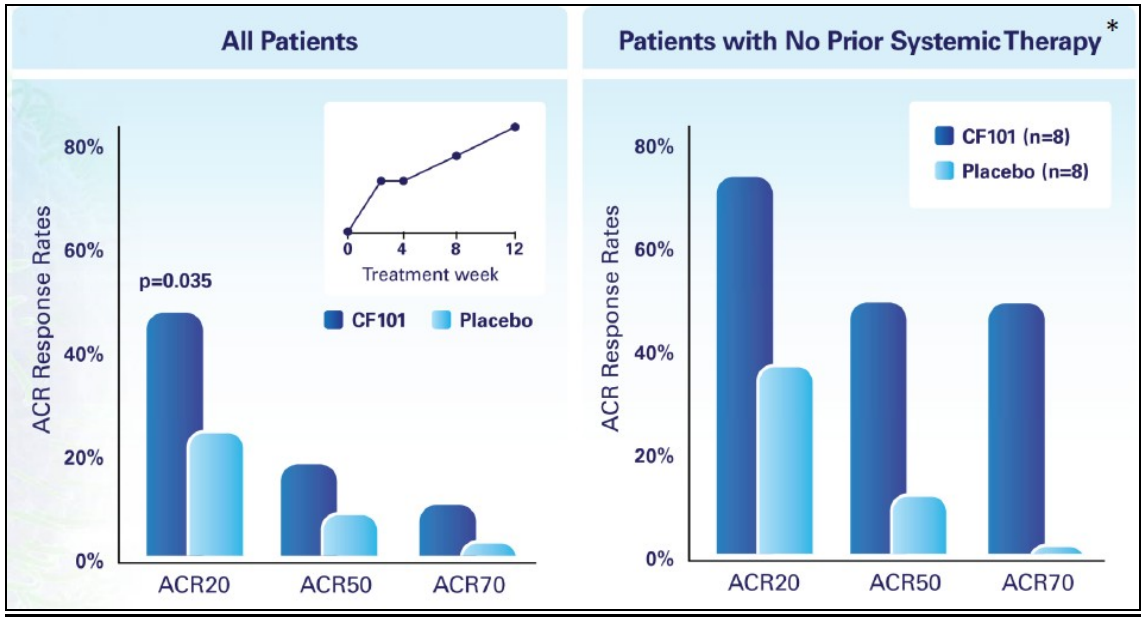
Source: Can-Fite Biopharma Ltd.

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The results from the Phase IIb 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 IIb** 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 = 0.035). 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, with no prior systemic therapy, 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%.



Based on the last positive Phase IIb study, Can-Fite plans to initiate a pivotal **Phase III** trial for the treatment of RA. The trial design has been completed, and we expect the initiation of this Phase III trial in late 2015.

The Phase III study will be a multicenter, randomized, double-blind, placebo-controlled, parallel-group study that will investigate the efficacy and safety of daily CF101 administered orally as a monotherapy for 12 weeks to patients with active RA. The study will have three arms, a 2 mg CF101 dose, a 3mg CF101 dose and placebo, given orally twice daily in the form of tablets. Approximately 300 patients are expected to be enrolled in the study, where sample size for each treatment group will be approximately 100 patients. The primary end point will be ACR 20 response at Week 12. The A_3 adenosine receptor biomarker will be evaluated prior to treatment and its correlation to patients' response to the drug will be analyzed upon study conclusion.

Although previous three Phase II trials (one Phase IIa, two Phase IIb) did not demonstrate statistically significant difference between CF101 and placebo, the company leaned the identified the relationship between A_3AR expression and response for CF101. Based on these findings, the company's last Phase IIb demonstrated positive data of CF101 for the treatment of RA patients based on the level of A_3AR expression. The Phase III trial uses the same criteria for screening RA patients, and therefore has a high possibility that it will replicate the results of the last Phase IIb trial.

Huge Market Opportunity for Rheumatoid Arthritis

Rheumatoid arthritis (RA) is a chronic, systematic, autoimmune inflammatory disease that manifests as joint pain, stiffness, and swelling. Peripheral joints, including the wrists, hands, shoulders, elbows, hips, knees, and ankles are most commonly affected, with a bilaterally symmetric distribution of relapsing and remitting symptoms. Systemic symptoms include early morning stiffness of the affected joints, generalized afternoon fatigue, anorexia, generalized weakness, and fever. The detailed cause of the disease is poorly understood. RA afflicts between 0.5-1% of the general population (Silman *et al*., 2002) with approximately 1.5 million adults in the U.S. having the disease (Sacks *et al*., 2010).

Historically the first-line of treatment for RA has included non-steroidal anti-inflammatory drugs **(NSAIDs)** and **steroids**. Both agents treat symptoms of RA and decrease inflammation, but do not alter the course of the disease, and dose is limited by side effects.

With more aggressive treatment goals now in place, disease-modifying anti-rheumatic drugs **(DMARDs)** are increasingly being used earlier in the treatment paradigm. The DMARD class consists of a variety of older, small molecule drugs that share no common mechanism of action, but which have been found empirically to alter the progression of RA. They exert minimal direct, nonspecific anti-inflammatory or analgesic effects and thus are commonly administered with NSAIDs. The appearance of benefit from these drugs is usually delayed for weeks to months. Members of this class include methotrexate (MTX), gold salts, leflunomide, minocycline, penicillamine, hydroxychloroquine (HC), and sulfasalazine among others. **Methotrexate** appears to have the best ratio of efficacy to adverse effects and is the most widely used.

Patients with negative prognostic features or failing to achieve minimal disease activity at 6-12 months will typically receive step-up therapy involving one of several **biologic agents** approved since the mid-1990's, usually in combination with methotrexate. The use of biologic therapies is strongly dominated by the TNF-α blockers Humira®, Enbrel®, and Remicade®. Other approved drugs include CTLA-4 agonist Orencia®, IL-6 antagonist Actemra®, and anti-B-cell agent Rituxan®. Among the most important recent advances is the availability of the first highly efficacious oral drug, Xeljanz®. Xeljanz® is an inhibitor of the enzyme janus kinase 3 (JAK3). The proportion of patients achieving ACR50 in the Xeljanz® clinical trials was similar to and possibly a bit greater than that seen in clinical trials of TNF-α blockers.

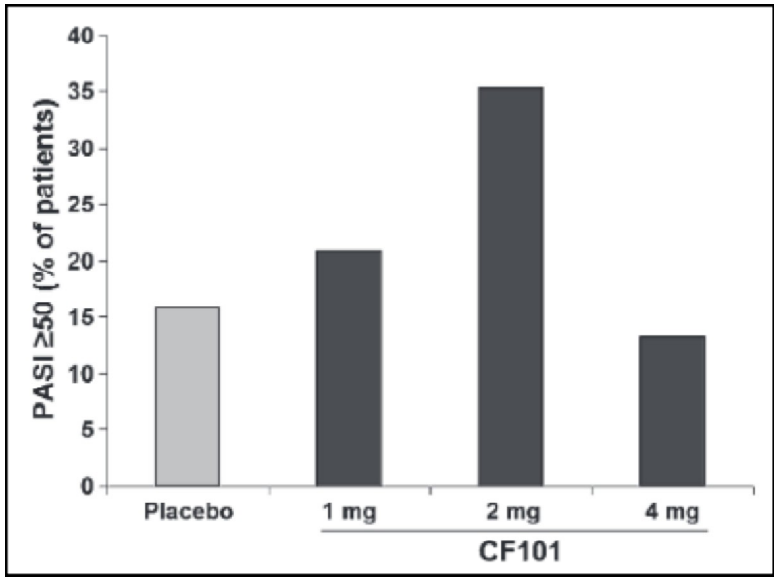
The RA is a multi-billion dollar market. The opportunity for CF101 in RA is quite large even though CF101 is likely to have somewhat less efficacy compared to biologic treatments (based upon the results from the Phase IIb monotherapy clinical trial), with the trade-off being a much more benign side effect profile. However, what intrigues us the most about the opportunity in RA is the potential to select patients most likely to respond to CF101 treatment through the use of a blood based biomarker test, an approach that was validated by the statistically significant increase in ACR20 in a population of patients pre-selected based on A_3AR expression level. In addition, the data showing increased efficacy in patients with no prior systemic treatment is quite exciting, and it will be interesting to see whether these results can be replicated in a larger patient population.

CF101 for the Treatment of Psoriasis

The Positive Phase II Trial

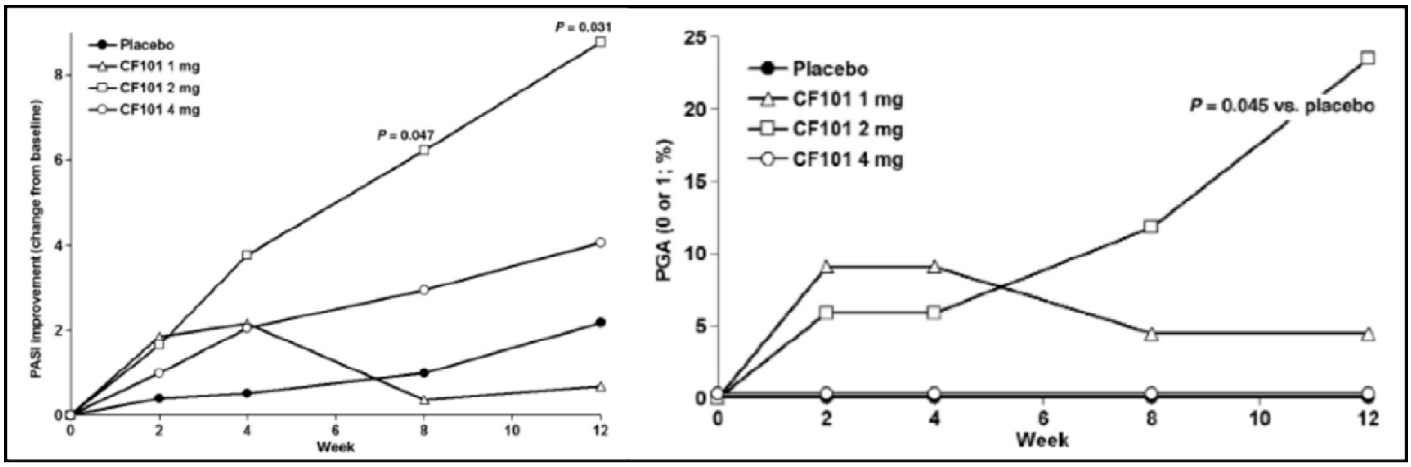
Can-Fite completed a **Phase II** trial of CF101. This was a multicenter, randomized, double blind, dose ranging, placebo controlled study in 76 patients age 18-70 who had moderate to severe chronic psoriasis for at least six months and a PASI score ≥ 10. Four cohorts were tested: 1 mg CF101 twice a day (n=25), 2 mg CF101 twice a day (n=17), 4 mg CF101 twice a day (n=15), or placebo (n=19). Patients were treated for 12 weeks with the exploratory efficacy endpoints being change in baseline in **PASI** (Psoriasis Area and Severity Index) scores and proportion of patients achieving PASI50 and PASI75. Of the 76 patients who were randomized into the trial, 64 (84%) completed the study.

As shown in the following figure, 35.3% of patients in the 2 mg dose cohort achieved PASI50, with both 1 mg and 4 mg dosages showing less therapeutic effect. This type of non-linear dose response is typical for agents that target GPCRs, as desensitization results in the receptor-mediated response to plateau and then diminish despite the continual presence of agonist (Krupnick *et al*., 1998).



***Source*: David *et al.*, 2011**

There was a progressive improvement in mean change from baseline in PASI score with a **significant difference** between the 2 mg cohort and placebo (***P* = 0.031).** In addition, analysis of **PGA** (Physician Global Assessment) data was performed for patients who entered the study with PGA > 1. At week 12, 23.5% of patients in the 2 mg cohort achieved a PGA score of 0 or 1, compared with 0% in the placebo group (P < 0.045). The percentage of patients who presented with a PGA score of 0 or 1 increased throughout the study in the 2 mg cohort.

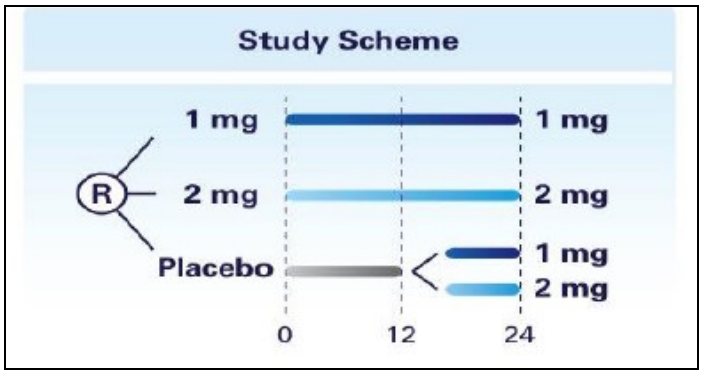


***Source*: David *et al.*, 2011**

Overall, CF101 was found to be safe and well tolerated. The percentage of patients with adverse events in each dosing cohort were 58.3%, 17.6%, and 13.3% in the 1, 2, and 4 mg groups, respectively. A total of 20 adverse events were reported in the study, with 15 of them judged to be possibly related to the study drug. All of them were mild to moderately severe, with the exception of one exacerbation of psoriasis that was judged to be severe (in a patient in the 1 mg cohort).

The Phase II/III Trial

As a follow on to the Phase II study, Can-Fite initiated a **Phase II/III** clinical trial of CF101 in patients with moderate to severe psoriasis in 2011 (NCT01265667). Total of 326 patients were enrolled 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 24 weeks, and subsequently extended to 32 weeks. **The primary end point** is PASI75 in 12 weeks.

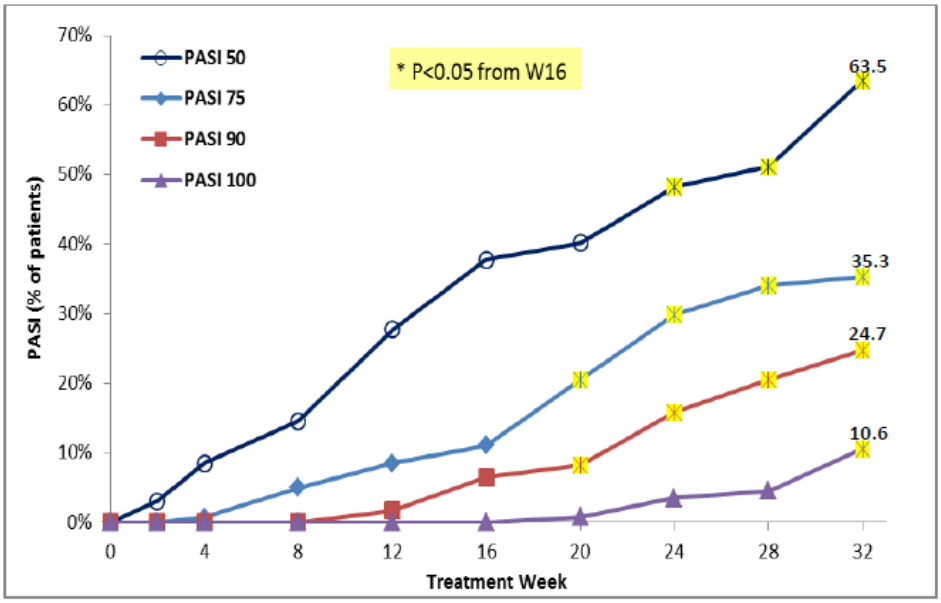


On March 30, 2015 Can-Fite announced topline results from the Phase II/III study showing that treatment with CF101 **did not achieve the study's primary endpoint** after **12 weeks of treatment**. The proportion of patients treated with CF101 who achieved PASI75 was 8.5% compared to 6.9% in the placebo 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.

However, further analysis of the entire study period revealed that **by 32 weeks** of treatment with CF101, 35.3% of the patients achieved PASI 75 while the mean percent of improvement in PASI score was 57% ($p<0.001$) . This was a **statistically significant** cumulative and linear improvement during weeks 16 to 32.

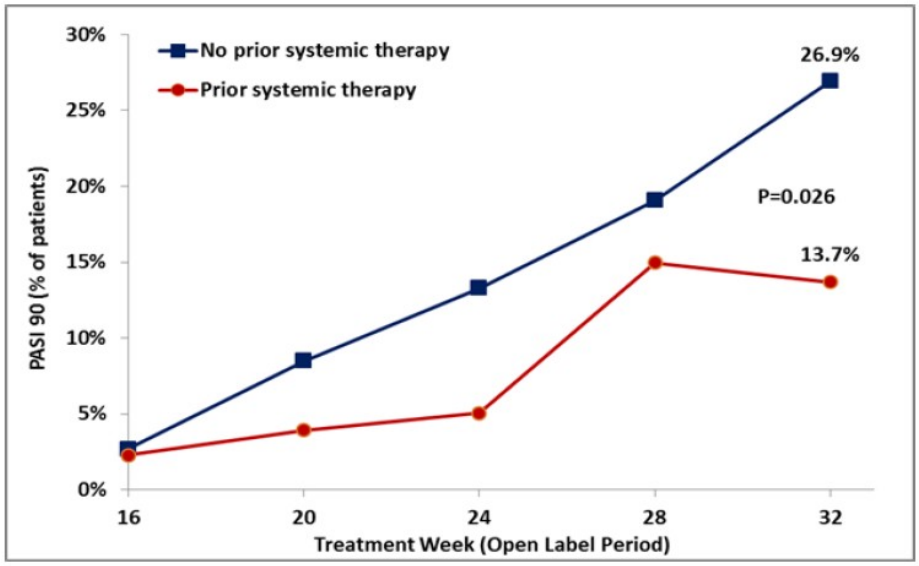
Most significantly, by week 32 of the study, 24.7% of the study patients reached PASI 90, a result demonstrating a response rate of 90% clearing of skin lesions. PASI 90 is one of the most stringent and difficult to meet clinical endpoints for measuring responses to psoriasis treatments.

Significant linear PASI scores through 32 weeks of treatment



Moreover, the PASI 90 subset analysis further suggests a higher and significant ($p=0.026$) CF101 response rate of 26.9% among patients previously untreated with systemic psoriasis therapy compared to patients pre-treated with systemic drugs.

Statistically significant linear PASI90 response



We think the cumulative and linear improvement in CF101's efficacy over a longer period of time is a very significant finding for Can-Fite and the psoriasis treatment market. Based on the new data and the favorable safe profile, Can-Fite intends to continue the development of CF101 for the treatment of psoriasis and has initiated work on the design of the next **advanced–stage** clinical trial protocol.

We are especially encouraged by the fact that CF101 has the potential as a first-line systemic therapy for patients with moderate-severe psoriasis and for patients who do not want to be treated with the current systemic drugs due to safety issues. Currently there is no universally accepted first-line systemic therapy for patients diagnosed with psoriasis, and therefore CF101, an orally bioavailable drug with an excellent safety profile can be positioned for this unmet need.

Still a Huge Market Opportunity for Psoriasis

Psoriasis is a common, chronic, noncontagious, multisystem inflammatory condition that most commonly presents on the skin of the elbows, knees, scalp, back, and thighs. There are multiple types of psoriasis, with plaque psoriasis, being the most common and affecting 80-90% of all individuals with psoriasis. Plaque psoriasis involves the hyperproliferation of epidermal keratinocytes that results in red or white, scaly, and typically itchy skin lesions. In addition, approximately 20% of psoriasis patients suffer from psoriatic arthritis, an inflammatory joint disease associated with psoriasis (Zacharlae, 2003). There is no known cure for the disease, thus depending upon the severity of the condition and how responsive it is to treatment, some patients are on therapy for life.

While psoriasis itself is not life-threatening, there are several conditions that are associated with the disease, including cardiovascular disease (Shlyankevich *et al*., 2014) and hypertension (Armstrong *et al*., 2013). In addition, patients with psoriasis have an increased risk for a number of non-skin cancers, including cancer of the lung, upper gastrointestinal tract, urinary tract, liver, and pancreas (Richard *et al*., 2013).

There are approximately 8 million individuals in the U.S. with psoriasis, with 10% of those affected suffering from the moderate or severe form (Cheng *et al*., 2014). The pathogenesis of the disease is poorly understood; however, at its most basic psoriasis is simply the result of new skin cells forming every 3-5 days as opposed to every 28-30 days in a healthy individual (Gottlieb, 2005). The initiating factor(s) for this phenomenon are still being elucidated, however what is known is that there is substantial leukocyte recruitment to the dermis and epidermis that results in the formation of the characteristic plaques. The epidermis is infiltrated by a number of activated T-cells that release pro-inflammatory

cytokines such as tumor necrosis factor-α (TNF-α) and interleukin-22 (Nestle *et al*., 2009). The secreted inflammatory signals are what prompt the proliferation of keratinocytes.

The treatment of mild psoriasis typically involves the use of topical treatments, including corticosteroids, vitamin D, and moisturizers such as mineral oil or petroleum jelly. These treatments may be combined with phototherapy, typically psoralen-ultraviolet A (PUVA) therapy, which causes skin cells to grow less rapidly. Psoralen is a photosensitizer that is orally ingested prior to PUVA and makes the skin more sensitive to phototherapy.

Systemic treatments are typically employed for treating moderate to severe psoriasis. There are a number of options available, including both small molecule and biologic treatments:

Apremilast (Otezla®): Marketed by Celgene, Otezla is a small molecule inhibitor of phosphodiesterase 4 (PDE4), an enzyme responsible for the degradation of cAMP. Thus, an inhibitor of PDE4 results in an increase in cAMP, which is similar to CF101's mechanism of action. Otezla® was approved for the treatment of psoriatic arthritis in March 2014, and then for the treatment of psoriasis in September 2014. The drug was approved for the treatment of psoriasis based on two phase III clinical trials involving over 1200 patients. After 16 weeks of treatment, 33.1% and 28.8% of Otezla® treated patients achieved PASI75, compared to 5.3% and 5.8% treated with placebo. The most common side effects associated with Otezla® are gastrointestinal symptoms including diarrhea, nausea, and vomiting. Otezla® costs approximately $22,500 per year.

Anti-TNF-α biologics: This class of compounds works by blocking the effect of TNF-α and preventing its activation of T-cells. There are several TNF-α targeting therapies on the market, including the monoclonal antibodies Humira® and Remicade® and the recombinant TNF receptor Enbrel®. Each of these compounds is approved for treating multiple inflammatory conditions, with psoriasis and psoriatic arthritis being two of them. The anti-TNF-α therapies are highly effective, with PASI75 scores of 70-80% after 12 weeks of treatment; however, this efficacy is associated with sometimes severe side effects, including opportunistic infections, as well as inconvenient dosing. These medications cost approximately $40,000 per year.

Ustekinumab (Stelara®): This is a monoclonal antibody directed against interleukin-12 and interleukin-23, two cytokines that activate T-cells. Stelara® was approved by the FDA in 2009 for the treatment of psoriasis. Similarly to the anti-TNF-α targeting therapies, Stelara® is highly effective (PASI75 between 60-70% after 12 weeks of treatment); however, patients on this medication run the risk of developing serious infections. The compound is administered via subcutaneous injection and costs approximately $40,000 per year.

Secukinumab (Cosentyx®): This is a monoclonal antibody that binds to interleukin-17a, a cytokine produced by T-cells and induced by interleukin-23. Costenyx® was approved for the treatment of moderate to severe psoriasis on Jan. 21, 2015 based on the results of two Phase III clinical trials where the drug was shown to be highly effective (PASI75 off 77% and 81% after 12 weeks of treatment). However, as with other cytokine targeting therapies, patients taking Cosentyx® have an increased risk of serious infection.

We envision CF101 potentially competing with Otezla®, as the Phase II/III data showed CF101 to have a similar or slightly favorable efficacy profile, with CF101 also having the convenience of oral dosing (as compared to the biologic treatments that are administered via infusion or subcutaneously) and a favorable safety profile.

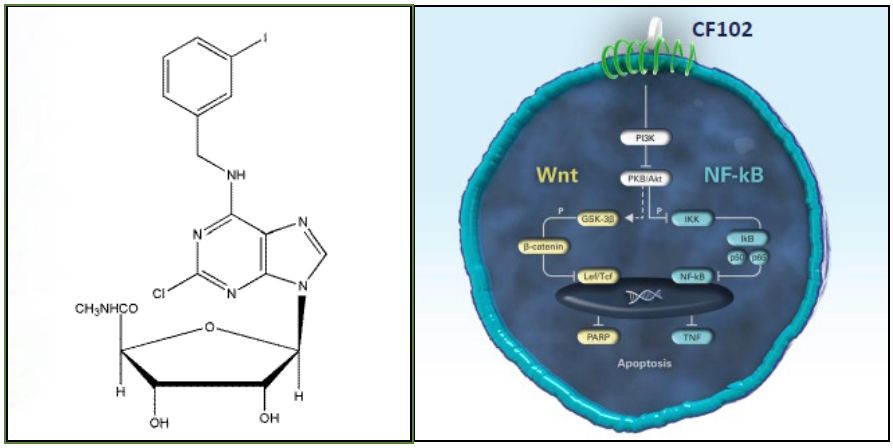
One big potential of CF101 is that this drug may have the potential as a **first-line systemic therapy** for patients with moderate-severe psoriasis since currently there is no universally accepted first-line systemic therapy for patients diagnosed with psoriasis.

CF101 Compares favorably to Otezla

	PASI Improvement from Baseline	PASI 90	PASI 100
CF101, Can-Fite	57.1% at week 32 no plateau at week 32	24.7% at week 32 no plateau at week 32	10.6% at week 32 no plateau at week 32
Otezla, Celgene	~57% at week 24 start to plateau at week 20	11.4% at week 16 16.7% at week 24	Not analyzed as there were too few participants at week 16

CF102 for Hepatocellular Carcinoma

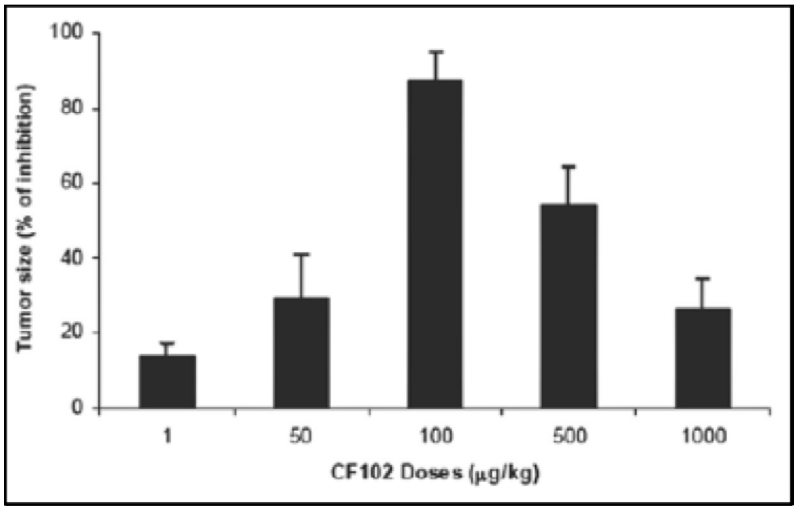
Similar to CF101, CF102 is also a highly specific A_3AR agonist. Can-Fite is developing CF102 as a potential treatment for liver cancer (hepatocellular carcinoma). CF102 has been granted **orphan drug status** and **fast track designation** for liver cancer by the US FDA.



CF102 Pre-Clinical Data

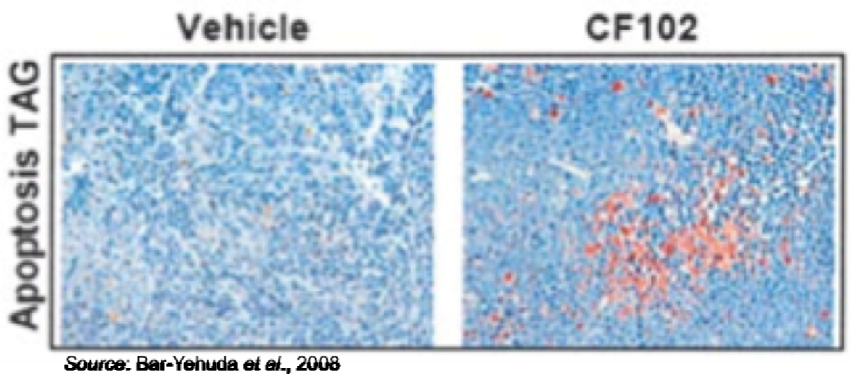
Can-Fite has generated a plethora of data showing that A_3AR agonists have anti-cancer activity in a wide range of tumor types, including melanoma (Fishman *et al*., 2002; Madi *et al*., 2003), prostate cancer (Fishman *et al*., 2003), colon cancer (Fishman *et al*., 2004), and HCC (Bar-Yehuda *et al*., 2008; Cohen *et al*., 2011). Interestingly, HCC was the most responsive to treatment with CF102 among all the tumor types tested.

Preclinical data showed that A_3AR is highly expressed in HCC tissues compared to adjacent healthy tissues, thus justifying the use of an A_3AR agonist 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. In an orthotopic **rat model,** the growth of HCC was inhibited by treatment with CF102, which exhibited a bell shaped dose-dependent inhibitory effect, as shown in the following figure.



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

CF102 treatment also induced **apoptosis** in liver cancer cells. Up-regulation of the pro-apoptotic proteins Bax and Bad was noted in tumors derived from CF102-treated animals, while no expression of those proteins was found in tumors from control-treated animals. In addition, a much larger number of apoptotic cells were noted in tumors derived from CF102-treated animals compared with tumors from control-treated animals, as shown in the following figure.



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

CF102 Phase I/II Clinical Trial in HCC

The encouraging preclinical results noted above with CF102 in HCC were followed up by a **Phase I/II** trial in HCC patients (NCT00790218). 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 (Stemmer *et al*., 2013). In a subpopulation of patients (n=5) who were **Child-Pugh B** (liver disease staging system; indicative of significant liver disease), 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. Perhaps most importantly, CF102 had no adverse effect on routine measures of liver function over a six-month period in 12 patients treated for at least that duration, suggesting that CF102 could be utilized safely in patients with cirrhosis or decreased liver function.

The Ongoing Global Phase II Trial of CF102 for HCC

Based on the above positive Phase I/II study, Can-Fite initiated a **global Phase II** trial in December 2014. This is a randomized, double-blind, placebo controlled trial to be conducted in the U.S., Europe and Israel with an estimated **78 patients** to be enrolled. CF 102 is being evaluated for efficacy and safety as a

second-line treatment for advanced HCC in subjects with **Child-Pugh B** cirrhosis who failed Nexavar (sorafenib) as a first line treatment. Patients are treated twice daily with 25 mg of CF102.

The **primary endpoint** of the study is overall patient survival. **Secondary endpoint** include: time to progression (TTP), progression-free survival (PFS), objective response (OR) rate, and disease control (DC) rate.

Top line data from this Phase II trial are expected to be available in mid-2016.

Opportunity in Liver Cancer

Hepatocellular carcinoma (HCC) is the most common form of primary liver cancer, with over 700,000 individuals affected worldwide, and is the third leading cause of cancer death in the world (ACS). HCC is relatively rare in the U.S. (approximately 35,000 individuals in the U.S. will be diagnosed with HCC in 2015) and other countries where hepatitis infections are not widespread, as most cases of HCC are due to hepatitis infection (both hepatitis B and C). Most cases of liver cancer in countries with low hepatitis rates are due to metastasis of other primary tumors.

A vast majority of HCC cases (>80%) occur in sub-Saharan Africa and in Eastern Asia (El-Serag *et al*., 2012). This is most likely due to the prevalence of hepatitis viruses in these populations. Hepatitis B infection is the dominant risk factor in most areas of Asia and sub-Saharan Africa, with the exception of Japan, where the major risk factor is Hepatitis C infection. HCC is now the leading cause of cancer death in Japan.

There is no cure for advanced HCC; thus, there exists a significant unmet need for an effective therapy. The only agent approved for use in advanced HCC is sorafenib (Nexavar®), a multi-kinase inhibitor that disrupts signaling in the RAS/MAPK pathway. Sorafenib was approved based upon the results of two randomized, double blind, placebo controlled clinical trials. The first trial involved 602 patients with advanced HCC, with the median overall survival being 10.7 months in the sorafenib group compared to 7.9 months in the placebo group (P<0.001) (Llovet *et al*., 2008). In the second trial, conducted in Asia, 271 patients were assigned to sorafenib (n=150) or placebo (n=76) with results showing a median overall survival for the sorafenib group of 6.5 months compared to 4.2 months in the placebo group (P=0.01) (Cheng *et al*., 2009). Thus, sorafenib increases survival by an average of 2.3 to 2.8 months and is the standard of care for patients with advanced HCC. 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). Further, there is no treatment option for those patients who are refractory to sorafenib treatment.

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 I/II trial and did not appear to have toxic effects on the liver. With a favorable 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.

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. This is another reason so few therapeutics are available for these patients, as they typically have advanced liver disease and are less able to tolerate harsh chemotherapeutic agents. 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 it is warranted based on the positive preclinical data and

Phase I/II data showing the drug to be both safe and effective in that cohort. The reward could be immense if the strategy pays off, as there is no current treatment option for advanced liver cancer patients.

Other Clinical Programs

CF101 is also being evaluated in a **Phase II** study of in patients with **glaucoma** or related syndromes of ocular hypertension in **Israel** and **Europe** via the company's subsidiary OphthaliX. The study is a randomized, double-masked, placebo-controlled, parallel-group study of the safety and efficacy of daily CF101 administered orally in subjects with elevated intraocular pressure (IOP). The objective of this study is to determine the safety and efficacy of oral CF101 in lowering IOP when administered twice a day for 16 weeks in subjects with elevated IOP. OphthaliX has enrolled 44 subjects in the first segment of the study, randomized in a 3:1 ratio to CF101 1.0 mg treatment to the placebo. OphthaliX is currently in the process of enrolling approximately 44 subjects to the second segment randomized in a 3:1 ratio to CF101 2.0 mg treatment to the placebo. We anticipate full study data to be announced in late 2016 or early 2017. No investigation new drug (IND) application has been filed for glaucoma as CF101 is not currently being clinically tested in the U.S. and the company has no near-term plans to do so.

CF602 is an allosteric modulator that enhances the affinity of the natural ligand, adenosine, to the A_3AR. The compound was tested in an experimental **animal model** of diabetic rats, which is similar to diabetic patients, suffer from **sexual dysfunction**. Erectile dysfunction 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. This data is similar to that achieved by sildenafil (Viagra®) in preclinical studies. In addition, treatment with CF602 reversed smooth muscle and endothelial damage, in a dose dependent manner, leading to the improvement in erectile dysfunction. 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.

Strong Balance Sheet

As of June 30, 2015, Can-Fite had cash and cash equivalents of $7.75 million.

In September, 2015, the company closed a registered direct offering with institutional investors for gross proceeds of $9 million. In connection with the offering, the Company issued 2,068,966 registered American Depository Shares (ADSs) of Can-Fite at a purchase price of $4.35 per ADS in a registered direct offering. Additionally, for each ADS purchased by investors, the investors received an unregistered warrant to purchase one-half of an ADS. The warrants have an exercise price of $5.25 per ADS, shall be exercisable six months following the issuance date and will expire five and one-half years from the issuance date.

Further in October, 2015, the same institutional investors who participated in September's round have invested again in Can-Fite's registered direct offering. This time, Can-Fite will issue 1,109,196 registered American Depository Shares (ADSs) of Can-Fite at a purchase price of $4.35 per ADS in a registered direct offering. Additionally, for each ADS purchased by investors, the investors will receive an unregistered warrant to purchase 40% of an ADS. The warrants have an exercise price of $5.25 per ADS, shall be exercisable six months following the issuance date and will expire five and one-half years from the issuance date. Can-Fite received gross proceeds of approximately $4.8 million.

These two new financings not only boost Can-Fite's balance sheet immediately, but further validate its technology and clinical programs.

Current cash at hand can carry the company's operations into mid-2017 according to our financial model.

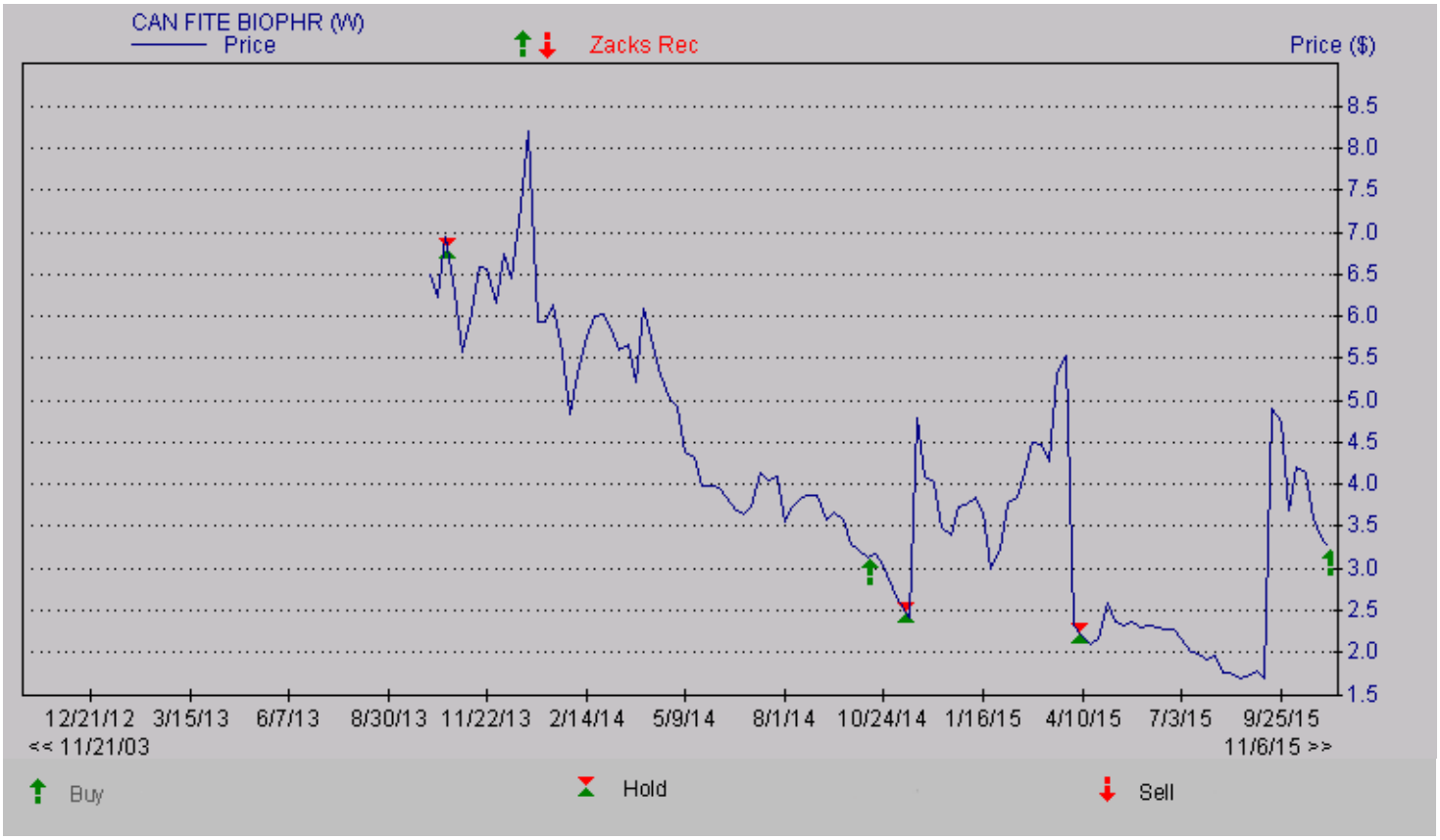
PROJECTED FINANCIALS

Can-Fite Biopharma Ltd.	2014 A	Q1 A	Q2 A	Q3 E	Q4 E	2015 E	2016 E	2017 E	2018 E	2019 E	2020 E
CF101 (Psoriasis)	$0	$0	$0	$0	$0	$0	$0	$0	$0	$10	$35
YOY Growth	-	-	-	-	-	-	-	-	-	-	-
CF101 (RA)	$0	$0	$0	$0	$0	$0	$0	$0	$0	$15	$45
YOY Growth	-	-	-	-	-	-	-	-	-	-	-
CF101 (Glaucoma)	$0	$0	$0	$0	$0	$0	$0	$0	$0	$0	$0
YOY Growth	-	-	-	-	-	-	-	-	-	-	-
CF102 (HCC)	$0	$0	$0	$0	$0	$0	$0	$0	$0	$0	$5
YOY Growth	-	-	-	-	-	-	-	-	-	-	-
Grants & Collaborative Revenue	$0	$0	$0	$0	$0	$0	$0	$0	$0	$0	$0
YOY Growth	-	-	-	-	-	-	-	-	-	-	-
Total Revenues	**$0**	**$0**	**$0**	**$0**	**$0**	**$0**	**$0**	**$0**	**$0**	**$25**	**$85**
YOY Growth	-	-	-	-	-	-	-	-	-	-	*240.00%*
Cost of Sales	$0	$0	$0	$0	$0	$0	$0	$0	$0	$5	$17
Product Gross Margin	-	-	-	-	-	-	-	-	-	*80.0%*	*80.0%*
Research & Development	$4.2	$0.6	$0.9	$1.0	$1.0	$3.5	$6.0	$8.0	$10.0	$12.0	$16.0
Sales, General & Administrative	$3.0	$0.6	$0.6	$0.7	$0.9	$2.8	$3.5	$5.0	$8.5	$15.0	$25.0
Other Expenses	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0
Operating Income	($7.1)	($1.2)	($1.5)	($1.7)	($1.9)	($6.3)	($9.5)	($13.0)	($18.5)	($7.0)	$27.0
Operating Margin	-	-	-	-	-	-	-	-	-	-	-
Non-Operating Expenses (Net)	$0.6	$0.8	($0.2)	$0.3	$0.3	$1.2	($0.1)	($0.1)	($0.1)	($0.1)	($0.1)
Pre-Tax Income	($6.6)	($0.4)	($1.7)	($1.4)	($1.6)	($5.1)	($9.6)	($13.1)	($18.6)	($7.1)	$26.9
Income Taxes Paid	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$9.5
Tax Rate	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*35%*
Net Income	**($6.6)**	**($0.4)**	**($1.7)**	**($1.4)**	**($1.6)**	**($5.1)**	**($9.6)**	**($13.1)**	**($18.6)**	**($7.1)**	**$17.4**
Net Margin	-	-	-	-	-	-	-				
Reported earnings per ADS	**($0.75)**	**($0.03)**	**($0.15)**	**($0.11)**	**($0.12)**	**($0.42)**	**($0.60)**	**($0.75)**	**($0.98)**	**($0.34)**	**$0.78**
YOY Growth	-	-	-	-	-	-	-	-	-	-	-
Basic ADS Outstanding	8.773	10.925	11.640	12.500	13.500	12.141	16.000	17.500	19.000	21.000	22.500

Source: company filings and Zacks estimates

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