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Appili Therapeutics Inc. (T.APL-TSX)

T.APL: Advancing Multiple Programs to Combat Infectious Diseases…

Based on our probability adjusted DCF model that takes into account potential future revenues of ATI-2307, ATI-1701, ATI-1801, and ATI-1501 APLI.T is valued at CAD$0.60/share. This model is highly dependent upon continued clinical success of the company's pipeline and will be adjusted accordingly based on future clinical results.

Current Price (09/01/22)	CAD$0.06
Valuation	**CAD$0.60**

OUTLOOK

On August 12, 2022, Appili Therapeutics Inc. (APLI.T) announced financial results for the first quarter of fiscal year 2023 that ended June 30, 2022 and provided a business update. In February 2022, the company received a commitment of over US$10 million from DTRA to advance ATI-1701, a vaccine to prevent tularemia caused by *Francisella tularensis*. The company also announced a new late-stage clinical program (ATI-1801) for the treatment of cutaneous leishmaniasis, a disfiguring skin condition caused by a single celled parasite spread by the sandfly. Since it's a Tropical Disease, ATI-1801 may be eligible for a priority review voucher (PRV) if approved by the FDA. This is the third such program in the company's pipeline that could lead to a PRV.

SUMMARY DATA

52-Week High	**$1.14**
52-Week Low	**$0.06**
One-Year Return (%)	**-91.86**
Beta	**0.89**
Average Daily Volume (sh)	**88,020**
Shares Outstanding (mil)	**121**
Market Capitalization ($mil)	**$8**
Short Interest Ratio (days)	**N/A**
Institutional Ownership (%)	**20**
Insider Ownership (%)	**21**
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 2019 Estimate	**N/A**
P/E using 2020 Estimate	**N/A**

Risk Level	**High**
Type of Stock	**Small-Blend**
Industry	**Med-Biomed/Gene**

ZACKS ESTIMATES

Revenue
(in millions of CAD$)

	Q1 (Jun)	Q2 (Sep)	Q3 (Dec)	Q4 (Mar)	Year (Mar)
2022	0.0 A	0.0 A	1.4 A	0.0 A	1.4 A
2023	0.0 A	0.0 E	0.0 E	0.0 E	0.0 E
2024					0.0 E
2025					0.0 E

Earnings per Share
(in CAD$)

	Q1 (Jun)	Q2 (Sep)	Q3 (Dec)	Q4 (Mar)	Year (Mar)
2022	-$0.12 A	-$0.18 A	-$0.05 A	-$0.05 A	-$0.38 A
2023	-$0.03 A	-$0.02 E	-$0.02 E	-$0.02 E	-$0.09 E
2024					-$0.07 E
2025					-$0.06 E

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WHAT'S NEW

Business Update

New Late-Stage Program in Cutaneous Leishmaniasis

In April 2022, Appili Therapeutics Inc. (APLI.TO) announced the addition of ATI-1801, a late stage clinical program to treat cutaneous leishmaniasis. The product, a topical formulation of paromomycin, was licensed from the U.S. Department of Defense (DOD) via the U.S. Army Medical Material Development Activity (USAMMDA). Appili now holds the full clinical dossier for ATI-1801, which includes the results of a successful randomized, double blind, placebo controlled Phase 3 trial that evaluated the safety and efficacy of ATI-1801 for the treatment of cutaneous leishmaniasis in Tunisia. The results of the study showed that ATI-1801 applied topically once daily for 20 days resulted in a statistically significant improvement in the rate of clinical cure for the index lesion compared to placebo (82% vs. 58%; $P<0.001$).

Appili plans to request a meeting in the second half of 2022 with the FDA to discuss the Phase 3 data and determine what will be necessary for a registration package to support a new drug application submission. The company will be pursuing non-dilutive funding and partnership opportunities with non-government organizations (NGOs) and government agencies to assist in completing any remaining development work. In addition, since cutaneous leishmaniasis is a tropical disease, ATI-1801 will likely be eligible for a priority review voucher (PRV) upon approval by the FDA. A PRV allows the holder to accelerate the review of a drug application by the FDA from the standard 10 months to 6 months. PRVs are fully transferable, and a number of them have sold recently for approximately $100 million each. This would be Appili's third PRV-eligible development product in addition to ATI-1701, a vaccine to prevent infection by the potential bioterror agent *Francisella tularensis*, and ATI-2307, the company's novel antifungal candidate.

Cutaneous leishmaniasis is a debilitating skin disease caused by approximately 30 different species of the single-celled parasite Leishmania. The disease is spread by the bite of the Phlebotominae sandfly and is endemic in 88 countries throughout Africa, Asia, Europe, and North and South America. While only 50-100 cases are diagnosed each year in the U.S., approximately 1.5 to 2 million new cases are diagnosed each year around the world (AAFP.org). Current treatment options include pentavalent antimony, but this has a high incidence of side effects including fatigue, gastrointestinal issues, liver enzyme elevations, leukopenia, and anemia. Thus, there is an urgent need for additional treatment options.

Appili Awarded >US$10 Million Contract for ATI-1701

In February 2022, Appili announced that the U.S. Department of Defense (DoD), via the Joint Science and Technology Office of the Defense Threat Reduction Agency (DTRA), has awarded the company a contract worth >US$10 million for the continued development of ATI-1701, the company's biodefense vaccine for the prevention of tularemia.

This new contract will replace and expand upon the previous contract to support the advanced development and manufacturing of ATI-1701 that had been awarded to one of Appili's development partners. Appili will now serve as the prime contractor, with covered activities including regulatory, nonclinical, and manufacturing to support an IND submission to the FDA. The expected amount of the contract is >US$10 million, however the total funding amount will be determined following negotiations between Appili and the DTRA.

ATI-1701 is a vaccine for the prevention of tularemia caused by *Francisella tularensis*, a pathogen that is a Tier 1 biological threat agent according to the CDC (Dennis *et al*., 2001). Its potential as a bioterror agent is based on the fact that only a very small number of *F. tularensis* cells (10-50) can cause disease and the organism can be aerosolized to infect a large area. Inhalation of *F. tularensis* and development of pneumonic tularemia can lead to breathing difficulties and ultimately be fatal if not treated. Based on its highly infectious nature and ability to cause severe illness, the U.S. government and other governments around the world have made medical countermeasures against *F. tularensis* a high biodefense priority.

Since it is unacceptable to test the efficacy of a tularemia vaccine in a human population, ATI-1701 is being developed via the FDA Animal Rule. Products developed via this pathway are required to show efficacy in two animal models, one of which being a non-human primate, along with safety in a healthy adult population.

Appili previously presented data showing that ATI-1701 protected 100% of rats for 365 days and cynomolgus macaques for 90 days following immunization. This was tested by challenging vaccinated animals with aerosolized *F. tularesnsis*, which resulted in 100% fatality in non-vaccinated rats, rats immunized with the legacy *F. tularensis* vaccine, and non-vaccinated macaques. The company also recently announced positive one-year challenge results with non-human primates showing a survival rate of 29% (2/7) in the ATI-1701 vaccinated cohort compared to 0% (0/5) in placebo vaccinated controls.

Since it is being developed as a medical countermeasure, ATI-1701 would qualify for a priority review voucher (PRV) upon its approval. A PRV allows the holder of the voucher to receive an expedited six-month review from the FDA for a new drug application (NDA) or biologics license application (BLA) instead of the usual ten-month review. PRVs are fully transferrable and have sold consistently for the previous couple of years for approximately $100 million each.

Phase 2 Clinical Trial for ATI-2307 to Initiate 2H22

In November 2019, Appili acquired ATI-2307 from FUJIFILM Toyama Chemical Co., LTD. It is a broad-spectrum, novel arylamidine antifungal agent that belongs to the same class of aromatic diamidines as pentamidine and furamidine (Mitsuyama *et al*., 2008). It has a highly differentiated novel mechanism of action that could potentially be used to treat infections caused by a number of clinically important and high priority pathogens, including *Cryptococcus*, *Candida*, and *Aspergillus*.

ATI-2307 has been successfully tested in multiple Phase 1 clinical trials. In addition, the compound has been tested in 80 human subjects in three single ascending dose and/or multiple ascending dose clinical studies conducted in the U.S. in which it was safe and well tolerated at all doses tested.

Appili is currently conducting proof of concept nonclinical studies to evaluate the therapeutic effect of ATI-2307 in rabbit and mouse intracranial *Cryptococcus* infection models and earlier this year published the results of studies evaluating the drugs activity *in vitro* against a panel of clinical isolates (Gerlach *et al*., 2021). The work is being conducted in collaboration with researchers at Duke University and the University of Texas Health Science Center at San Antonio. A portion of the work is being supported by the U.S. National Institute of Allergy and Infectious Diseases (NIAID).

In anticipation of the successful completion of PK/PD studies in the second half of 2022 and to support a potential Phase 2 trial start, Appili transferred the analytical methods and manufacturing process for ATI-2307 to a contract manufacturing organization. Subject to funding and other priorities, the company may initiate GMP production of clinical trial material and initiate clinical and regulatory activities later in 2022.

Appili is also evaluating the potential for ATI-2307 as a treatment for invasive *Candida* infections. These infections are caused by a number of *Candida* species, including *Candida albicans* and the newly emerging pathogen *Candida auris*, and are generally treated with an echinocandin or azole. However, an increase in antifungal resistance is decreasing the efficacy of those compounds, and with the highly toxic amphotericin B used for refractory *Candida* infections, there exists the need for safer and more effective treatment options.

ATI-2307 may be eligible for development under the Limited Population Pathway for Antibacterial and Antifungal Drugs (LPAD), which provides a mechanism for accelerated clinical development for antibiotics and antifungals. In addition, ATI-2307 could be eligible for Orphan Drug Designation (ODD) from the FDA if developed as a treatment for cryptococcal meningitis or invasive candidiasis. ODD designation is accompanied by seven years of regulatory exclusivity following FDA approval. ATI-2307 may also be eligible for an additional five years of exclusivity if approved to treat either *Candida* or *Cryptococcus* as both those are qualifying pathogens for Qualified Infectious Disease Product (QIDP) designation. Lastly, the drug may be eligible for a tropical disease Priority Review Voucher (PRV) if it is the first compound approved for cryptococcal meningitis.

ATI-1503 Update

The ATI-1503 program is devoted to developing antibiotic compounds that target Gram-negative bacteria, including CDC priority pathogens such as *Enterobacteriaceae*, *Acinetobacter*, and *Pseudomonas*. The program is based off of negamycin, a naturally occurring compound that shows activity against Gram-negative bacteria.

Negamycin was originally isolated from cultures of *Streptomyces purpeofuscus* where it showed activity in immunocompetent mouse models of sepsis caused by Gram-negative pathogens such as *P. aeruginosa* and *Klebsiella Pneumoniae* (Hamada *et al*., 1970). It exerts its antibiotic effect by targeting protein synthesis (Mizuno *et al*., 1970). Negamycin has a number of positive attributes, however the compound itself is not potent enough for development as an antibiotic, with minimum inhibitor concentration (MIC) values of 16-64 μg/mL. To improve upon its characteristics, researchers at AstraZeneca produced analogues of negamycin and a lead compound was identified that showed 4-fold improvement in MIC against a panel of 100 clinical isolates of *P. aeruginosa* (McKinney *et al*., 2015).

Appili has identified two novel and structurally distinct lead molecules based on the negamycin scaffold, which each have low, single-digit MIC values against many Gram-negative bacteria. In addition, these compounds have shown *in vivo* proof-of-concept against *Klebsiella* and *Escherichia*. The compounds are continuing to be evaluated in multiple in vivo efficacy models, safety screening, and pharmacokinetic evaluations.

ATI-1501 Update

ATI-1501 is a taste-masked liquid oral suspension formulation of the antibiotic metronidazole. This was the company's initial R&D program initiated in the first quarter of 2015. Metronidazole is an antibiotic used to treat various protozoan and anaerobic bacterial infections, including giardiasis, trichomoniasis, and amebiasis (Freeman *et al*., 1997). It is a widely used antibiotic, with more than 10 million oral prescriptions written each year (IQVIA™ 2017).

In December 2019, Appili announced a commercial agreement with Saptalis Pharmaceuticals for ATI-1501, in which Appili will be eligible to receive multiple milestones and royalty payments based on the sale of ATI-1501 in the U.S. Saptalis will be responsible for overseeing the regulatory review, manufacturing, and preparation for the anticipated commercialization of ATI-1501 in the U.S. We anticipate an NDA being filed in 2022.

The commercial agreement was amended earlier this year to expand the territories that Saptalis will commercialize ATI-1501 to include Europe and Latin America. Saptalis will be responsible for all development and commercialization efforts in those two regions and Appili will be eligible to receive royalties on sales.

Financial Update

On August 13, 2022, Appili announced financial results for the first quarter of fiscal year 2023, which ended June 30, 2022. Net loss for the first quarter of fiscal year 2023 was CAD$2.3 million, or CAD$0.03 per share, compared to a net loss CAD$7.4 million, or CAD$0.12 per share, for the quarter ending June 30, 2021. The decrease was primarily due to an CAD$5.1 million decrease in R&D expenditures.

R&D expenses for the first quarter of fiscal year 2023 were CAD$1.0 million, compared to CAD$6.1 million for the first quarter of fiscal year 2022. The decrease was primarily due to a decrease in the favipiravir clinical trials. G&A expenses for the first quarter of fiscal year 2023 were CAD$1.08 million, compared to CAD$1.14 million for the first quarter of fiscal year 2022. The decrease was primarily due to decreased salaries and benefits along with decreased stock-based compensation.

As of June 30, 2022, Appili had approximately CAD$5.6 million in cash, cash equivalents, and short-term investments along with approximately US$2.3 million remaining on the PRMRP government grant and approximately US$1.65 million remaining on the DTRA grant. We estimate Appili has sufficient capital to fund operations into the second calendar quarter of 2023. As of June 30, 2022, Appili had approximately 121.3 million shares outstanding and, when factoring in stock options and warrants, a fully diluted share count of approximately 179.7 million.

Conclusion

Appili's late stage program in cutaneous leishmaniasis is an exciting addition to the company's pipeline and could potentially lead to a PRV. This is the third program in the company's pipeline that may lead to a PRV, which have recently been selling for US$100 million each. We look forward to updates on ATI-1801 following Appili's meeting with the FDA regarding the regulatory path forward. Our current valuation is CAD$0.60.

PROJECTED FINANCIALS

Appili Therapeutics Inc. Fiscal Year Ends Mar. 31 / in Canadian dollars	FY2022 A	Q1FY23 A	Q2FY23 E	Q3FY23 E	Q4FY22 E	FY2023 E	FY2024 E	FY2025 E
ATI-2307	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0
ATI-1701	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0
ATI-1503	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0
ATI-1501	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0
Other Income	$1.4	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0
Total Revenues	**$1.4**	**$0.0**	**$0.0**	**$0.0**	**$0.0**	**$0.0**	**$0.0**	**$0.0**
Cost of Sales	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0
Product Gross Margin	-	-	-	-	-	-	-	-
Research & Development	$20.7	$1.0	$1.4	$1.4	$1.5	$5.3	$7.0	$8.0
General & Administrative	$4.6	$1.1	$1.2	$1.2	$1.2	$4.7	$5.0	$5.2
Business Development	$0.7	($0.0)	$0.2	$0.2	$0.2	$0.6	$1.0	$1.0
Other (Income) Expense	$0.5	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0
Operating Income	($25.1)	($2.1)	($2.8)	($2.8)	($2.9)	($10.6)	($13.0)	($14.2)
Operating Margin	-	-	-	-	-	-	-	-
Non-Operating Expenses (Net)	$0.0	($0.3)	$0.0	$0.0	$0.0	($0.3)	$0.0	$0.0
Pre-Tax Income	($25.1)	($2.3)	($2.8)	($2.8)	($2.9)	($10.8)	($13.0)	($14.2)
Income Taxes	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0	$0
Tax Rate	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*
Net Income	**($25.1)**	**($2.3)**	**($2.8)**	**($2.8)**	**($2.9)**	**($10.8)**	**($13.0)**	**($14.2)**
Net Margin	-	-	-	-	-	-	-	-
Reported EPS	**($0.38)**	**($0.03)**	**($0.02)**	**($0.02)**	**($0.02)**	**($0.09)**	**($0.07)**	**($0.06)**
YOY Growth	-	-	-	-	-	-	-	-
Basic Shares Outstanding	66.7	91.0	122.0	122.0	122.0	114.3	175.0	225.0

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

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