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Motif Bio Plc

(MTFB-NASDAQ)

MTFB: NDA for Iclaprim Accepted by FDA; PDUFA Date of Feb. 13, 2019…

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 (08/21/18)	$8.62
Valuation	**$28.00**

OUTLOOK

On August 14, 2018, Moti Bio Plc (MTFB) announced that the FDA has accepted the new drug application (NDA) for iclaprim for the treatment of acute bacterial skin and skin structure infections (ABSSSI). Since the NDA has been granted Priority Review, on account of iclaprim being a Qualified Infectious Disease Product (QIDP), a target decision date under the Prescription Drug User Fee Act (PDUFA) has been set for Feb. 13, 2019.

Earlier in August 2018, the company announced a Notice of Allowance for two US Patent Applications, with claims relating to the use of iclaprim to treat patients with bacterial infections, hospital-acquired bacterial pneumonia, and Staphylococcus aureus lung infections in cystic fibrosis patients. The two patents will expire in Nov. 2037.

SUMMARY DATA

52-Week High	**$11.84**
52-Week Low	**$6.97**
One-Year Return (%)	**20.27**
Beta	**-0.05**
Average Daily Volume (sh)	**2,427**
Shares Outstanding (mil)	**15**
Market Capitalization ($mil)	**$128**
Short Interest Ratio (days)	**N/A**
Institutional Ownership (%)	**7**
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 2018 Estimate	**N/A**
P/E using 2019 Estimate	**N/A**

Risk Level	**Above Avg.**
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)
2017	0.0 A	0.0 A	0.0 A	0.0 A	0.0 A
2018	0.0 E	0.0 E	0.0 E	0.0 E	0.0 E
2019					11.0 E
2020					49.0 E

Earnings per ADS

	Q1 (Mar)	Q2 (Jun)	Q3 (Sep)	Q4 (Dec)	Year (Dec)
2017	-$1.50 A	-$1.50 A	-$1.07 A	-$1.07 A	-$3.87 A
2018	-$0.45 E	-$0.45 E	-$1.08 E	-$1.09 E	-$2.09 E
2019					-$1.85 E
2020					-$0.48 E

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WHAT'S NEW

Business Update

Motif Bio Plc (MTFB) 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 has completed Phase 3 testing for the treatment of acute bacterial skin and skin structure infections (ABSSSI), with the company announcing positive results from the two studies earlier in 2017. In addition, the U.S. Food and Drug Administration (FDA) has granted iclaprim orphan drug designation (ODD) for the treatment of bacterial infections in patients with cystic fibrosis caused by *Staphylococcus aureus*.

NDA Accepted by FDA

On August 14, 2018, Motif announced that the U.S. Food and Drug Administration (FDA) has accepted the company's new drug application (NDA) for iclaprim, the company's lead antibiotic candidate, for the treatment of acute bacterial skin and skin structure infections (ABSSSI). Acceptance of the NDA means that the FDA has deemed it suitable for a full review. Since iclaprim was designated a Qualified Infectious Disease Product (QIDP) the NDA was assigned Priority Review and the FDA as a target decision date under the Prescription Drug User Fee Act (PDUFA) of Feb. 13, 2019. If approved by the FDA, iclaprim would be eligible for 10 years of market exclusivity; five years due to being a new chemical entity and an additional five years from QIDP designation.

Additional Iclaprim Patents

On August 8, 2018, Motif announced that the U.S. Patent and Trademark Office (USPTO) issued Notice of Allowances for U.S. Patent Applications 15/586,021 and 15/586,815. The claims of those two applications relate to the use of iclaprim for the treatment of patients with bacterial infections, hospital-acquired bacterial pneumonia, and *Staphylococcus aureus* lung infections in patients with cystic fibrosis. The issued patents will have expiration dates of November 2037. Importantly, these patents relate to the use of the optimized 80 mg fixed dosage of iclaprim, and thus the company will have nine years post-QIDP exclusivity in which another company would have to launch at a suboptimal dose if it wished to commercialize a generic form of iclaprim during that time.

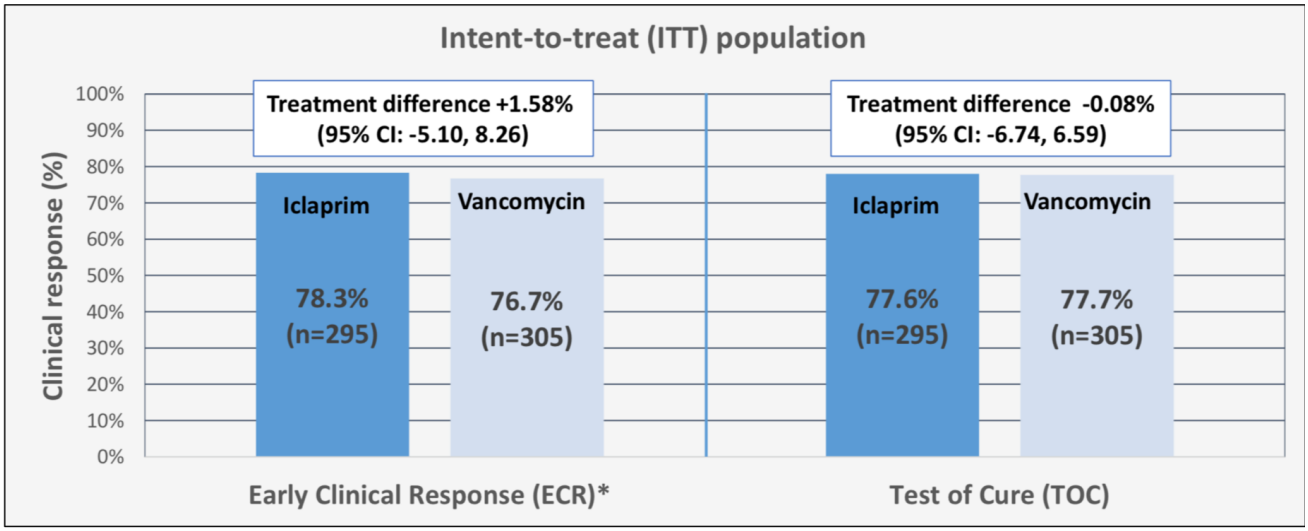
Presentations at ECCMID 2018

Earlier in 2018, Motif had three presentations related to iclaprim at the 28th European Congress of Clinical Microbiology and Infectious Diseases (ECCMID 2018).

REVIVE-2: A phase 3, Randomized, double-blind, multicenter study to evaluate the safety and efficacy of intravenous Iclaprim versus Vancomycin in the treatment of acute bacterial skin and skin structure infections suspected or confirmed to be due to Gram-positive pathogens

Dr. Thomas Holland gave a presentation on the results from REVIVE-2, the Phase 3 clinical trial of iclaprim for the treatment of acute bacterial skin and skin structure infections (ABSSSI). Dr. Holland began his presentation by providing an overview of the advantages for iclaprim, including the fact that its targeted to treat Gram-positive infections (including those caused by MRSA), its concentration is highest in areas of infection (including skin and lung), there have been no reports of nephrotoxicity (in contrast to vancomycin), it has an optimized fixed dosing schedule, it has demonstrated clinical efficacy in two Phase 3 clinical trials, and it uses an underutilized mechanism of action targeting dihydrofolate reductase.

The following slide shows the results for both early clinical response (ECR, defined by FDA as ≥20% reduction in lesion size at 48-72 hours [early time point, ETP] compared to baseline) and test of cure (TOC). Iclaprim was within the -10% non-inferiority margin compared to vancomycin for each endpoint.



Source: Holland, 2018

The following slide shows the safety results from the trial. Iclaprim was well tolerated with similar levels of study drug related treatment-emergent adverse events (TEAEs) and TEAE related serious AEs. Of note is the large difference in mean serum creatinine change from baseline to TOC for iclaprim (0.7) compared to vancomycin (7.7), again showing the lack of nephrotoxicity for iclaprim.

	Iclaprim N=299	Vancomycin N=302
Study drug related TEAEs	42 (14.0%)	39 (12.9%)
TEAE related serious AEs	14 (4.7%)	12 (4.0%)
Mean QTcF prolongation msec (SD)	9.9 (14.6)	3.8 (16.3)
Mean serum creatinine change from baseline to TOC umol/L (SD)	0.7 (18.0)	7.7 (39.8)
Mean serum creatinine change from baseline to TOC, mg/dL (SD)	0.008 (0.20)	0.09 (0.45)
Deaths	0	1 (0.3%)
TEAEs >4%		
Nausea	17 (5.7%)	17 (5.6%)
Infusion site extravasation	13 (4.3%)	12 (4.0%)
Headache	7 (2.3%)	13 (4.3%)

75% of adverse events in REVIVE-2 categorized as mild

Source: Holland, 2018

These data support the use of iclaprim for the treatment of ABSSSI suspected to be due to the Gram-positive pathogens as the drug was safe and efficacious with few drug-related AEs.

Potential Cost Savings Opportunities with Targeted Use of Iclaprim (ICL) Compared to Vancomycin (VAN) among Hospitalized Patients with Acute Bacterial Skin and Skin Structure Infections Due to Potential Avoidance of VAN-Associated Acute Kidney Injury V-A AKI.

This study involved the generation of a cost-minimization model from the hospital perspective to estimate the potential cost savings by replacing VAN with iclaprim for the treatment of SSSI. VAN is currently the most prescribed antibiotic for the treatment of ABSSSI, however acute kidney injury (AKI) is a relatively common side effect, occurring in 9.2% of patients (based on the rate seen in hospitalized patients at the Veterans Affairs Medical Center). The following table shows the overall cost of treating a patient with vancomycin-associated AKI depending upon the daily hospitalization cost and whether specialty physician consultations are needed. These costs ranged from $8,377 to $19,464, thus replacing vancomycin with iclaprim would result in significant cost savings for hospitals due to the avoidance of vancomycin-associated AKI.

Daily Costs Of Hospitalization

Daily Hospitalization Cost	$1,585.69/day	$2,000/day	$2,500/day	$3,000/day
Vancomycin-associated AKI only	$8,377	$10,448	$12,948	$15,448
Vancomycin-associated AKI and specialty physician consultation	$10,802	$12,873	$15,373	$17,873
Vancomycin-associated AKI, specialty physician consultation and acute dialysis	$12,393	$14,464	$16,964	$19,464
Overall neutral iclaprim cost-threshold over vancomycin	$172.89	$200.12	$232.98	$265.83

Source: Patel *et al.*, 2018

Surveillance of iclaprim activity: *in vitro* susceptibility of *Staphylococcus aureus* resistant to clindamycin/tetracycline and beta-haemolytic streptococci resistant to macrolides/tetracyclines among skin and skin-structure pathogens colleted during 2015-2016 from Europe and North America

This study was performed to determine the susceptibility of skin and skin structure pathogens (*S. aureus* and beta-hemolytic streptococci) to iclaprim and comparator antibiotics that were collected from Europe and North America from 2015-2016. A total of 618 isolates of *S. aureus* and 313 beta-hemolytic streptococci were tested. The following table shows the iclaprim MIC values for *S. aureus* strains resistant to clindamycin (CLI-R) and tetracycline (TET-R) along with MIC values for streptococci, including those resistant to macrolides (AZI-R) and tetracyclines. Iclaprim was active against the majority of isolates (MIC_{90} value for all strains tested = 0.12 mg/L), although some MICs were higher for certain resistant subgroup phenotypes. MIC values for streptococci were only slightly changed for resistant subgroups.

Phenotype	n	MIC_{50}	MIC_{90}
S. aureus	618	0.03	0.12
S. aureus CLI-R	106	0.03	16
S. aureus TET-R	48	0.06	>32
MRSA CLI-R	94	0.03	16
MRSA TET-R	31	0.06	>32
MSSA CLI-R	12	0.06	16
MSSA TET-R	17	0.06	>32
BHS	313	0.03	0.25
BHS AZI-R	82	0.06	0.5
BHS TET-R	121	0.06	0.5

Source: Huang *et al.*, 2018

The results of this experiment show that iclaprim was active against a majority of these isolates, including some that were resistant to other antibiotics. Continued surveillance of clinical isolates will occur to monitor for resistance to iclaprim, and molecular characterization of the subgroups with higher MIC values may be necessary to determine any potential changes to those strains DHFR.

Presentations at ASM 2018

Motif presented two posters at ASM 2018 on pooled analysis of the REVIVE-1 and REVIVE-2 trials, with one poster focused on efficacy results and the other on safety results. The combined results were also published in the *International Journal of Antimicrobial Agents* (Huang *et al*., 2018). The following two tables show the combined efficacy and safety results demonstrating that iclaprim was non-inferior to the standard of care vancomycin and was safe and well tolerated.

	REVIVE-1		REVIVE-2		Combined REVIVE-1/2	
	Iclaprim (N=298)	Vancomycin (N=300)	Iclaprim (N=295)	Vancomycin (N=305)	Iclaprim (N=593)	Vancomycin (N=605)
Early Clinical Response, n (%)	241 (80.9)	243 (81.0)	231 (78.3)	234 (76.7)	472 (79.6)	477 (78.8)
% Difference (iclaprim-vancomycin)	-0.13		1.58		0.75	
95% CI	-6.42, 6.17		-5.10, 8.26		-3.84, 5.35	

Source: Huang *et al*., 2018

	REVIVE-1		REVIVE-2		Combined REVIVE-1/2	
	Iclaprim (N=293)	Vancomycin (N=297)	Iclaprim (N=299)	Vancomycin (N=302)	Iclaprim (N=592)	Vancomycin (N=599)
Patients with:						
Any TEAE	151 (51.5)	128 (43.1)	140 (46.8)	133 (44.0)	291 (49.2)	261 (43.6)
Study Drug Related TEAEs	57 (19.5)	53 (17.8)	42 (14.0)	39 (12.9)	99 (16.7)	92 (15.4)
TEAE with Discontinuation of Study Drug	8 (2.7)	13 (4.4)	16 (5.4)	17 (5.6)	24 (4.1)	30 (5.0)
SAEs	9 (3.1)	14 (4.7)	16 (5.4)	14 (4.6)	25 (4.2)	28 (4.7)
Deaths	0	2 (0.7)[4]	0	1 (0.3)	0	3 (0.5)
MedDRA Preferred Terms:						
Nausea	29 (9.9)	17 (5.7)	17 (5.7)	17 (5.6)	46 (7.8)	34 (5.7)
Headache	30 (10.2)	23 (7.7)	7 (2.3)	13 (4.3)	37 (6.3)	36 (6.0)
Cellulitis	9 (3.1)	5 (1.7)	18 (6.0)	9 (3.0)	27 (4.6)	14 (2.3)
Infusion site extravasation	14 (4.8)	12 (4.0)	13 (4.3)	12 (4.0)	27 (4.6)	24 (4.0)
Skin bacterial infection	15 (5.1)	9 (3.0)	8 (2.7)	2 (0.7)	23 (3.9)	11 (1.8)
Vomiting	14 (4.8)	15 (5.1)	7 (2.3)	7 (2.3)	21 (3.5)	22 (3.7)
Pyrexia	12 (4.1)	12 (4.0)	7 (2.3)	5 (1.7)	19 (3.2)	17 (2.8)
Fatigue	18 (6.1)	9 (3.0)	0	4 (1.3)	18 (3.0)	13 (2.2)
Diarrhea	5 (1.7)	14 (4.7)	8 (2.7)	11 (3.6)	13 (2.2)	25 (4.2)
AST increased	6 (2.0)	7 (2.4)	6 (2.0)	5 (1.7)	12 (2.0)	12 (2.0)
Peripheral edema	8 (2.7)	9 (3.0)	4 (1.3)	3 (1.0)	12 (2.0)	12 (2.0)
Alanine aminotransferase increased	6 (2.0)	5 (1.7)	5 (1.7)	7 (2.3)	11 (1.9)	12 (2.0)
Anaemia	5 (1.7)	2 (0.7)	6 (2.0)	6 (2.0)	11 (1.9)	8 (1.3)
Pain in extremity	6 (2.0)	3 (1.0)	5 (1.7)	2 (0.7)	11 (1.9)	5 (0.8)
Hypertension	3 (1.0)	2 (0.7)	7 (2.3)	5 (1.7)	10 (1.7)	7 (1.2)
Hypokalaemia	1 (0.3)	2 (0.7)	6 (2.0)	11 (3.6)	7 (1.2)	13 (2.2)

Source: Huang *et al*., 2018

Conclusion

We're glad to see that the FDA has accepted the NDA filing for iclaprim and that a PDUFA data of Feb. 13, 2019 has been assigned. The FDA has not indicated that an advisory committee ("AdComm") meeting will be taking place for iclaprim, but it is not inconceivable that one will end up being scheduled. However, with the strong data from both REVIVE-1 and REVIVE-2, we don't believe that an AdComm, were it to take place, would be a negative.

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 published data (Halilovic *et al*., 2012). 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 a 90% probability of approval and a 15% discount rate leads to a net present value for iclaprim in ABSSSI of $475 million. After factoring in the company's cash position, potential cash from the exercise of outstanding warrants, and dividing by the fully diluted ADS share count of 18.6 million leads to a valuation of $28 per share. The stock continues to trade at a significant discount to our valuation, thus offering investors plenty of upside at the current price.

PROJECTED FINANCIALS

Motif Bio Plc
Income Statement

Motif Bio Plc	2017 A	1H18	2H18	2018 E	2019 E	2020 E
Iclaprim (ABSSSI)	$0	$0	$0	$0	$11	$49
YOY Growth		-	-			
Iclaprim (HABP)	$0	$0	$0	$0	$0	$0
YOY Growth		-	-			
Iclaprim (CF)	$0	$0	$0	$0	$0	$0
YOY Growth		-	-			
Grants & Collaborative Revenue	$0	$0	$0	$0	$0	$0
YOY Growth		-	-			
Total Revenues	**$0**	**$0**	**$0**	**$0**	**$11**	**$49**
YOY Growth		-	-			
Cost of Sales	$0	$0	$0	$0	$2	$8
Product Gross Margin		-	-			
Research & Development	$29.5	$6.0	$8.0	$14.0	$18.0	$20.0
General & Administrative	$8.5	$4.4	$8.0	$12.4	$25.0	$30.0
Other Expenses	$0	$0	$0	$0	$0	$0
Operating Income	($38.02)	($10.4)	($16.0)	($26.4)	($34.0)	($9.0)
Operating Margin		-	-			
Non-Operating Expenses (Net)	($6.8)	($1.5)	($1.5)	($3.0)	($3.0)	($3.0)
Pre-Tax Income	($44.8)	($11.9)	($17.5)	($29.4)	($37.0)	($12.0)
Income Taxes Paid	$0	$0	$0	$0	$0	$0
Tax Rate	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*
Net Income	**($44.8)**	**($11.9)**	**($17.5)**	**($29.4)**	**($37.0)**	**($12.0)**
Net Margin		-	-			
Net Loss per Share	**($0.19)**	**($0.05)**	**($0.06)**	**($0.10)**	**($0.09)**	**($0.02)**
Net Loss per ADS	**($3.87)**	**($0.90)**	**($1.17)**	**($2.09)**	**($1.85)**	**($0.48)**
YOY Growth		-	-			
Basic Shares Outstanding	231.5	264.0	300.0	282.0	400.0	500.0
ADS Oustanding	11.6	13.2	15.0	14.1	20.0	25.0

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

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