Zacks Small-Cap Research

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Contrafect Corp

(CFRX-NASDAQ)

CFRX: New PK/PD and Microbiologic Data Presented on CF-301…

Based on our probability adjusted DCF model that takes into account potential future revenues from CF-301 in bacteremia and CF-404 in influenza, CFRX is valued at $12/share. This model is highly dependent upon continued clinical success of CF-301 and CF-404 and will be adjusted accordingly based upon future clinical results.

Current Price (06/27/16)	$3.01
Valuation	**$12.00**

OUTLOOK

ContraFect Corp. recently presented new PK/PD and microbiologic data on CF-301 at the ASM Microbe 2016 Conference. The PK/PD modeling of animal data supports the use of a 0.25 mg/kg dose of CF-301, which will be utilized in the upcoming Phase 2 clinical trial. Serial passage studies of CF-301 with *Staphylococcus aureus* strains showed no high levels of resistance to CF-301. A strong post-antibiotic effect was also seen with CF-301 both alone and in combination with daptomycin.

These data are highly encouraging, and fully support the upcoming Phase 2 clinical trial of CF-301 in patients with bacteremia caused by *Staphylococcus aureus*, which we anticipate will begin in the fourth quarter of 2016.

SUMMARY DATA

52-Week High	**$5.65**
52-Week Low	**$2.19**
One-Year Return (%)	**-46.73**
Beta	**-1.00**
Average Daily Volume (sh)	**19,977**
Shares Outstanding (mil)	**27**
Market Capitalization ($mil)	**$83**
Short Interest Ratio (days)	**N/A**
Institutional Ownership (%)	**20**
Insider Ownership (%)	**15**
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	**Above Avg.,**
Type of Stock	**Small-Blend**
Industry	**Med-Drugs**

ZACKS ESTIMATES

Revenue
(in millions of $)

	Q1 (Mar)	Q2 (Jun)	Q3 (Sep)	Q4 (Dec)	Year (Dec)
2015	0 A	0 A	0 A	0 A	0 A
2016	0 A	0 E	0 E	0 E	0 E
2017					0 E
2018					0 E

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

	Q1 (Mar)	Q2 (Jun)	Q3 (Sep)	Q4 (Dec)	Year (Dec)
2015	-$0.24 A	-$0.33 A	-$0.22 A	-$0.28 A	-$1.08 A
2016	-$0.32 A	-$0.23 E	-$0.28 E	-$0.27 E	-$1.11 E
2017					-$0.89 E
2018					-$0.92 E

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WHAT'S NEW

CF-301 Data Presented at ASM 2016

ContraFect Corp. (CFRX) recently presented new data for CF-301 at the ASM Microbe 2016 Conference. The data presented was based on new pharmacokinetic/pharmacodynamics (PD/PD) data as well as new microbiologic data showing a lack of resistance to CF-301 among different *Staphylococcus aureus* strains and a strong post-antibiotic effect for CF-301 both alone and in combination with daptomycin.

Background on CF-301

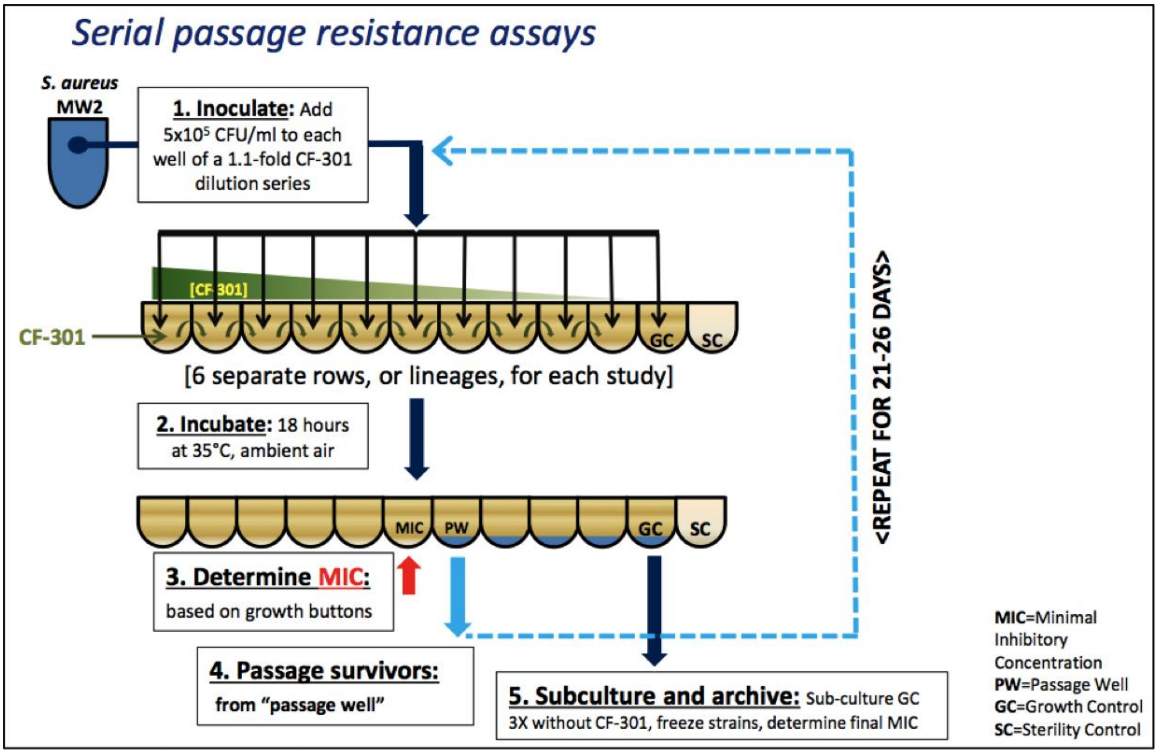
ContraFect's lead lysin product is CF-301. A lysin is a naturally occurring anti-bacterial hydrolytic enzyme that is produced by bacteriophages, which are virus' that infect and kill bacteria. Lysins are highly evolved enzymes that are able to target one of the five bonds in peptidoglycan (murein), the main component of bacterial cell walls. A typical lysin, such as CF-301, comprises two domains separated by a short linker region. The N-terminal domain catalyzes the hydrolysis of peptidoglycan whereas the C-terminal domain binds to the cell wall substrate, often a carbohydrate, which confers a great specificity and since the peptidoglycan structure is highly conserved, decreases the chance for bacterial resistance. Due to this, the use of lysins as antibacterial agents is designed to treat drug resistant strains and combat drug resistance to currently used antibiotics.

CF-301 will initially be targeted for the treatment of bacteremia, or infections of the bloodstream. Most studies estimate the incidence of *S. aureus* bacteremia (SAB) ranging from 20-50 cases/100,000 population (Klevens *et al*., 2007; Benfield *et al*., 2006; El Atrouni *et al*., 2009). Prior to the advent of antibiotics, the mortality rate from SAB was close to 80% (Mendell, 1939). The introduction of antibiotics, coupled with greater standards of care, has reduced the mortality rate, which appears to have stabilized at approximately 20-30% (Kaasch *et al*., 2014). SAB can frequently lead to infective endocarditis (IE), an infection of the endocardial surface of the heart (Fowler *et al*., 2005). The prevalence of IE is estimated to be anywhere from 11 to 50% of patients with SAB. Development of IE leads to an increased risk of embolic event and death (Miro *et al*., 2005).

The treatment of choice for *S. aureus* infections is penicillin, however in most countries penicillin resistance is extremely common. Resistance to penicillin is due to the activity of the enzyme penicillinase, which cleaves the β-lactam ring of the penicillin molecule. Penicillinase-resistant β-lactam antibiotics include methicillin, oxacillin, and flucoxacillin. *S. aureus* strains that have acquired resistance to methicillin have an altered penicillin-binding protein (PBP2a) that has lower affinity for binding β-lactam antibiotics, thus rendering them ineffective. Strains that have acquired this resistance are referred to as methicillin-resistant *S. aureus* (MRSA). The current gold standard for treatment of MRSA is vancomycin. However, vancomycin is far from ideal due to poor tissue penetration, slow bactericidal activity, and a number of side effects (Gould, 2008). Additional antibiotics utilized include teicoplanin, tegecyline, linezolid, daptomycin, and televancin. Each of those medications has their own shortcomings, including the development of resistance, thus there exists a significant unmet medical need for newer therapies, particularly those that are not susceptible to the development of resistance. Pre-clinical data shows that CF-301 synergizes with standard-of-care antibiotics, which results in a very high survival rate in mouse models of bacteremia.

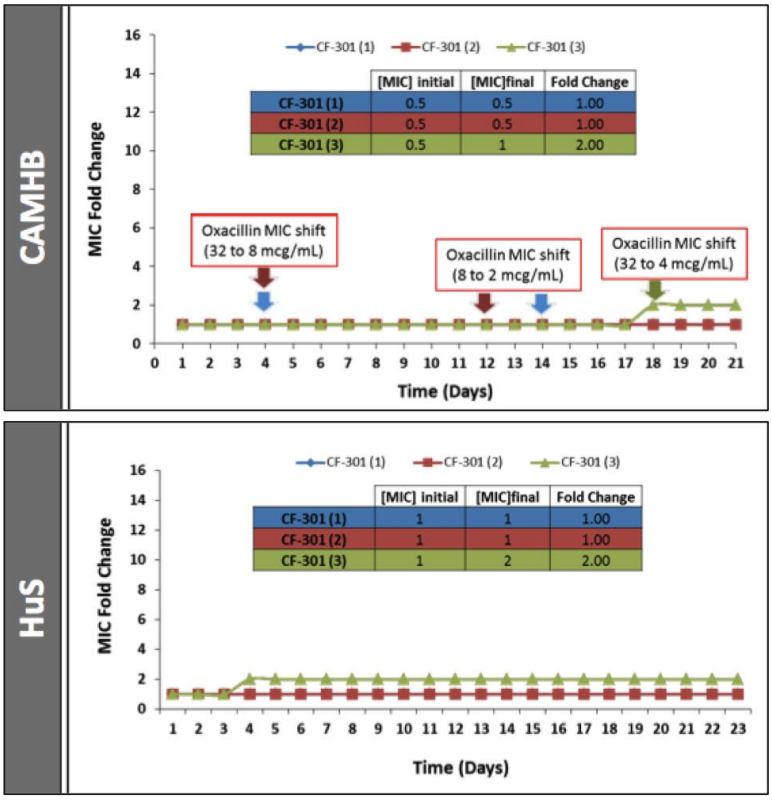
Resistance to CF-301

In an oral presentation titled "*Staphylococcus aureus* Resistance to Lysin CF-301 Does Not Arise in Human Serum", data was presented on the propensity of different *S. aureus* strains to develop resistance to treatment with CF-301. A serial passage study is the standard means of testing for the development of resistance *in vitro*. The assay is performed as depicted in the following figure. A constant number of bacterial cells are grown in the presence of serially diluted antibiotic (e.g., CF-301). After growing the cultures for 18 hours, the minimal inhibitory concentration (MIC) is determined, which is the lowest concentration of antimicrobial agent that will prevent bacterial growth. Bacterial cells from the next lowest concentration of antimicrobial agent (the "passage well") are than re-cultured in the presence of decreasing concentration of antimicrobial agent. This process is then repeated for a total of approximately three weeks. The purpose of this study is to encourage the development and proliferation of drug resistant strains, if possible. It also enables the determination of a response of the bacteria to sub-MIC levels of an antimicrobial agent. Changes in the MIC are recorded to determine if the cultures are developing resistance to these sub-MIC levels of the antimicrobial agent being tested.



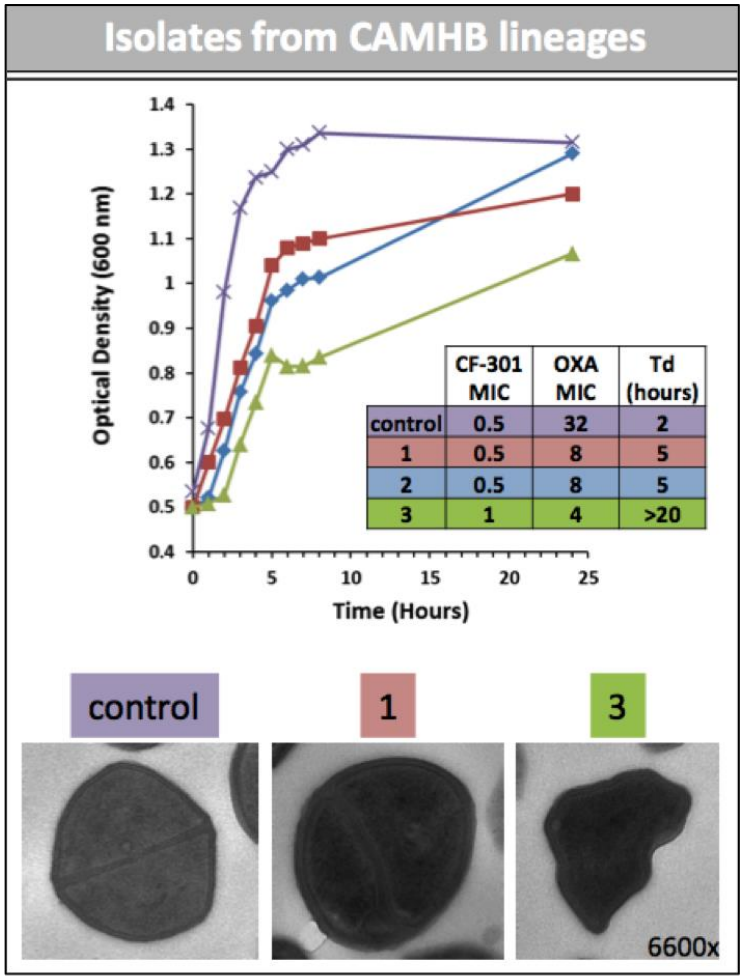
Source: ContraFect Corp.

This experiment was performed with CF-301 in both media (CAMHB) and human serum (HuS). The results are shown in the following figure. The three colors represent experiments done with three different strains of *S. aureus*, which were all methiciliin resistant (MRSA). No strain exhibited higher than a two-fold increase in MIC during the experiment. Interestingly, susceptibility to oxacillin increased in response to sub-MIC levels of CF-301. The most important take away from this experiment is that high-level resistance to CF-301 does not develop.



Source: ContraFect Corp.

While the bacteria do not develop high-level resistance to CF-301, they are still changed upon exposure to sub-MIC levels of the lysin. The following figure shows that bacteria exposed to sub-MIC levels of CF-301 have a decreased growth rate (exhibited by an elongated Td, or doubling time) and a change in cell morphology. What is particularly interesting is that in the strain that became less sensitive to CF-301 (shown by an increase in MIC to 1.0 compared to 0.5 for the control strain), there was a large decrease in oxacillin resistance and a large increase in Td. Thus, the most important conclusion from these experiments is that the risk of developing resistance to CF-301 is low, and it appears that if any change in sensitivity did develop it would come at a cost to the bacteria of being more susceptible to antibiotic therapy or immune surveillance, and slower bacterial growth.



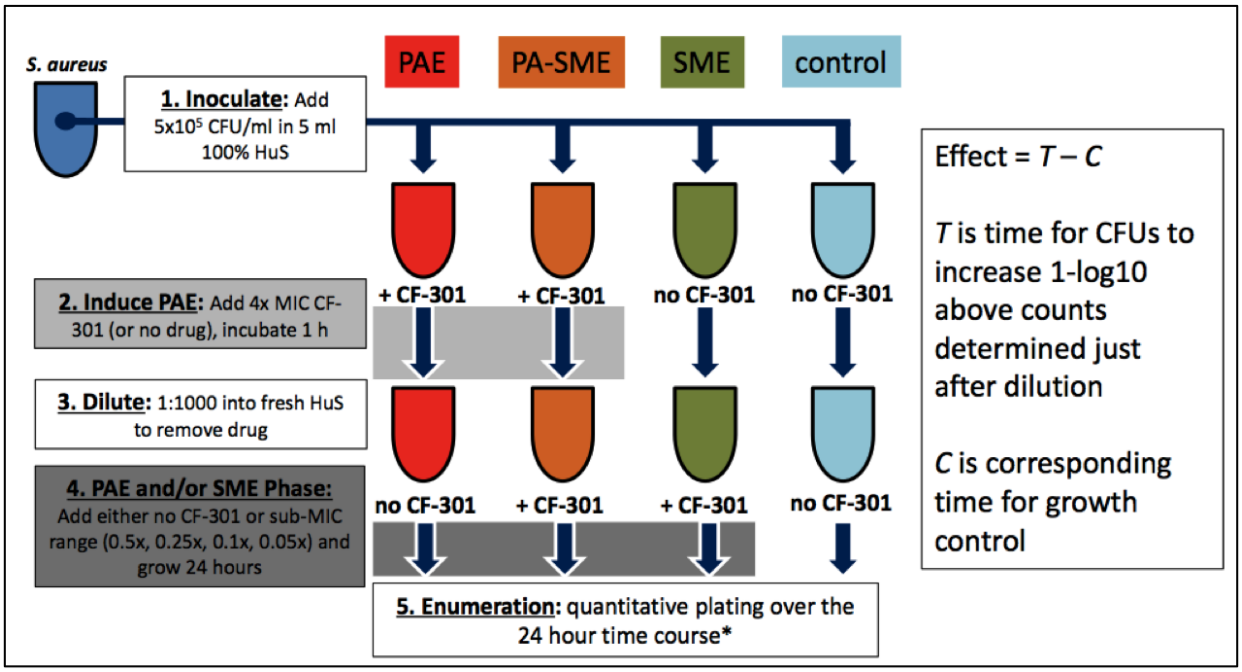
Source: ContraFect Corp.

Post-Antibiotic Effect of CF-301

In a presentation titled "Post-Antibiotic Effects of Lysin CF-301 Against *Staphylococcus aureus* in Human Serum" data was presented on the *in vitro* pharmacodynamic properties of CF-301 in relation to suppressed bacterial growth after levels of the lysin fall below the MIC. The post-antibiotic effect (PAE) is a phenomenon related to the time it takes for normal cell growth to resume following removal of an antibiotic treatment (Spivey, 1992). Additional parameters that were examined for CF-301 included:

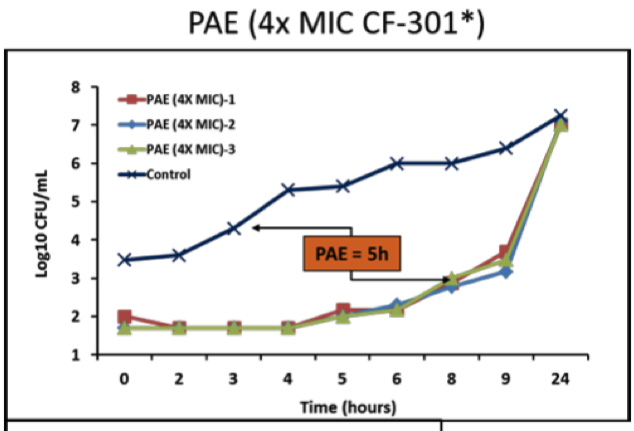
- Post-Antibiotic Sub-MIC Effect (PA-SME): the effect of sub-MIC levels of CF-301 during the PAE phase
- Sub-MIC Effect (SME): direct effect of sub-MIC levels of CF-301 without previous antibiotic exposure

The following slide shows how the PAE, PA-SME, and SME experiments were conducted. *S. aureus* cultures were added to human sera and 4x MIC levels of CF-301 were added to the PAE and PA-SME cultures while the SME and control cultures were given no drug. After one hour, these cultures were diluted 1:1000 in fresh human sera to remove the drug. Sub-MIC levels of CF-301 were then added to the PA-SME and SME cultures while the PAE and control cultures received no additional treatment. Cultures were grown for 24 hours and the PAE, PA-SME, or SME was defined as the difference in time between control and treated wells to increase CFUs by 1-log10 above the counts just after dilution.



Source: ContraFect Corp.

The following figure shows the results from the PAE experiment with a single strain of *S. aureus*. The graph shows the delay in growth of the *S. aureus* cultures following removal of CF-301 (time = 0). It took three hours for the control culture CFU's to increase 1-log10, while it took eight hours for the CF-301 treated culture CFU's to increase by the same amount, thus the PAE was calculated as five hours. The table on the right shows the effects on growth with different multiples of CF-301 MIC. These results point to the fact that even following treatment with CF-301 when the lysin concentration has fallen below the MIC, there is still a window of opportunity where treatment with antibiotics or even the patient's immune system could more easily fight a bacterial infection due to the fact that cell growth is inhibited.



PAE ranging studies

PAE Induction [CF-301] (xMIC)	PAE Phase	Mean Effect (h)
4	No CF-301	5.0
2		3.0
1		2.0
0.5		2.0
0.25		2.0
0.1		1.0

Source: ContraFect Corp.

The effect of PAE, PA-SME, and SME were further evaluated against 14 *S. aureus* strains, all of which had resistance to at least one class of antibiotic. The results show that the mean PAE effect was 4.8 hours. This effect was enhanced when sub-MIC levels of CF-301 were added following the PAE induction phase (PA-SME results). Similar results were seen with sub-MIC levels of CF-301 as the primary exposure (SME results).

	PAE Induction [CF-301] (xMIC)	PAE and/or SME Phase (xMIC)	Mean Effect (h)
PAE	4x	0	4.8
PA-SME	4x	0.5x	7.5
		0.25x	7.2
		0.1x	5.6
		0.05x	4.9
SME	0	0.5x	7.8
		0.25x	7.1
		0.1x	3.6
		0.05x	1.1

Source: ContraFect Corp.

Since CF-301 is going to be tested in conjunction with standard of care antibiotics, the effect of daptomycin and CF-301 in combination on PAE and PA-SME was tested. The results show an additive effect when CF-301 and daptomycin were used in combination, with a synergistic effect (i.e. more than additive) when the two drugs were utilized in a staggered dosing scheme (the PA-SME results). Whether CF-301 or daptomycin was used during the PAE induction phase did not appear to alter the results considerably.

		PAE Induction		PAE and/or SME Phase		Mean Effect (h)		
		[CF-301]	[DAP]	[CF-301]	[DAP]	Total	Synergy*	
PAE	Induce PAE with CF-301 and DAP	0.5x	1.5x	no		3	0	PAE
		0.25x				3	0	
		0.1x				2	0	
PA-SME	PAE with CF-301, SME with DAP	4x	no	no	0.25x	12	7	PA-SME
					0.1x	6	2	
					0.05x	6	2	
					0.01x	6	2	
PA-SME	PAE with DAP, SME with CF-301	no	1.5x	0.5x	no	12	4	PA-SME
				0.25x		12	5	
				0.1x		5	0	

Source: ContraFect Corp.

*single-agent-only contributions were subtracted out

CF-301 treatment results in pronounced PAE, PA-SME, and SME affects both alone and in combination with daptomycin. The combination results are particularly important as they fully support the clinical development plan for CF-301, which involves administering the drug in combination with standard of care antibiotics.

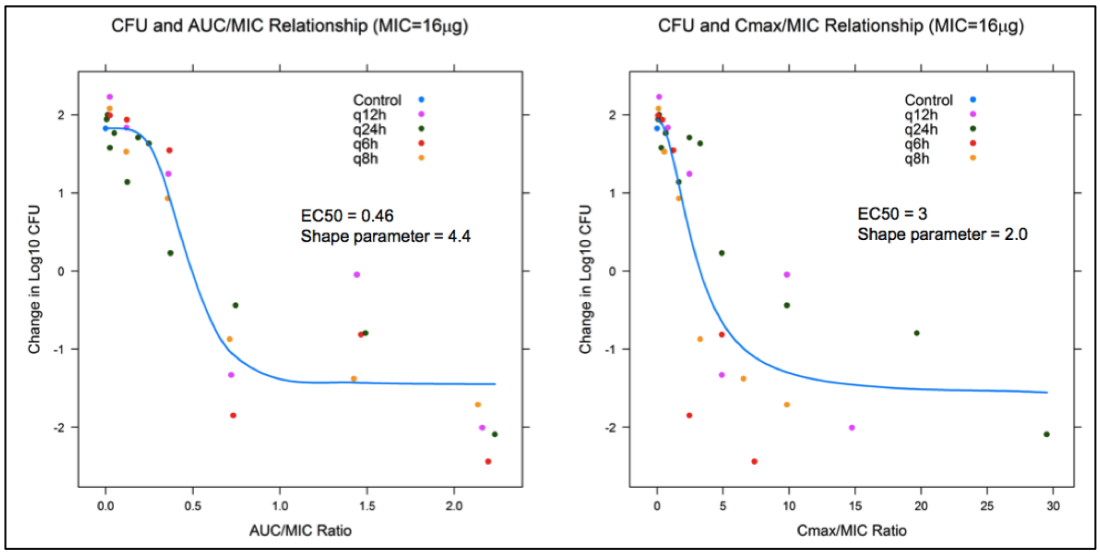
PK/PD Modeling Supports the Selected Dose Level for Phase 2 Study

In a poster titled "PK-PD Driver of Efficacy for CF-301, a Novel Anti-Staphylococcal Lysin: Implications for Human Target Dose", researchers utilized a murine thigh infection model to characterize CF-301 pharmacokinetics/pharmacodynamics (PK/PD) parameters to determine the optimal dosing of CF-301 both alone and in combination with standard-of-care antibiotics such as daptomycin.

The two most common parameters that are evaluated in PK modeling are C_{max} and AUC. C_{max} refers to the maximal concentration of an agent in the bloodstream following administration. Area Under the Curve (AUC) refers to the

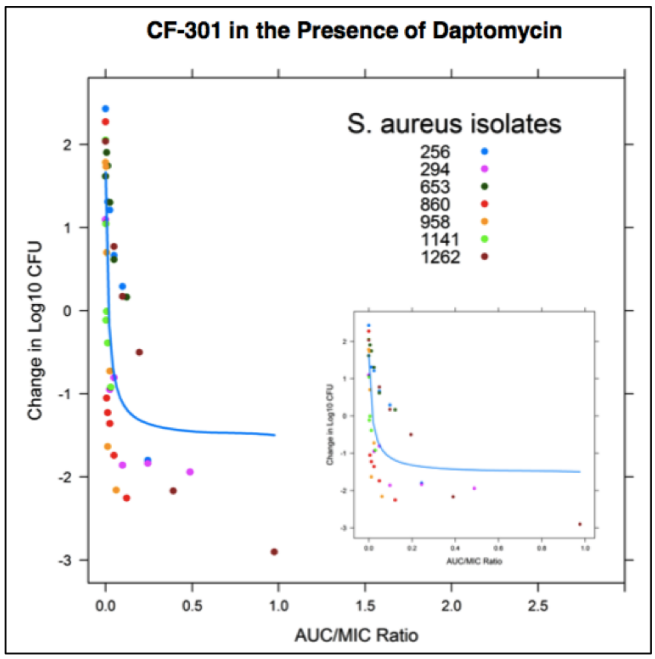
actual body exposure to a drug after administration and is dependent upon how much drug is administered and the rate of elimination from the body.

Experiments were performed with different concentrations of CF-301 to determine the effect of dose on change in bacterial cell counts. The following graphs show how increasing amounts of CF-301 (depicted as a ratio of either Cmax/MIC or AUC/MIC) leads to decreases in bacterial cell counts. CF-301 was administered in 1, 2, 3, or 4 doses over a 24-hour period, at which time cell growth was quantified. The blue line is fitted to the data, with the shape parameter indicative of how "good" a fit the line is. AUC/MIC was determined to be the optimal parameter for predicting change in bacterial cell growth, with an AUC/MIC value > 1.0 necessary for optimal efficacy.



Source: Rotolo *et al*., 2016

When this experiment was performed in combination with daptomycin, the AUC/MIC ratio needed for maximal efficacy decreased to 0.5, as shown in the following figure. This experiment was performed with multiple *S. aureus* strains.



Source: Rotolo *et al*., 2016

To calculate what dose in humans is required to achieve an AUC/MIC ratio of 0.5 it is necessary to know the average AUC following CF-301 administration (which is shown in the following table on the left from a Phase 1 clinical study) as well as MIC levels for various *S. aureus* isolates (which is shown in the following table on the right).

Summary of PK Parameters for CF-301				
Parameter*	0.04 mg/kg n=4	0.12 mg/kg n=4	0.25 mg/kg n=4	0.4 mg/kg n=1
C_{max} (ng/mL)	205 (14.2)	489 (16.1)	731 (25.4)	1,212
$AUC_{(0-t)}$ (hr×ng/mL)	498 (12.8)	1,121 (16.0)	1,749 (25.0)	3,311
$AUC_{(0-inf)}$ (hr×ng/mL)	503 (12.6)	1,126 (16.0)	1,758 (24.8)	3,316
$t_{1/2}$ (hr)	6.58 (52.6)	4.37 (6.79)	6.05 (64.9)	11.3
*Geometric mean (geometric CV)				

Strain Number	MHB MIC	Mus MIC	HuS MIC
CFS-256	8	8	0.5
CFS-294	32	16	0.5
CFS-311	16	8	1
CFS-653	8	16	1
CFS-860	64	16	2
CFS-958	64	32	0.5
CFS-968	16	16	1
CFS-988	32	128	0.5
CFS-1141	32	64	0.5
CFS-1262	2	2	0.5

Source: Rotolo *et al.*, 2016

According to the above right table, the MIC for the *S. aureus* strains tested range from 0.5 to 2.0, which is expressed in µg/mL. The AUC data in the above left table is expressed in ng/mL, thus the values for 0.12 mg/kg and 0.25 mg/kg dosing are 1.1 and 1.7 hr x µg/mL, respectively. In order to achieve an AUC/MIC ratio of 0.5 for the "worst case" strain (MIC of 2.0), it would be necessary to have an AUC >1.0 (AUC/MIC = 0.5; 1.0/2.0 = 0.5). This is consistently achieved with a CF-301 dose of 0.25 mg/kg, thus justifying that dosing level in the upcoming Phase 2 clinical trial.

Next Steps in Development of CF-301

The company has recently disclosed details for a Phase 2 clinical trial of CF-301 in patients with bacteremia, including those with endocarditis, which is caused by both MRSA and methiciliin-sensitive strains that is scheduled to begin in the fourth quarter of 2016. It will be an international, multicenter, randomized, double blind, placebo controlled trial with a superiority comparison between CF-301 combined with the standard of care antibiotics compared to placebo with the standard of care antibiotics. The study will include 115 patients randomized 3:2 to receive a single dose of 0.25 mg/kg CF-301 administered via a two-hour infusion or placebo. The primary endpoint of the study will be early clinical response. Safety, tolerability, and pharmacokinetics will also be examined along with additional exploratory clinical and health economic endpoints. We anticipate that the trial will cost anywhere from $10 to $20 million to run and topline results should be available in the second quarter of 2018. The company is not planning to perform an interim analysis.

Conclusion and Valuation

Due to the increasing prevalence of antibiotic resistant bacteria, novel treatments to combat bacterial infections are of vital interest. We believe the unique nature by which CF-301 kills bacteria, along with a low propensity to induce resistance and the ability to work in conjunction with standard of care antibiotics, could lead to a paradigm shift in the treatment of bacterial infections.

The PK/PD and microbiological data discussed in this report are important as they justify the company's plan in terms of both dosing of CF-301 and its use in conjunction with standard of care antibiotics. When combined with the fact that no hypersensitivity reactions were seen during the Phase 1 safety study, we are increasingly confident that CF-301 will prove to be highly efficacious in patients with bacteremia.

Our probability adjusted discounted cash flow model, which takes into account potential future revenues from CF-301 and the company's influenza treatment CF-404, yields a valuation of $12 per share. We continue to be highly enthusiastic about the lysin technology and ContraFect's prospects, and believe that those interested in the anti-infective space should consider taking a close look at ContraFect.

PROJECTED INCOME STATEMENT

ContraFect Corp.
Income Statement

ContraFect Corp.	2015 A	Q1 A	Q2 E	Q3 E	Q4 E	2016 E	2017 E	2018 E
CF-301 (Bacteremia)	$0	$0	$0	$0	$0	$0	$0	$0
YOY Growth	-	-	-	-	-	-		
CF-404 (Flu)	$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	$15.0	$4.4	$3.5	$4.8	$5.3	$18.0	$18.0	$21.0
General & Administrative	$10.1	$4.7	$2.9	$3.0	$3.0	$13.6	$13.0	$14.0
Other Expenses	$0	$0	$0	$0	$0	$0	$0	$0
Operating Income	($25.1)	($9.2)	($6.4)	($7.8)	($8.3)	($31.7)	($31.0)	($35.0)
Operating Margin	-	-	-	-	-	-		
Non-Operating Expenses (Net)	($0.1)	$0.2	($0.1)	($0.1)	($0.1)	$0.1	($0.1)	($0.1)
Pre-Tax Income	($25.1)	($8.9)	($6.5)	($7.9)	($8.4)	($31.6)	($31.1)	($35.1)
Income Taxes Paid	$0	$0	$0	$0	$0	$0	$0	$0
Tax Rate	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*
Net Income	**($25.1)**	**($8.9)**	**($6.5)**	**($7.9)**	**($8.4)**	**($31.6)**	**($31.1)**	**($35.1)**
Net Margin	-	-	-	-	-	-		
Reported EPS	**($1.08)**	**($0.32)**	**($0.23)**	**($0.28)**	**($0.27)**	**($1.11)**	**($0.89)**	**($0.92)**
YOY Growth	-	-	-	-	-	-		
Basic Shares Outstanding	23.3	27.5	27.5	28.0	31.0	28.5	35.0	38.0

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

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