Zacks Small-Cap Research

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Motif Bio Plc

MTFB - NASDAQ

MTFB: Initiating Coverage of Motif Bio Plc; Novel Antibiotic With Positive Phase 3 Results…

Based on our probability adjusted DCF model that takes into account potential future revenues from Iclaprim, MTFB is valued at $28 per share. This model is highly dependent upon continued clinical and commercial success of Iclaprim and will be adjusted accordingly based upon future clinical results and the company's execution.

Current Price (09/05/2017)	$7.24
Valuation	**$28.00**

INITIATION

Motif Bio Plc is a British biopharmaceutical company developing novel antibiotic products for the treatment of life-threatening infections in hospitalized patients caused by multi-drug resistant bacteria. The company's lead product, iclaprim, is a novel inhibitor of bacterial dihydrofolate reductase (DHFR), a differentiated mechanism of action that is only utilized by one other FDA approved antibiotic.

The company has successfully completed one Phase 3 clinical trial of iclaprim in patients with acute bacterial skin and skin structure infection (ABSSSI) and results from a second Phase 3 clinical trial in ABSSSI are due to be released in the second half of 2017. If approved, iclaprim will be entering a potential $2.8 billion opportunity in the U.S. alone and we project peak sales could top $700 million worldwide.

SUMMARY DATA

52-Week High	**$10.67**
52-Week Low	**$5.29**
One-Year Return (%)	**N/A**
Beta	**N/A**
Average Daily Volume (sh)	**2,279**
Shares Outstanding (mil)	**13**
Market Capitalization ($mil)	**$95**
Short Interest Ratio (days)	**N/A**
Institutional Ownership (%)	**43**
Insider Ownership (%)	**16**
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 #Lin Estimate	**N/A**
P/E using #Lin Estimate	**N/A**

Risk Level	**N/A**
Type of Stock	**Large-Growth**
Industry	**Med-Biomed/Gene**

ZACKS ESTIMATES

Revenue
(In millions of $)

	Q1 (Mar)	Q2 (Jun)	Q3 (Sep)	Q4 (Dec)	Year (Dec)
2016	0.0 A	0.0 A	0.0 A	0.0 A	0.0 A
2017	0.0 E	0.0 E	0.0 E	0.0 E	0.0 E
2018					0.0 E
2019					11.0 E

Earnings per ADS

	Q1 (Mar)	Q2 (Jun)	Q3 (Sep)	Q4 (Dec)	Year (Dec)
2016	-$1.21 A	-$1.40 A	-$1.90 A	-$2.41 A	-$6.92 A
2017	-$0.93 E	-$0.80 E	-$0.69 E	-$0.70 E	-$3.06 E
2018					-$3.38 E
2019					-$2.30 E

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WHAT'S NEW

Initiating Coverage

We are initiating coverage of Motif Bio Plc with a $28 valuation. Motif is a biopharmaceutical company developing novel antibiotic treatments for patients with life threatening multi-drug resistant infections. The company's lead compound, iclaprim, is being developed for the treatment of acute bacterial skin and skin structure infections (ABSSSI) and hospital-acquired bacterial pneumonia (HABP). Iclaprim is currently being tested in a Phase 3 program (REVIVE) for the treatment of ABSSSI. In April 2017, the company announced positive results from the REVIVE-1 study, which compared the safety and efficacy of iclaprim with vancomycin (which is used in approximately three-quarters of ABSSSI patients). The results showed that iclaprim achieved the primary endpoint of non-inferiority at the early time point at 48 to 72 hours after the start of treatment. In addition, iclaprim achieved non-inferiority at the test of cure endpoint at 7 to 14 days after discontinuing treatment. As it is a nearly identical study simply performed at different clinical sites, we anticipate similar results in the REVIVE-2 study.

Iclaprim has a number of positive attributes that we believe could lead it to become a commercially successful antibiotic treatment, including:

- **Novel Mechanism of Action**. Iclaprim is an inhibitor of bacterial dihydrofolate reductase (DHFR), which is a differentiated mechanism of action compared to other antibiotics. Trimethoprim is a DHFR inhibitor that is used along with a sulfonamide due to their synergism, however the use of a sulfonamide with iclaprim is unnecessary due to its increased potency. In addition, a certain mutation in some bacterial DHFR proteins confers resistance to trimethoprim, however iclaprim can overcome this resistance.

- **Strong Safety Record**. Iclaprim has been tested in over 1,300 patients and healthy volunteers during Phase 1, 2, and 3 clinical trials with no outstanding safety issues reported.

- **Ability to Treat Patients With Renal Impairment**. Thus far, iclaprim has not shown any signs of nephrotoxicity in clinical trials and there is no need for monitoring or dosage adjustment in patients with renal insufficiency. This is in contrast to vancomycin, which is known to cause nephrotoxicity and require dosage adjustment in patients with decreased renal function.

- **Expandable to Other Indications**. Iclaprim has compelling Phase 2 data showing increased activity and decreased side effects compared to vancomycin in patients with HABP. The company is planning to initiate a Phase 3 clinical trial in HABP before the end of 2017.

- **Entering a Large Market**. Motif is targeting the approximately 25% of the 3.6 million ABSSSI patients in the U.S. that have renal insufficiency. Vancomycin, which is currently used in approximately three-quarters of patients hospitalized with methicillin-resistant *Staphylococcus aureus* (MRSA) infections, requires therapeutic drug monitoring as it has been associated with nephrotoxicity.

The company has a very important milestone coming up in the second half of 2017 with the release of topline data from the REVIVE-2 study. Positive results will lead to a new drug application (NDA) filing in the first half of 2018. Since iclaprim is designated a qualified infectious disease product (QIDP), which grants the compound Fast Track designation and priority review, approval could occur before the end of 2018. QIDP also confers an additional five-years of market exclusivity, which is added sequentially to the five-years of exclusivity granted to New Chemical Entities, for a total of ten years starting from the date of approval.

INVESTMENT THESIS

Motif Bio is a biopharmaceutical company focused on the development of antibiotic compounds for difficult to treat bacterial infections. The company's lead asset, iclaprim, is a novel diaminopyrimidine molecule that is currently in Phase 3 testing for the treatment of acute bacterial skin and skin structure infections (ABSSSI). Motif has already announced positive results from the first Phase 3 study, and we anticipate results from the second Phase 3 study will be announced in the second half of 2017. A second Phase 3 program in hospital acquired bacterial pneumonia (HBAP) is expected to initiate later in 2017. The company has a number of near term milestones that could potentially result in FDA approval in late 2018 in a market that is currently valued at approximately $2.8 billion.

New Antibiotics Needed

There is a pressing need for new antibiotics due to the development of antibiotic resistance. The Centers for Disease Control (CDC) published a report in 2013 on antibiotic resistance in the U.S. and the potential for catastrophic consequences if nothing is done to correct the problem. Each year, at least 2 million individuals in the U.S. contract a serious infection involving a bacterium that is resistant to one or more antibiotics, with at least 23,000 people dying each year as a result of antibiotic-resistant infections. In fact, methicillin-resistant *Staphylococcus aureus* (MRSA) infections in U.S. hospitals are responsible for more deaths than HIV/AIDS and tuberculosis combined (Klevens *et al*., 2006; Boucher *et al*., 2009).

Sir Alexander Fleming, the discoverer of penicillin, first warned against the development of antibiotic resistant bacteria shortly after the widespread use of antibiotics began in the 1950's. The rate of antibiotic resistant strains of bacteria has been growing rapidly since the 1980's, with more than 70% of hospital acquired infections resistant to at least one of the drugs commonly used to treat them. Antibiotic resistance is fueled by the misuse and overuse of antibiotics in both the clinical and veterinary setting. It is estimated that a total of 23×10^6 kg of antibiotics are used annually in the U.S.; half of which is used for the treatment of disease in people with the other half reserved for agriculture and given to livestock animals (Harrison *et al*., 1998). The widespread use of antibiotics results in the survival and selection for organisms that harbor mechanisms for self-preservation, and with the ability of microorganisms to share genetic material these self-preserving principles are spreading rapidly and leading to an abundance of antibiotic-resistant microbes.

The rise of antibiotic resistance not only affects the ability to fight routine infections, but it also undermines the treatment of infectious diseases in patients with other diseases. A number of medical advancements were possible due to the ability to fight infections with antibiotics. These include joint replacements, organ transplants, cancer therapy, and the treatment of various chronic diseases.

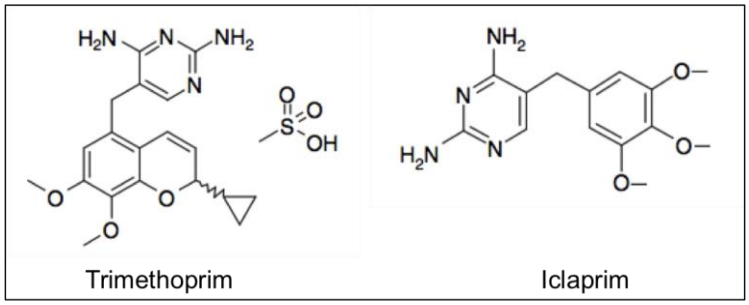
Adding to the urgency of antibiotic resistance, typically when an organism develops resistance to one member of a class of antibiotics it quickly develops resistance to that entire class. For example, resistance to penicillin quickly gave rise to resistance to all penicillin-like molecules, thus rendering an entire group of compounds ineffective. For this reason, not only are new antibiotics required, but more importantly antibiotics with differentiated mechanisms of action.

Iclaprim's Differentiated Mechanism of Action

Tetrahydrofolic acid (THF) is a folic acid derivative that serves as a cofactor in a number of important biochemical reactions, including the synthesis of amino acids and nucleic acids. THF is produced through a series of enzymatic steps, with the final step being catalyzed by dihydrofolate reductase (DHFR) (Fierke *et al*., 1987). DHFR is the sole source of THF, and rapidly dividing cells are particularly sensitive to its inhibition as THF and its cofactors play an important role in cell growth and proliferation. Due to this, a number of anticancer and antimicrobial drugs have been developed to exploit this mechanism of action (Schweitzer *et al*., 1990).

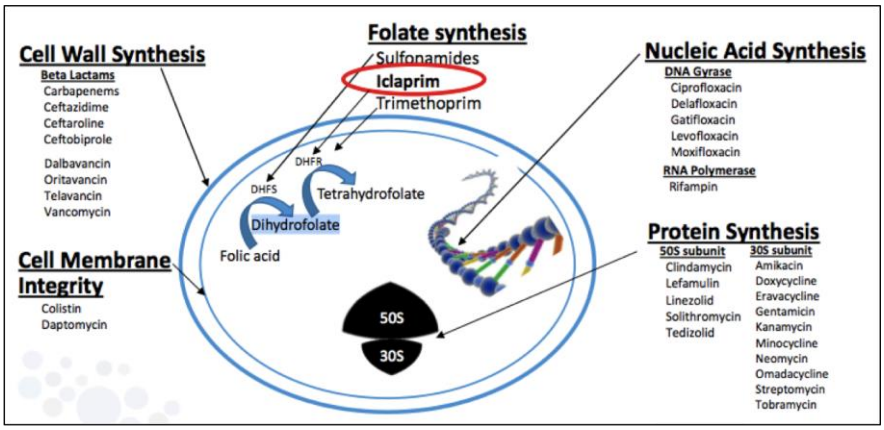
Bacterial and human DHFR differ in a number of parameters, and these differences led to the discovery of the antibiotic trimethoprim (TMP). TMP is a diaminopyrimidine that binds to bacterial DHFR with an affinity 10^5 times greater than human DHFR (Hitchings *et al*., 1965). It is active against most aerobic Gram-negative and Gram-positive bacteria (Bushby, 1973). TMP is typically prescribed in combination with sulfonamides, which are known to have a high incidence of hypersensitivity reactions, some of which can be serious. Resistance to TMP is common in *Staphylococcus aureus* due to a single amino acid substitution in DHFR, Phe98->Tyr98 (Dale *et al*., 1997).

Due to increasing resistance to TMP, and the side effects caused by the use of sulfonamides with TMP, researchers at Roche developed a series of diaminopyrimidine molecules in order to identify improved DHFR inhibitors. Iclaprim emerged as a potent inhibitor of bacterial DHFR, with activity against a broad range of Gram-positive pathogens, including *S. aureus* strains that are resistant to TMP as well as other clinically relevant antibiotics such as methicillin and oxacillin (e.g., methicillin-resistant *S. aureus*, MRSA).



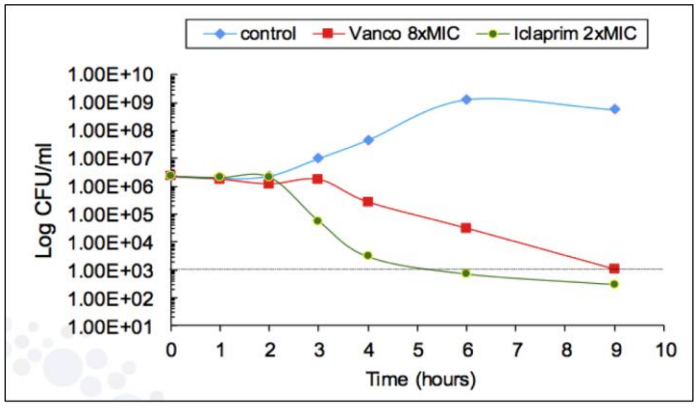
Source: Kohlhoff *et al*., 2007

As shown in the following figure, TMP is the only approved antibiotic that targets DHFR. This is important in regards to the development of antibiotic resistance. As mentioned previously, when a bacterial species acquires resistance to a certain antibiotic, it is typically resistant to all members of that class of compounds (e.g., molecules that inhibit cell wall synthesis). However, since iclaprim targets a unique metabolic pathway, bacteria that develop resistance to one class of compounds (e.g., cell wall synthesis inhibitors) are unlikely to also be resistant to iclaprim.



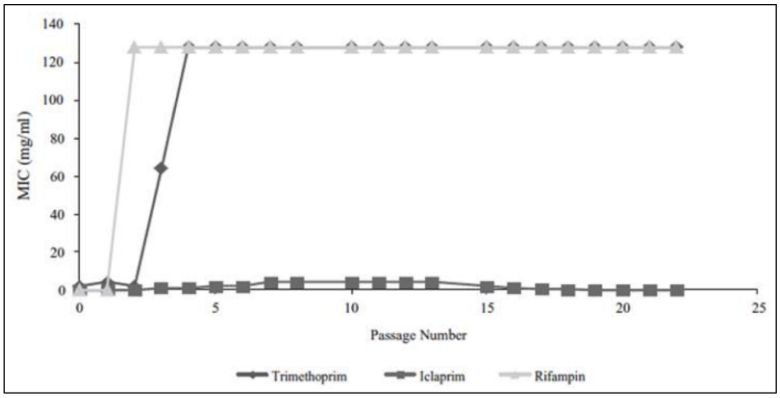
Source: Motif Bio Plc

Iclaprim's differentiated mechanism of action is further enhanced by its rapid bactericidal activity *in vitro*. The following graph shows a representative time kill curve for a 15 Gram-positive strains tested. Iclaprim kills 99.9% of MRSA within four to six hours at 2x the minimum inhibitory concentration (MIC). The MIC is the minimum concentration of a drug that is required to prevent visible growth of a bacterium. In contrast to iclaprim, vancomycin takes eight to ten hours when tested at 8x MIC. For patients with severe bacterial infections, the ability to rapidly eliminate the causative agent is crucial in order to have a positive outcome.



Source: Motif Bio Plc

In addition, *in vitro* studies show that iclaprim does not show a propensity to induce antibiotic resistance. The following graph shows the results of a serial passage study that tested iclaprim, TMP, and rifampin against a total of 30 *S. aureus* strains. Bacteria were grown in the presence of sub-MIC levels of drug, and even after 22 passages *S. aureus* resistance to iclaprim was very low compared to resistance to TMP and rifampin, which showed resistance in as early as three passages.



Source: Motif Bio Plc

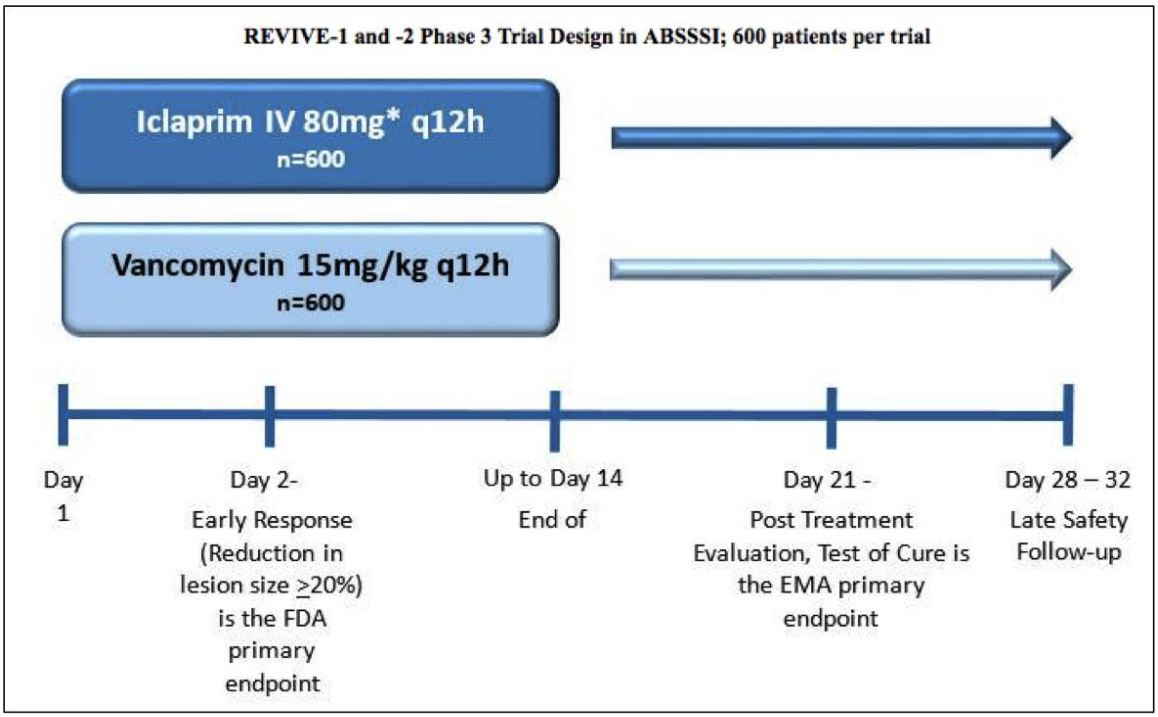
To summarize, the following chart gives some of the characteristics of iclaprim along with vancomycin, daptomycin, and linezolid.

Empiric Treatment Considerations: Hospitalized ABSSSI with Renal Impairment/Diabetes		Standard of Care Gram Positive Hospital Antibiotics		
	Iclaprim	Vancomycin	Daptomycin	Linezolid
Mechanism of Action	Underutilized MOA Diaminopyrimidine	Glycopeptide	Lipopeptide	Oxazolidinone
Cidality (*in vitro*)	Rapidly cidal;	Cidal	Cidal	Static
MRSA in-vitro activity MIC_{90} / MIC_{50} µg/mL n=582 isolates[2]	0.5/0.06	1/1	0.5/.25	1/1
Spectrum of Activity	Gram +	Gram +	Gram +	Gram +
Propensity for Resistance	Low propensity for resistance *in vitro*	MIC "creep," VISA, VRSA	Resistance reported	Resistance reported
Safety; considerations for use in diabetics	Low incidence of QTc prolongation and AEs leading to discontinuation	Nephrotoxic, ototoxic, infusion related events	Myopathy, rhabdomyolysis; eosinophilic pneumonia; peripheral neuropathy	Myelo-suppression serotonin syndrome; hypoglycemia when insulin or oral hypoglycemics are co-administered
Use in Renal Impairment	No dosage adjustment or monitoring/no nephrotoxicity observed	Nephrotoxicity risk especially with higher doses (*eg.* obese patients); dosage adjustment	Dosage adjustment required; decreased efficacy with moderate renal impairment	Primary metabolites accumulate; increases with severity of renal dysfunction; more frequent adverse events[3]
Dosing	Fixed	Weight based, monitoring required	Weight based; high drug cost in obese patients	Fixed

Source: Motif Bio Plc

Phase 3 Development Plan

Motif is currently conducting the REVIVE Phase 3 program for iclaprim in the treatment of ABSSSI that includes two randomized, double blind clinical trials (REVIVE-1 and REVIVE-2). Each 600-patient trial will have two arms, with patients receiving either iclaprim or vancomycin. The trials will evaluate both the FDA endpoint of an early clinical response of at least 20% reduction in a lesion size at 48-72 hours and the EMA endpoint of clinical cure at test of cure one to two weeks after antibiotic treatment ends. A fixed dose of 80 mg of iclaprim will be used, as the company believes that pharmacokinetic data from previous Phase 3 studies shows that as the optimal dose to maximize potential clinical efficacy and safety outcomes. The following diagram summarizes the REVIVE Phase 3 clinical trials.



Source: Motif Bio Plc

REVIVE-1 Results

On April 18, 2017, Motif announced positive results from the REVIVE-1 trial. Iclaprim achieved the primary endpoint of non-inferiority (10% margin) compared to vancomycin at the early time point (ETP) 48 to 72 hours after the start of administration of study drug in the intent-to-treat population. In addition, iclaprim achieved non-inferiority at the test of cure (TOC) endpoint, 7 to 14 days after study drug discontinuation in the intent-to-treat population. The following table shows the results for the two primary endpoints.

Time point	Endpoint	Iclaprim N=298	Vancomycin N=300	% Difference (95% CI)
ETP	Early Clinical Response (ECR)	241 (80.9%)	243 (81.0%)	-0.13 (-6.42, 6.17)
TOC	Clinical cure	251 (84.2%)	261 (87.0%)	-2.77 (-8.39, 2.85)

Source: Motif Bio Plc

In one pre-specified secondary endpoint, 60.4% of iclaprim-treated patients demonstrated resolution or near resolution at end of therapy compared to 58.3% of vancomycin-treated patients (treatment difference: 2.07%, 95% CI [-5.80% to 9.95%]). In another pre-specified secondary endpoint, using a modified clinical cure at the TOC endpoint (defined by a ≥90% reduction in lesion size at TOC, no increase in lesion size since ETP, and no requirement for additional antibiotics) clinical cure was seen in 68.5% of iclaprim-treated patients and 73.0% of vancomycin-treated patients (treatment difference: -4.54%, 95% CI [-11.83% to 2.74%]).

Importantly, Iclaprim was well tolerated in the study and most of the adverse events were categorized as mild, as shown in the following table.

	Iclaprim N=293	Vancomycin N=297
TEAEs (Treatment Emergent Adverse Events)	151 (51.5%)	128 (43.1%)
Study drug related TEAEs	57 (19.5%)	53 (17.8%)
TEAEs leading to discontinuation of study drug	8 (2.7%)	13 (4.4%)
TEAE related SAEs (Serious AEs)	8 (2.7%)	12 (4.0%)
Deaths	0 (0.0%)	1 (0.3%)

Source: Motif Bio Plc

We anticipate topline data from REVIVE-2, which was conducted just as REVIVE-1 except at different clinical sites, in the second half of 2017.

Previous Phase 3 Development of Iclaprim

Iclaprim was originally licensed by Roche to Arpida AG in 2001, after which Arpida completed a comprehensive development program that included two Phase 3, two Phase 2, and 14 Phase 1 clinical trials involving over 600 patients.

Phase 3 cSSSI Trials

Arpida conducted two parallel randomized, evaluator blinded, multicenter Phase 3 clinical trials (ASSIST-1 and ASSIST-2) in patients with complicated skin and skin structure infection (cSSSI). The trials were designed to compare the safety and efficacy of IV iclaprim to linezolid in patients with cSSSI known or suspected to be caused by susceptible pathogens (e.g., *S. aureus*). The primary endpoint of the studies was clinical cure rates at 7-14 days after the end of treatment. The studies were powered to demonstrate non-inferiority to linezolid with a lower bound of the 95% confidence interval (CI) of -12.5%.

ASSIST-1: In December 2006, Arpida reported positive results from the ASSIST-1 trial that enrolled a total of 497 patients with cSSSI. Subjects were randomized 1:1 to receive either IV iclaprim (0.8 mg/kg) or IV linezolid (600 mg) for 10-14 days. The results showed that iclaprim was well tolerated. The overall clinical cure rate for the intent-to-treat (ITT) population was 83.1% with iclaprim and 88.7% for linezolid (treatment difference and 95% CI: -5.6% [-11.7% to 0.6%]). There were a higher percentage of drug-related adverse events in linezolid-treated patients compared to iclaprim-treated patients (20.2% vs. 16.4%, respectively). Lastly, microbiological eradication rates were similar for the two drugs, with MSSA bacteria eradication occurring in 85.0% and 86.5% of iclaprim and linezolid patients, respectively, while MRSA bacteria eradication occurred in 80.0% and 83.8%, respectively.

ASSIST-2: In July 2007, Arpida reported positive results based on Arpida's analysis of the data from the ASSIST-2 trial, which enrolled a total of 494 patients with cSSSI. The overall clinical cure rates were 81.3% and 81.9% for iclaprim and linezolid, respectively (treatment difference and 95% CI: -0.6% [-7.7% to 6.5%]). Microbial eradications rates for MSSA bacteria were 82.2% and 83.4% for iclaprim and linezolid, respectively, while for MRSA it was 74.3% and 75.0%, respectively. Just as in the ASSIST-1 trial, there were a higher percentage of drug-related adverse events in linezolid-treated patients compared to iclaprim-treated patients (34.6% vs. 27.9%, respectively).

Combined Safety and Efficacy Data: When examining the combined data from both ASSIST-1 and ASSIST-2, the clinical cure rates were similar for iclaprim (82.2%) and linezolid (85.3%) treated patients for the intent to treat (ITT) population (treatment difference and 95% CI: -3.1% [-7.9% to 1.6%]). The data is summarized in the table below.

	0.8 mg/kg iclaprim	600 mg linezolid	Treatment Difference and 95% CI
ASSIST-1	N=249 Clinical Cure=207 (83.1%)	N=248 Clinical Cure=220 (88.7%)	-5.6% [-11.7% to 0.6%]
ASSIST-2	N=251 Clinical Cure=204 (81.3%)	N=243 Clinical Cure=199 (81.9%)	-0.6% [-7.7% to 6.5%]
Combined	N=500 Clinical Cure=411 (82.2%)	N=491 Clinical Cure=419 (85.3%)	-3.1% [-7.9% to 1.6%]

Source: Motif Bio Plc

Iclaprim was found to have a safety and tolerability profile that was comparable to linezolid. A total of 22 serious adverse events (SAEs) occurred in 20 (4%) of the iclaprim-treated patients, compared to a total of 21 SAEs that occurred in 16 (3.3%) of the linezolid-treated patients. The following table shows adverse events reported by ≥5% of patients in either treatment group.

	Iclaprim	Linezolid
Number of Patients	N=500	N=491
Alanine aminotransferase (ALT) increased	33 (6.6%)	31 (6.3%)
Aspartate aminotransferase (AST) increased	32 (6.4%)	26 (5.3%)
Nausea	30 (6.0%)	39 (7.9%)
Diarrhea	29 (5.8%)	22 (4.5%)
Constipation	27 (5.4%)	19 (3.9%)
Pyrexia	26 (5.2%)	10 (2.0%)
Headache	30 (6.0%)	28 (5.7%)
QT prolongation	4 (0.8%)	2 (0.4%)

Source: Motif Bio Plc

A total of six deaths occurred in ASSIST-1 (five in the iclaprim group and one in the linezolid group) while two deaths occurred in ASSIST-2 (1 in each treatment group). The investigators determined that all deaths were unrelated to iclaprim (two cases of sepsis, one case of alcoholic cardiomyopathy, one case of acute cardiac failure, one case of acute renal failure, and one case of colon cancer). Lastly, the incidence of QTc prolongation (which measures delays in the depolarization and repolarization of the heart's ventricles) was similar in the iclaprim- and linezolid-treated groups. Treatment with iclaprim resulted in a mean increase in QTc interval of approximately 5-6 ms greater than that observed with linezolid, which means that iclaprim is not considered a QTc-prolonging drug.

ABSSSI vs cSSSI

A skin and skin structure infection is a bacterial infection of skin and associated tissues. It may be complicated (denoted by a lower case "c") or uncomplicated. The uncomplicated category includes simple abscesses, impetiginous lesions, furuncles, and cellulitis mainly cause by *S. aureus* (including MRSA) and *Streptococcus pyogenes*. The complicated category includes infections involving deeper soft tissue or requiring significant surgical intervention. Since 2008, the FDA has referred to complicated skin and skin structure infections (cSSSI) as acute bacterial skin and skin structure infections (ABSSSI) and standardized the definition to include "cellulitis/erysipelas, wound infection, and major cutaneous abscess having a minimum lesion surface area of approximately 75 cm^2".

Regulatory Review

The primary efficacy endpoint for clinical trials for most new antibiotics is a non-inferiority comparison between the new compound and the standard of care (e.g., iclaprim vs. linezolid or vancomycin). Non-inferiority means that the new compound is either equivalent or superior to the current standard of care. Statistically speaking, equivalent means that the results obtained between the two treatments being compared are similar enough that no difference can be determined.

Statistical analysis using non-inferiority margins are used to determine the level of difference between the treatments being compared. The non-inferiority margins are the maximal difference that is allowed before declaring the new treatment to be clinically inferior.

While Arpida was developing iclaprim, the FDA was re-evaluating the requirement for the non-inferiority margin to support approval of new antibiotics. The accepted non-inferiority margin when the ASSIST clinical trials initiated was -12.5%. However, in 2008 the FDA decided that compounds for the treatment of skin and skin structure infections required a non-inferiority margin of -10% instead of -12.5%.

When Arpida conducted the data analysis from the ASSIST trials the agreed upon non-inferiority margin was -12.5%, thus the company believed that the two trials each had positive outcomes. Following submission of the NDA, the FDA "moved the goalposts" and evaluated the data for iclaprim using a non-inferiority margin of -10%, which was consistent with the revised guidelines. The ASSIST-1 trial did not meet the -10% non-inferiority margin, and thus Arpida received a complete response letter (CRL) from the FDA. The FDA did not indicate that there were any concerns related to the way Arpida conducted the Phase 3 trials, however the agency did request that additional studies be conducted to demonstrate the effectiveness of iclaprim, which could include non-inferiority studies comparing iclaprim to an approved comparator. Had Arpida been aware of the -10% non-inferiority margin requirement, the ASSIST trials likely would have been designed to include more patients in order to increase the statistical power.

Other Antibiotics With Similar Regulatory Pathway as Iclaprim

Iclaprim was not the only antibiotic to fall victim to the FDA altering the guidelines for non-inferiority testing in 2008. The FDA rejected oritavancin and dalbavancin each at approximately the same time as iclaprim based on clinical data that did not meet the 10% non-inferiority cutoff. However, both oritavancin and dalbavancin were studied in additional Phase 3 clinical trials (employing the same design as the REVIVE trials with vancomycin as the comparator) and each was approved for the treatment of ABSSSI in 2014. While some investors may be nervous about a compound that was previously rejected by the FDA, the fact that other antibiotics that were not approved for a similar reason as iclaprim have now gone on to be approved, should give investors confidence that Motif is following the correct regulatory pathway for iclaprim.

Early Stage Clinical Development of Iclaprim

Phase 2 cSSSI Trial: In December 2003, Arpida completed a randomized, double blind comparator controlled Phase 2 trial of iclaprim for the treatment of cSSSI. It included 87 hospitalized patients and compared the safety and efficacy of two different doses of iclaprim (0.8 or 1.6 mg/kg) with a standard of care antibiotic, vancomycin (1 g). Each medication was administered by intravenous (IV) infusion two or three times daily for 10 days. Patients were examined for clinical and microbiological response at the conclusion of therapy and 20 days after therapy. The primary endpoint was clinical cure and secondary endpoints included tolerability and microbiological responses. Results showed a clinical cure rate of 92.9% (26/28 patients) with iclaprim 0.8 mg/kg, 90.3% (28/31 patients) with iclaprim 1.6 mg/kg, and 92.9% (26/28 patients) with vancomycin. Gram-positive eradication rate was 89.7% with iclaprim 0.8 mg/kg, 80.0% with iclaprim 1.6 mg/kg, and 72.0% with vancomycin. The results are summarized in the table below.

Phase 2 Trial of Iclaprim in Patients with cSSSI (N=87)

	0.8 mg/kg iclaprim	1.6 mg/kg iclaprim	1 g vancomycin
Intent to Treat Population (N=)	28	31	28
Clinical Cure (N=)	26	28	26
% Clinical Cure	*92.9%*	*90.3%*	*92.9%*
Gram-positive eradication rate	*89.7%*	*80.0%*	*72.0%*
S. aureus *eradication rate*	*80.0%*	*72.2%*	*58.8%*

Source: Motif Bio Plc

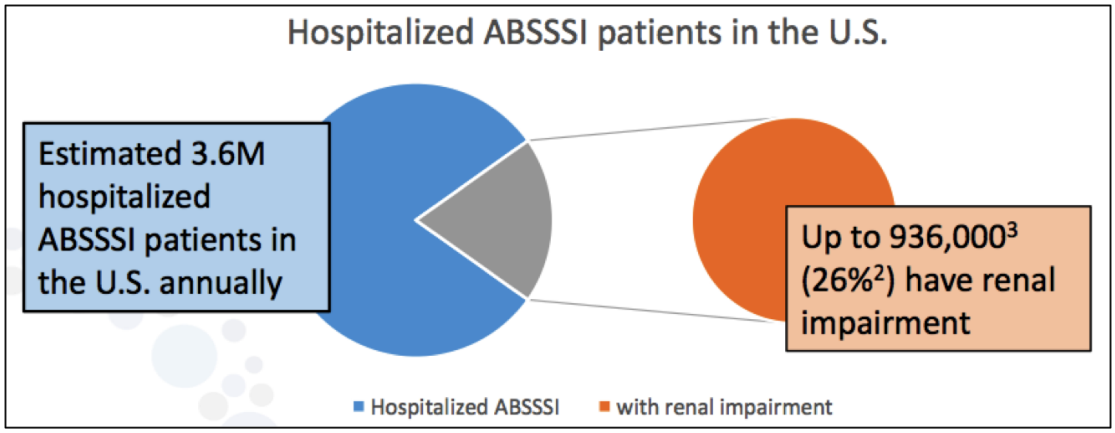
Phase 1 Clinical Trials: Iclaprim has been studied in single and multiple ascending dose studies. Single IV doses of iclaprim up to 3.2 mg/kg, repeated doses of 60 or 120 mg of iclaprim administered twice daily for 10 days, and doses of 0.8 mg/kg and 1.6 mg/kg administered twice daily for up to 10 days all resulted in safety and tolerability profiles similar to both vancomycin and linezolid. Formal QT/QTc studies showed dose-dependent transient and rapidly reversible prolongation of the corrected QT interval. However, 0.8 and 1.6 mg/kg iclaprim infused over 30- and 60-minute intervals were determined to be safe for clinical use. The QTc increase after a 30-minute infusion of 0.8 mg/kg iclaprim was approximately 10 ms at maximal plasma levels and declined rapidly thereafter.

ABSSSI Market

The worldwide antibiotic market is estimated to be approximately $40 billion. Two antibiotics targeting Gram-positive infections in hospitalized infections achieved blockbuster status in the past five years: Cubicin® (daptomycin), which had peak worldwide sales of $1.2 billion in 2015, and Zyvox® (linezolid), which had peak worldwide sales of $1.3 billion in 2014 (EvaluatePharma).

The most widely prescribed antibiotic for treating MRSA infections in the U.S. (which includes ABSSSI) is vancomycin, which accounted for an estimated 74% of patient days on therapy for MRSA in 2013, 2014, and 2015. While vancomycin is an effective antibiotic, it is associated with a number of adverse side effects and consequences, including nephrotoxicity, ototoxicity, the necessity for therapeutic drug monitoring for dosage adjustments, and extended treatment periods (average = 13 days). Patients with any type of renal impairment need to be monitored closely while on vancomycin, which results in an estimated cost to treat those patients of $28,000 (compared to approximately $23,600 for patients without renal impairment). Lastly, resistance to vancomycin is increasing in MRSA infections.

It is estimated that of the approximately 3.6 million ABSSSI patients in the U.S., approximately one-quarter of them have some type of renal impairment (Halilovic *et al*., 2012). Iclaprim has never shown nephrotoxicity in the over 900 patients that it has been tested in thus far. In addition, iclaprim does not require therapeutic drug monitoring or dosage adjustments based on renal toxicity. Thus, targeting ABSSSI patients with renal insufficiency is a logical market for Motif to focus on and represents a >$2 billion opportunity.



Source: Motif Bio Plc

ABSSSI drugs that have been recently approved could prove formidable competition for iclaprim, although Motif is targeting a niche market (hospitalized ABSSSI patients with renal insufficiency) that may ensure sufficient differentiation from drugs such as Sivextro®, Dalvance®, and Orbactiv®. In the case of Dalvance®, and Orbactiv®, both of those drugs only require a single shot, thus making them a convenient option for patients and physicians. However, Orbactiv® has a number of contra-indications (e.g., anti-coagulants) and Dalvance® can result in anaphylaxis, a side effect that has not bee reported for iclaprim thus far.

Secondary Indication in HABP and VABP Offers Additional Upside

In addition to treating ABSSSI, Motif is preparing to test iclaprim in a Phase 3 program as a treatment for hospital acquired bacterial pneumonia (HABP) and ventilator associated bacterial pneumonia (VBAP). HBAP refers to a pneumonia that is acquired following at least 48 hours in the hospital while VABP refers to pneumonia that develops 48 hours or more after mechanical ventilation.

Motif has produced data showing that iclaprim's concentration in epithelial lining fluid (ELF) and alveolar macrophages (AM) is elevated in comparison to serum levels, as shown in the following chart following dosing of healthy volunteers. The concentration of iclaprim in ELF and AM was 20 to 30 times the serum concentration, which could lead to positive outcomes for treating lung infections.

Antibiotic	Dose	Epithelial lining fluid (mg/L)	Alveolar macrophages (mg/L)	Serum (mg/L)	ELF/serum concentration	AM/serum concentration
Iclaprim	1.6 mg/kg IV, single dose	40.9	67.7	1.8	22.7	37.6
Linezolid	600 mg q12h PO, 5 doses	622.8	27.2	190.0	3.3	0.14
Vancomycin	1 g q12h IV, 9 doses	92	926	367	0.25	2.5

Source: Motif Bio Plc

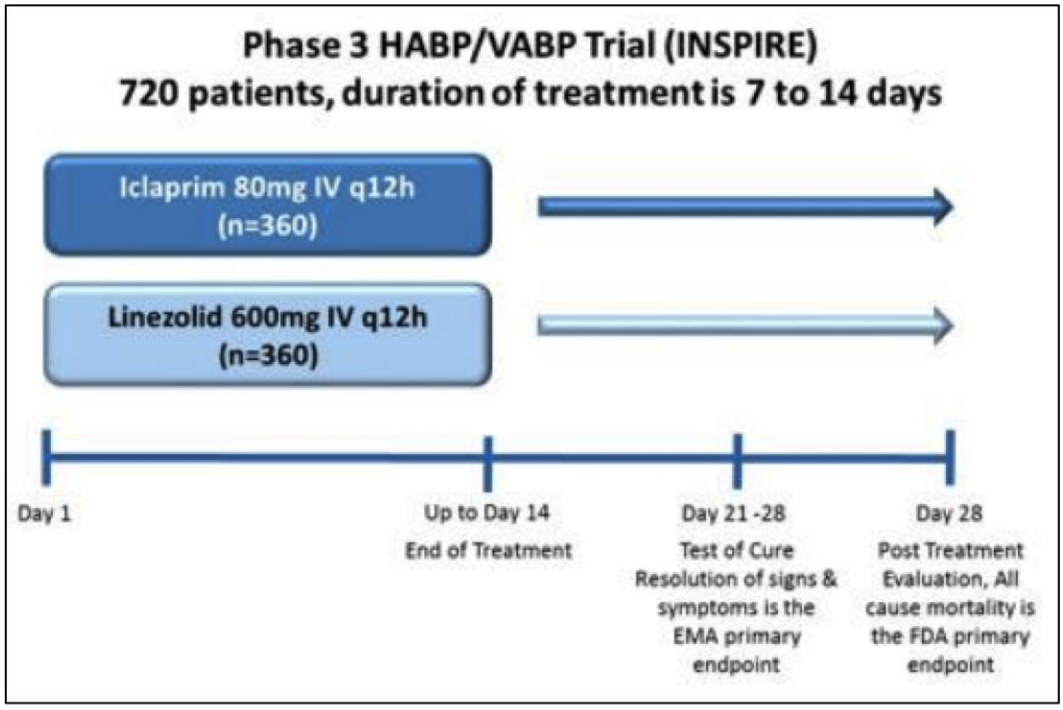
Arpida conducted a double blind, randomized, dose ranging Phase 2 proof of concept study in patients with HABP, including VABP. A total of 70 patients were randomized 1:1:1 to receive 0.8 mg/kg iclaprim, 1.2 mg/kg iclaprim, or 1 g vancomycin either two or three times daily. Results showed a clinical cure rate of 73.9% (17/23 patients) with 0.8 mg/kg iclaprim, 62.5% (15/24 patients) with 1.2 mg/kg iclaprim, and 52.2% (12/23 patients) with 1 g vancomycin. Results are summarized in the table below.

Phase 2 Trial of Iclaprim in Patients with HBAP (N=70)

	0.8 mg/kg iclaprim	1.2 mg/kg iclaprim	1 g vancomycin
Intent to Treat Population (N=)	23	24	23
Clinical Cure (N=)	17	15	12
% Clinical Cure	*73.9%*	*62.5%*	*52.2%*
Fatalities within 28 days	2	3	5
% Death rate	*8.7%*	*12.5%*	*21.7%*

Source: Motif Bio Plc

Motif has put together a Phase 3 clinical trial plan (INSPIRE) for iclaprim in HABP. It will be a randomized, double blind comparator controlled international study comparing the safety and efficacy of iclaprim to linezolid in the treatment of HABP, including VABP. Treatment with both iclaparim and linezolid is expected to be 7 to 14 days. A total of approximately 720 subjects will be studied with a non-inferiority margin of -10%. The primary endpoint of the study will be all cause mortality at Day 28, with a key secondary endpoint of clinical cure at one to two weeks after ending antibiotic treatment. An outline of the study is provided in the following graphic.



Source: Motif Bio Plc

Potential to Treat Cystic Fibrosis Patients

On July 6, 2017, Motif announced three posters will be presented at the Infectious Diseases Week Annual Meeting, which is taking place in San Diego, CA from Oct. 4-8, 2017. One of the posters will present results from an *in vivo* study of iclaprim and vancomycin using a strain of MRSA in an animal model of chronic infection that mimics the pathophysiology observed in cystic fibrosis patients, an area that the company will be pursuing in the near future.

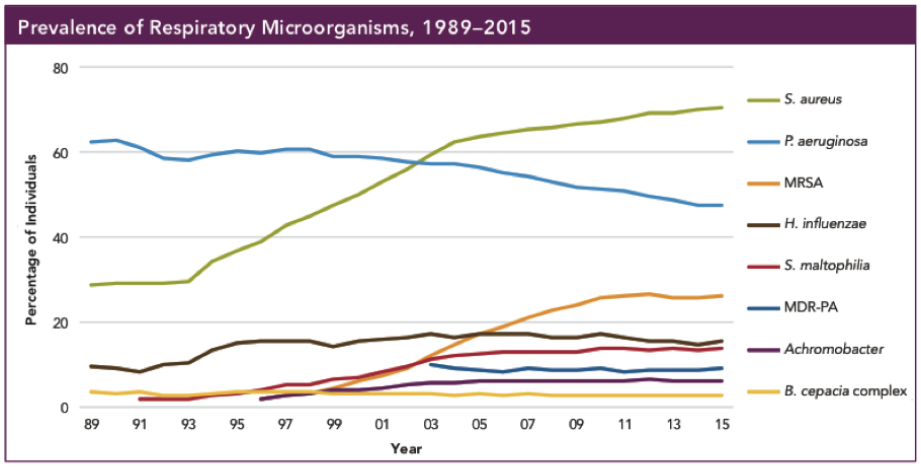
Cystic Fibrosis

Cystic Fibrosis (CF) is an autosomal recessive genetic disorder that affects close to 30,000 individuals in the U.S. and a total of 70,000 people worldwide. The hallmark of CF is a thick, sticky mucus build up in various organs throughout the body. Typically, mucus is a slippery, water substance produced by tissues that line organs and body cavities, such as the lungs and nose. However, due to abnormal sodium and chloride transport in the lungs, pancreas, liver, and digestive tract, patients suffering from CF have mucus that is thick and sticky and leads to blockages of the airways in the lungs and ducts in the pancreas (Boucher, 2004). The name refers to the characteristic scarring (fibrosis) and cyst formation seen in the pancreas.

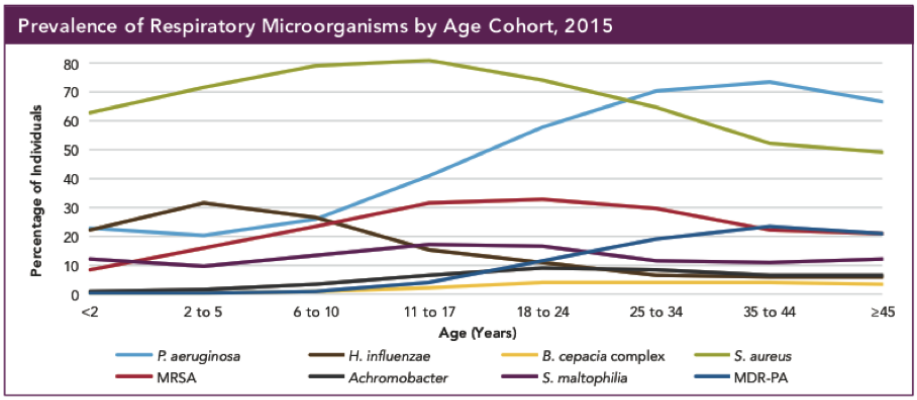
CF is caused by a mutation in the cystic fibrosis transmembrane conductance regulator (CFTR), a gene found on chromosome #7. The CFTR protein is a chloride ion channel that is involved in creating sweat, digestive juices, and mucus. When the protein is either not present or not functioning properly, there is a buildup of chloride ions inside the cells in the airway. While no one knows exactly how this leads to a buildup of thick mucus, one theory suggests that the malfunctioning CFTR protein leads to a paradoxical increase in sodium and chloride uptake, which in turn leads to increased water reabsorption, creating dehydrated and thick mucus.

The most serious complication associated with the disease is difficulty in breathing due to recurrent lung infections. Lung disease in patients with CF results from airway blockage and resulting inflammation. The build up of mucus is an ideal environment for bacteria to grow, and the inflammation and repeated infections result in injury and structural changes to the lungs. Early stages of the disease are characterized by excessive coughing, phlegm production and shortness of breath. These symptoms are exacerbated when the overgrowth of bacteria leads to pneumonia. *Staphylococcus aureus* and *Pseudomonas aeruginosa* are the two most common organisms that cause lung infections in CF patients. Lung infections are responsible for the deaths of 80% of CF patients (O'Sullivan *et al*., 2009).

The following two graphs are taken from the Cystic Fibrosis Foundation 2015 Patient Registry Report, which reports the prevalence of different bacterial pathogens for CF patients. As the first graph shows, the prevalence of *S. aureus* has been increasing for a number of years, with a significant proportion of the *S. aureus* infections being caused by MRSA. *S. aureus* is the causative pathogen in the majority of CF patients up until about the age of 25.



Source: CFF Patient Registry 2015



Source: CFF Patient Registry 2015

Based on the data showing the ratio of iclaprim concentration in the lungs compared to serum is so much greater than for other antibiotics, it seems appropriate to determine if iclaprim could be effective in treating lung infections cause by Gram-positive pathogens (particularly MRSA) in CF patients. Motif has already begun work to determine the optimal formulation for CF patients, and we anticipate learning more about the company's plan to advance iclaprim in CF in the coming months.

Financials and Capital Structure

As a foreign reporting entity, Motif releases financial information semi-annually. As of Dec. 31, 2016, the company reported approximately $21.8 million in cash and cash equivalents. In June 2017, Motif raised gross proceeds of approximately $25.7 million from the sale of 66.7 million shares of stock on the London stock exchange at 30 pence per share. We estimate that the company exited the first half of 2017 ending Jun. 30, 2017 with approximately $30 million in cash and cash equivalents. This should be sufficient to fund operations through the results from REVIVE-2 and the NDA filing for iclaprim in ABSSSI. However, the company will need to raise additional capital to fund the Phase 3 study of iclaprim in HABP.

Following the most recent financing, Motif has 262.9 million shares of stock that trade on the London stock exchange. The company also has American Depository Shares (ADSs) that trade on the Nasdaq Capital Market. Each ADS represents 20 of the company's ordinary shares. When factoring in the approximately 27.9 million stock options and 35.8 million warrants, the company has a fully diluted share count of approximately 326.5 million (or 16.3 million ADS).

Risks to Consider

Clinical Risk: While Motif has already announced positive results from REVIVE-1 that conform to the FDA's 10% non-inferiority guidance, there is no guarantee that the results from REVIVE-2 will match those of REVIVE-1 or that they will be within the FDA's 10% non-inferiority guidance. If the results from REVIVE-2 do not support a regulatory filing for approval of iclaprim, Motif's share price could be significantly impacted.

Motif's Phase 2 and exposure data for iclaprim are quite promising for the treatment of HABP. However, the Phase 2 trial was only conducted in 70 patients and there is no guarantee that the results seen in a Phase 3 trial conducted with approximately 720 patients will replicate those seen in the Phase 2 trial.

Commercialization Risk: If Motif acquires approval for iclaprim in ABSSSI, the company is currently planning to commercialize the drug on its own in the U.S. and seek a commercialization partner for regions outside the U.S. Building a sales force for iclaprim would be a very costly and time consuming endeavor, and there is no guarantee that the company would be successful in implementing that strategy. If Motif elects to enter into a partnership for selling iclaprim outside the U.S., the company would be entirely dependent upon the partner putting forth the requisite commitment to promoting the drug.

Financing Risk: Motif does not currently have any commercial products and does not generate any revenue. The company will need to raise additional capital in order to fund the Phase 3 clinical trial of iclaprim in HABP and to commercialize iclaprim in the U.S. for the treatment of ABSSSI, if approved. While the company has successfully raised capital previously, there is no guarantee that it will be able to so in the future or under terms that are favorable for shareholders.

Competition Risk: There are a number of antibiotics that have been approved for the treatment of ABSSI, including oritavancin (Orbactiv®), which is sold by The Medicines Company; dalbavancin (Dalvance®), which is sold by Allergan; tedizolid phosphate (Sivextro®), which is sold by Merck; ceftaroline fosamil (Teflaro®), which is sold by Allergan; and telavancin (Vibativ®), which is sold by Theravance Biopharma. Omadacycline, which is being developed by Paratek Pharmaceuticals, has successfully completed Phase 3 testing and we anticipate an NDA being filed in 2018. In addition, iclaprim will face competition from a number of generic versions of widely used antibiotics, including vancomycin, daptomycin, and linezolid.

Intellectual Property Risk: The only patent related to iclaprim expired on Dec. 2, 2016. However, iclaprim has been designated a Qualified Infectious Disease Product (QIDP) by the FDA. QIDP designation was introduced with the Generating Antibiotic Incentives Now Act (GAIN Act) in 2012. This designation allows for five years of marketing exclusivity, which is added sequentially to the five years of marketing exclusivity already provided upon approval of the drug as a new chemical entity. Thus, iclaprim should qualify for 10 years of market exclusivity in the U.S. This exclusivity is highly dependent upon the GAIN Act, and if this legislation were rescinded or otherwise altered, it could negatively affect the market exclusivity of iclaprim.

MANAGEMENT PROFILES

Graham Lumsden –Chief Executive Officer
Dr. Lumsden is responsible for all aspects of the strategy, management, and operations of the company. Prior to joining Motif, Dr. Lumsden was a senior executive at Merck & Co., Inc. where he held commercial leadership positions in worldwide businesses including contraceptives and osteoporosis. Dr. Lumsden has a proven record of success leading change and delivering results in subsidiary and global leadership positions, including new product launches, pre-clinical/clinical development, regulatory strategy, cross-functional team leadership, IP strategy/litigation, and domestic/international sales and marketing. Dr. Lumsden is a member of the Royal College of Veterinary Surgeons (MRCVS), holds a postgraduate diploma from the Chartered Institute of Marketing (MCIM), and is a dual citizen of the U.S. and UK.

Robert Dickey, IV – Chief Financial Officer
Mr. Dickey has broad senior leadership experience at public and private life sciences companies. Prior to Motif, he was CFO at Tyme Technologies, a publicly-traded oncology company. Prior to Tyme, he was CFO at NeoStem, Inc. (now Caladrius Biosciences), a public, regenerative medicines company. He previously served as SVP at Hemispherx Biopharma, SVP, CFO and Business Unit Manager at StemCyte, Inc., CFO at Locus Pharmaceuticals and COO and CEO at Protarga, Inc. Before that, he spent 18 years as an investment banker, mostly at Lehman Brothers, with a background split between M&A and capital markets transactions. Mr. Dickey holds an MBA from The Wharton School, University of Pennsylvania, and an AB from Princeton University.

David Huang, MD, PhD – Chief Medical Officer
Dr. Huang is a senior pharmaceutical research executive, and the former Chief Medical Officer at ContraFect Corporation. Dr. Huang also led a drug development group in anti-infectives at Pfizer. Dr. Huang has over 15 years of clinical, academic and research experience in infectious diseases. He has served as a faculty member at Baylor College of Medicine and currently as an adjunct Assistant Professor at Rutgers New Jersey Medical School. He continues to see patients at the Veterans Affairs Medical Center in Houston. His research interests include bacteriology and virology, especially the epidemiology, pathogenesis, and treatment of multi-drug resistant organisms. He is experienced in designing, executing and closing out Phase I – III clinical trials for both antibacterials and antiviral agents. Dr. Huang completed his medical school at the University of Texas at Houston Medical School, and completed his internship and residency in internal medicine at the University of Texas at Southwestern and fellowship in infectious diseases at Baylor College of Medicine. He is board-certified in both internal medicine and infectious diseases.

Rajesh B. Shukla, PhD – Vice President, Clinical Operations
Dr. Shukla brings drug discovery, clinical development, and clinical operations experience from entrepreneurial and established pharmaceutical companies as well as with HHS and DoD/MoD agencies. Prior to joining Motif, Dr. Shukla headed early through NDA stage clinical development programs in Infectious Diseases, Epilepsy, Oncology, Endocrinology, Asthma, and Anaphylaxis clinical programs at Pfizer, Bristol-Myers Squibb, Bracco Diagnostics, Teva and, most recently, Acorda Therapeutics. He began his pharmaceutical career at Bristol Myers-Squibb with a discovery focus in Oncology, CNS, and late clinical stage experience in Anti-infectives programs. Dr. Shukla completed his bachelor's degree in Biochemistry from Lehigh University and his Ph.D. from Carnegie-Mellon University followed by a postdoctoral fellowship at Yale University.

VALUATION

We are initiating coverage of Motif Bio Plc with a $28 valuation. Motif Bio is a biopharmaceutical company focused on the development of antibiotic compounds for difficult to treat bacterial infections. The company's lead asset, iclaprim, is a novel diaminopyrimidine molecule that is currently in Phase 3 testing for the treatment of acute bacterial skin and skin structure infecitons (ABSSSI). Motif has already announced positive results from the first Phase 3 study, and we anticipate results from the second Phase 3 study will be announced in the second half of 2017. A second Phase 3 program in hospital acquired bacterial pneumonia (HBAP) is expected to initiate later in 2017.

Numerous Acquisitions in Antibiotic Sector Point to Motif Being Undervalued

Over the past five years, there have been a number of acquisitions in the antibiotic sector that may help to put Motif's current valuation (~$100 million) in perspective.

- In 2013, Cubist Pharmaceuticals acquired Trius Therapeutics for $707 million plus up to $109 million in contingent payments based on future sales goals. Trius had one late-stage antibiotic candidate, tedizolid phosphate, which at the time of the acquisition had successfully met all primary and secondary endpoints in two Phase 3 clinical trials in ABSSSI. The company was planning to submit a New Drug Application in the U.S. in the second half of 2013 and a Marketing Authorization Application (MAA) in Europe in the first half of 2014. Trius had partnered with Bayer for the development and commercialization of tedizolid phosphate outside of the U.S., Canada, and the European Union. Tedizolid phosphate, now sold as Sivextro®, was approved in June 2014 and is currently sold by Merck.

- At the same time as the Trius deal, Cubist also bought Optimer Pharmaceuticals for $535 million plus up to $266 million in contingent payments based on future sales goals. Optimer sold Dificid®, which was approved by the FDA in 2011 for the treatment of *Clostridium difficile*-associated diarrhea (CDAD).

- In October 2014, Actavis bought Durata Therapeutics for $675 million plus contingent payments of up to $147 million based on future sales goals. Durata had received approval for dalbavancin (Dalvance®) in May 2014. Dalvance® is currently sold by Allergan, following its acquisition by Actavis in March 2015.

- In December 2014, Merck bought Cubist for $9.5 billion, which included the assumption of $1.1 billion of Cubist debt. While Cubist had a substantial pipeline, Merck purchased Cubist mostly for Cubicin® (daptomycin), which achieved peak sales of $1.1 billion.

The aforementioned deals all lend support to the idea that Motif is currently undervalued on a comparative basis, particularly the deal for Trius, as that company was in almost exactly the same position that Motif could find itself in over the next couple of months, assuming positive results from REVIVE-2.

In addition to the past deals mentioned above, we believe a reasonable current comparison could be made to Paratek Pharmaceuticals, which is developing omadacycline. The company has reported positive Phase 3 data for omadacycline in a Phase 3 trial of ABSSSI as well as a Phase 3 trial of community-acquired bacterial pneumonia (CABP). Paratek currently has a market cap of $710 million.

Valuation

We value Motif using a probability adjusted discounted cash flow model that takes into account potential future worldwide revenues for iclaprim in ABSSI. We anticipate Motif commercializing iclaprim on its own in the U.S. and signing a commercialization agreement with a multinational pharma company for sales outside the U.S. We estimate a 100-person sales force will likely be able to cover the approximately 1500 hospitals in the U.S. that are responsible for 70% of antibiotic prescriptions at a cost of approximately $20 million per year.

Topline results from REVIVE-2 should be released in the second half of 2017. Assuming a positive outcome, we anticipate Motif filing a New Drug Application in the first half of 2018, and because iclaprim has QIDP designation it qualifies for Priority Review (six month review time instead of 10), thus the drug could be approved in the second half of 2018 and launched in the beginning of 2019.

There are an estimated 3.6 million people hospitalized with ABSSSI every year. We conservatively estimate that 20% of patients have renal insufficiency, based on the results of Halilovic *et al*. We believe iclaprim could attain peak market share among these patients of 20%. We model for a full course of treatment costing $3000 and an inflation rate of 2%, which leads to peak sales of approximately $500 million in the U.S. Outside the U.S., we believe Motif will sign a commercialization agreement that will result in an average 15% royalty on net sales, which we estimate will peak at approximately $225 million. Using an 80% probability of approval and a 15% discount rate leads to a net present value for iclaprim in ABSSSI of $452 million. Dividing this by the fully diluted ADS share count of 16.3 million leads to a valuation of $28 per share. Motif currently trades at a significant discount to our valuation, and we believe that positive results from REVIVE-2 is likely to result in a significant revaluation of the company more in line with our valuation.

PROJECTED FINANCIALS

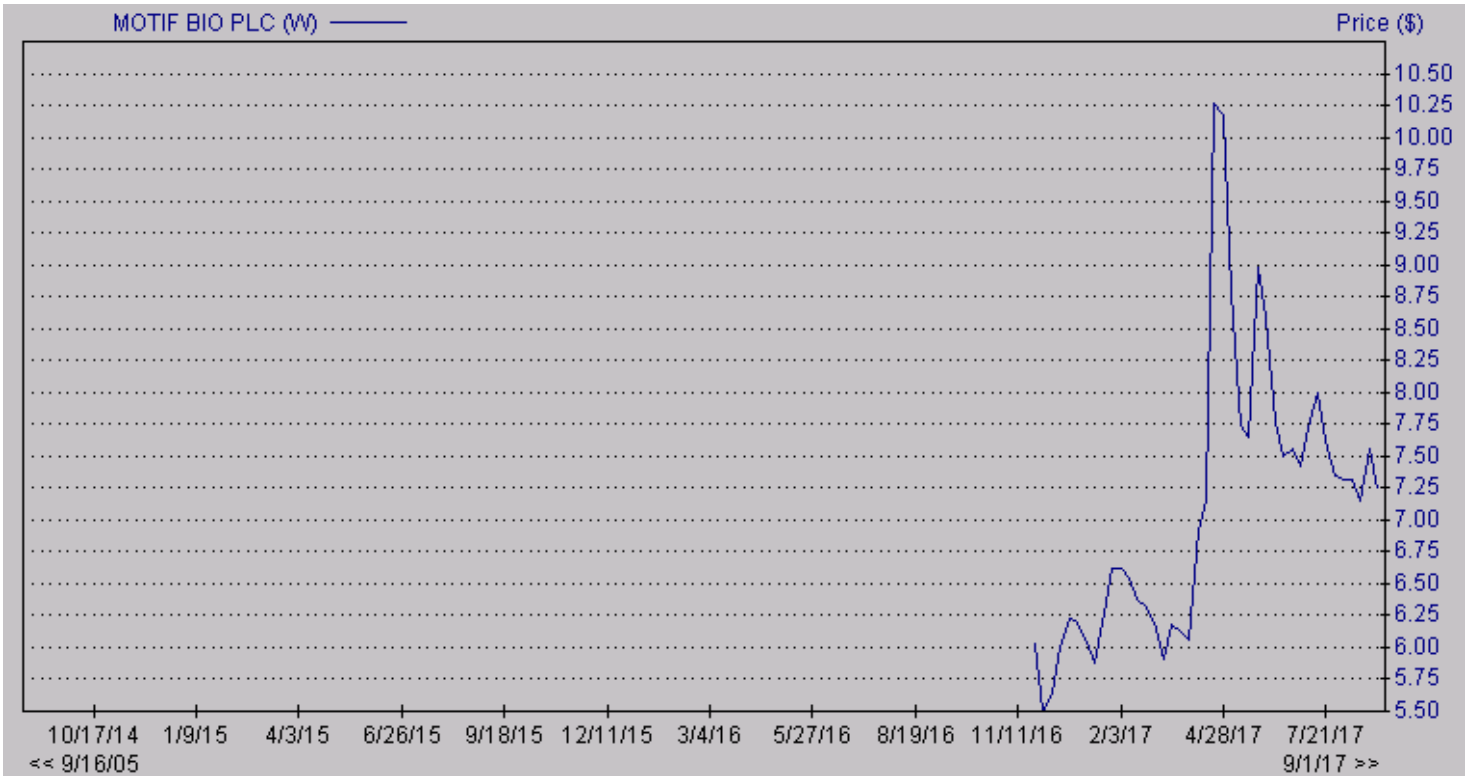
Motif Bio Plc
Income Statement

Motif Bio Plc	2016 A	Q1 E	Q2 E	Q3 E	Q4 E	2017 E	2018 E	2019 E
Iclaprim (ABSSSI)	$0	$0	$0	$0	$0	$0	$0	$11
YOY Growth	-	-	-	-	-			
Iclaprim (HABP)	$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**	**$11**
YOY Growth	-	-	-	-	-			
Cost of Sales	$0	$0	$0	$0	$0	$0	$0	$2
Product Gross Margin	-	-	-	-	-			
Research & Development	$34.8	$7.0	$7.3	$7.5	$7.8	$29.6	$35.0	$30.0
General & Administrative	$4.9	$1.2	$1.3	$1.3	$1.3	$5.1	$20.0	$25.0
Other Expenses	($0)	$0	$0	$0	$0	$0	$0	$0
Operating Income	($39.6)	($8.20)	($8.6)	($8.8)	($9.1)	($34.7)	($55.0)	($46.0)
Operating Margin	-	-	-	-	-			
Non-Operating Expenses (Net)	($0.7)	($0.2)	($0.2)	($0.2)	($0.2)	($0.8)	$0.0	$0.0
Pre-Tax Income	($40.3)	($8.4)	($8.8)	($9.0)	($9.3)	($35.5)	($55.0)	($46.0)
Income Taxes Paid	($0)	$0	$0	$0	$0	$0	$0	$0
Tax Rate	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*
Net Income	**($40.3)**	**($8.4)**	**($8.8)**	**($9.0)**	**($9.3)**	**($35.5)**	**($55.0)**	**($46.0)**
Net Margin	-	-	-	-	-			
Net Loss per Share	**($0.35)**	**($0.05)**	**($0.04)**	**($0.03)**	**($0.04)**	**($0.15)**	**($0.17)**	**($0.11)**
Net Loss per ADS	**($6.92)**	**($0.93)**	**($0.80)**	**($0.69)**	**($0.70)**	**($3.06)**	**($3.38)**	**($2.30)**
YOY Growth	-	-	-	-	-			
Basic Shares Outstanding	116.6	180.0	220.0	262.0	265.0	231.8	325.0	400.0
ADS Oustanding	5.8	9.0	11.0	13.1	13.3	11.6	16.3	20.0

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

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