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Appili Therapeutics Inc. (V.API-TSXV)

V.API: Initiating Coverage of Appili Therapeutics, Inc; A Pipeline of Anti-Infective Agents…

Based on our probability adjusted DCF model that takes into account potential future revenues of ATI-2307, ATI-1701, and ATI-1501, APLI is valued at CAD$4.00/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 (01/29/20)	CAD$0.88
Valuation	**CAD$4.00**

OUTLOOK

We are initiating coverage of Appili Therapeutics, Inc. (APLI.V) with a CAD$4.00 valuation. Appili is a biopharmaceutical company developing novel treatments for infectious diseases. The company's pipeline includes four major programs: ATI-2307, ATI-1701, ATI-1503, and ATI-1501. ATI-2307 is a broad spectrum, clinical stage antifungal agent that is being developed first for the treatment of cryptococcal meningitis, a condition eligible for a Tropical Disease Priority Review Voucher (PRV). ATI-1701 is a vaccine against *Francisella tularensis*, a pathogen that is 1000x more infectious than anthrax, and may qualify for a Medical Countermeasure PRV. ATI-1503 is a program to design additional broad-spectrum Gram-negative antibiotics based on negamycin. ATI-1501 is a taste-masked liquid suspension reformulation of metronidazole, for which Appili recently signed a commercial agreement with Saptalis Pharmaceuticals.

SUMMARY DATA

52-Week High	**$1.09**
52-Week Low	**$0.32**
One-Year Return (%)	**22.86**
Beta	**N/A**
Average Daily Volume (sh)	**15,750**
Shares Outstanding (mil)	**34**
Market Capitalization ($mil)	**$21**
Short Interest Ratio (days)	**N/A**
Institutional Ownership (%)	**54**
Insider Ownership (%)	**42**
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-Growth**
Industry	**Med-Biomed/Gene**

ZACKS ESTIMATES

Revenue
(in millions of CAD$)

	Q1 (Jun)	Q2 (Sep)	Q3 (Dec)	Q4 (Mar)	Year (Mar)
2018	0.0 A	0.0 A	0.0 A	0.0 A	0.0 A
2019	0.0 A	0.0 A	0.1 E	0.0 E	0.1 E
2020					0.9 E
2021					0.0 E

Earnings per Share
(in CAD$)

	Q1 (Jun)	Q2 (Sep)	Q3 (Dec)	Q4 (Mar)	Year (Mar)
2018	-$0.01 A	-$0.04 A	-$0.04 A	-$0.05 A	-$0.14 A
2019	-$0.06 A	-$0.03 A	-$0.04 E	-$0.04 E	-$0.18 E
2020					-$0.28 E
2021					-$0.32 E

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WHAT'S NEW

Initiating Coverage



Source: Appili Therapeutics Inc.

We are initiating coverage of Appili Therapeutics Inc. (APLI.V) with a valuation of CAD$4.00. Appili is a biopharmaceutical company developing novel treatments for infectious diseases. The company's pipeline includes four programs: ATI-2307 for the treatment of invasive fungal infections; ATI-1701 for protection against *Francisella tularensis*, a Category A pathogen and potential biological weapons threat; ATI-1503 for development of new Gram-negative antibiotics; and ATI-1501 is a taste-masked liquid suspension reformulation of metronidazole.

Large Unmet Need in Cryptococcal Meningitis
Cryptococcus infections that lead to cryptococcal meningitis are a serious health risk for immunosuppressed patients and the current standard of care, amphotericin B, is associated with significant toxicity, including the potential for renal failure. ATI-2307 is a novel antifungal compound with a unique mechanism of action that has been safe and well tolerated in the 80 human subjects tested as part of three Phase 1 clinical trials. The drug has shown excellent activity in multiple pre-clinical animal models, including superior activity to amphotericin B in a model of cryptococcosis.

Potential for Multiple PRVs
Both ATI-2307 and ATI-1701, if approved, may qualify for a Priority Review Voucher (PRV) under the Tropical Disease and Medical Countermeasure statutes, respectively. 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 multiple PRVs have sold for $80-$100 million each over the past two years.

Targeting Gram-negative Bacterial Infections
The ATI-1503 program is developing novel antibiotics for Gram-negative pathogens based on the naturally occurring, broad-spectrum antibiotic negamycin. The Center for Disease Control (CDC) 2019 report on antibiotic resistant infections includes data on multiple species of antibiotic-resistant bacteria and fungi categorized by the level of concern to human health (urgent, serious, and concerning). Included in the "urgent" category are the Gram-negative bacteria *Acinetobacter* and *Enterobacteriaceae*, which are responsible for hospitalizing thousands of patients each year. The report makes clear that additional antibiotics targeting these high-priority Gram-negative pathogens are needed.

Recent Deal for Taste-Masked Metronidazole
Appili recently entered a commercial agreement with Saptalis Pharmaceuticals for ATI-1501, a taste-masked liquid formulation of the antibiotic metronidazole, whereby Saptalis will be responsible for overseeing the regulatory review, manufacturing, and commercialization of ATI-1501 in the U.S. Metronidazole is a widely prescribed antibiotic, however its terrible taste makes taking it difficult for those who must crush or re-suspend the tablet due to swallowing difficulties. We estimate an NDA for ATI-1501 will be filed within the next 18 months.

INVESTMENT THESIS

Appili Therapeutics Inc. (APLI.V) is a biopharmaceutical company devoted to acquiring and developing novel treatments for infectious diseases. The company was founded in 2015, and since that time has focused on building a diverse pipeline of anti-infective programs, which includes the following four lead programs: ATI-2307 for the treatment of fungal infections; ATI-1701 for the prevention of *Francisella tularensis* infection; ATI-1503 for the development of novel Gram-negative targeting antibiotics; and ATI-1501 is a taste-masked liquid oral suspension formulation of metronidazole.



Source: Appili Therapeutics Inc.

ATI-2307

ATI-2307 was recently acquired from FUJIFILM Toyama Chemical Co., LTD. It is a broad-spectrum, novel antifungal agent with 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*. The company is currently performing preclinical evaluations to determine the optimal Phase 2 development plan, with an initial target indication likely being the treatment of cryptococcal meningitis.

Cryptococcal Meningitis

Cryptococcus neoformans is a fungus that is found throughout the world and most individuals are exposed to it through inhalation. *C. neoformans* infections (cryptococcosis) are very rare in healthy people with a fully functioning immune system and the vast majority of cases occur in those with weakened immune systems, particularly in HIV/AIDS patients. However, beginning around the year 2000, an outbreak of cryptococcosis cases in the Pacific Northwest of the U.S. occurred due to the emergence of *Cryptococcus gattii* that resulted in a number of cases in otherwise healthy individuals (Harris *et al*., 2011). Cryptococcal infections can potentially occur in any part of the body, however the most commonly affected sites are in the lungs and the central nervous system (CNS), with cryptococcal meningitis (CM) resulting in the highest mortality (Sabiiti *et al*, 2012).

CM is a subacute meningoencephalitis in which patients typically present with headache (and other neurological symptoms) along with fever, nausea, and vomiting. The typical time from onset of symptoms to presentation is approximately two weeks in patients with HIV/AIDS and six to 12 weeks for non-HIV cases (Williamson *et al*., 2017). Patients who are not able to receive treatment will go on to experience seizures, loss of consciousness, coma, and potentially death.

There were an estimated 220,000 cases of CM worldwide in 2014, with approximately three-quarters of those cases occurring in sub-Saharan Africa (Rajasingham *et al*., 2017). In the U.S., the incidence of CM is approximately 1 in 100,000 individuals per year (Williamson *et al*., 2017) and is particularly problematic in transplant recipients and other immunosuppressed patients.

Treatment of CM

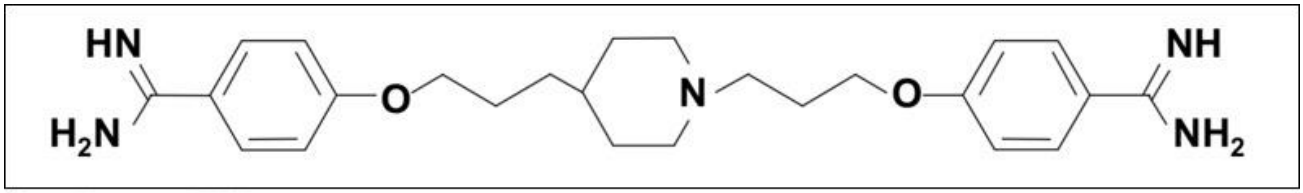
First-line therapy for CM with antifungal agents has not changed much over the past decade and consists of a three-part 'induction, consolidation, and maintenance' approach based on the Mycoses Study Group trial (van der Horst *et al*., 1997). The induction phase consists of amphotericin B deoxycholate or liposomal amphotericin B in combination with flucytosine, which is utilized for two weeks for HIV patients, at least two weeks for transplant recipients, and four to six weeks for all other patients. The consolidation phase consists of eight weeks of treatment with fluconazole and maintenance therapy is a reduced daily dose of fluconazole for at least one year.

Amphotericin B (AmB) is the gold standard for systemic antifungal drugs with a 50+ year history of intravenous (IV) therapy. No oral formulations of AmB are currently commercially available given the poor bioavailability of the drug. Although some patients are able to tolerate the IV injection, many experience localized and systemic side effects associated with IV administration of the drug. For example, the Side Effect & Drug Interactions section of the AmBisome® prescribing information includes warnings on renal impairment, hepatic impairment, febrile reactions, fever accompanied by shaking, chills, normochromic and normocytic anemia, musculoskeletal pain, anaphylactic reactions, dermatologic reactions, including Steven-Johnson syndrome, neurologic reactions, including convulsions, tinnitus, and vertigo, hematological reactions, and injection site reactions. Worldwide sales of the perceived "least toxic" formulation of AmB, AmBisome®, were $597 million in 2018, up 13% from 2017.

While AmB is effective in treating cryptococcosis its use is associated with a number of potentially serious side effects, particularly renal impairment. Thus, what would be most beneficial is a broad-spectrum antifungal agent that did not carry the risk of serious side effects.

ATI-2307

Appili's lead antifungal agent, ATI-2307, is a novel arylamidine that belongs to the same class of aromatic diamidines as pentamidine and furamidine (Mitsuyama *et al*., 2008). It exhibits broad-spectrum activities against a number of different fungal pathogens, including *Candida*, *Cryptococcus neoformans*, and *Aspergillus fumigatus*. The structure of ATI-2307 is shown below.



Source: Mitsuyama *et al*., 2008

ATI-2307 has been tested in multiple *in vitro* and *in vivo* experiments to determine its mechanism of action along with its antifungal activity. The results of some of these assays are summarized below.

Mitsuyama *et al*., 2008: The minimum inhibitory concentration (MIC), the lowest concentration of an antimicrobial agent that prevents visible growth of a microorganism, and the minimum fungicidal concentration (MFC), the minimum concentration of an antimicrobial agent required to achieve a 99% (2-log) reduction in the initial inoculum, was established for ATI-2307 against various yeast and filamentous fungi. As shown in the following table, ATI-2307 (denoted T-2307) exhibited broad-spectrum and potent activity against a wide range of fungal species. Also included in the table are MIC/MFC values for the reference compounds fluconazole (Diflucan®), voriconazole (Vfend®), micafungin (Mycamine®), and amphotericin B.

Strain	MIC/MFC (μg/ml)				
	T-2307	Fluconazole	Voriconazole	Micafungin	Amphotericin B
Candida albicans ATCC 10261	0.001/>64	0.125/>64	0.0039/>64	0.0313/0.25	1/2
Candida albicans ATCC 24433	0.001/>64	0.125/>64	0.0078/>64	0.0313/0.25	1/1
Candida albicans ATCC 90028	0.001/>64	0.125/>64	0.0039/>64	0.0313/0.125	1/1
Candida albicans TIMM 1623	0.001/>64	0.125/>64	0.0039/>64	0.0625/4	1/>1
Candida dubliniensis ATCC MYA-577	0.001/>64	0.125/>64	0.0078/>64	0.125/8	1/2
Candida glabrata ATCC 90030	0.0039/>64	8/>64	0.25/>64	0.0313/0.0313	1/1
Candida guilliermondii IFO 10279	0.002/0.0078	4/>64	0.0625/0.5	0.5/8	0.5/1
Candida krusei IFO 0584	0.001/0.002	32/64	0.125/2	0.125/0.25	2/2
Candida parapsilosis NBRC 10219	0.001/>64	1/>64	0.0313/>64	2/>32	1/1
Candida tropicalis IFO 1400	0.0005/4	2/>64	0.0625/>64	0.0625/>64	1/1
Cryptococcus neoformans ATCC 90112	0.0078/0.0313	1/>64	0.0313/>64	>64/>64	1/1
Cryptococcus neoformans ATCC 90113	0.0078/0.0625	4/>64	0.0625/>64	>64/>64	2/2
Cryptococcus neoformans TIMM 0354[b]	0.0039/0.0156	2/>64	0.0313/>64	>64/>64	1/1
Malassezia furfur NBRC 0656[c]	0.0313/2	4/>64	0.0625/>64	>64/>64	0.5/64
Saccharomyces cerevisiae ATCC 24657	>64/>64	8/>64	0.125/>64	0.5/1	1/2
Trichosporon asahii JCM 2466	64/>64	1/>64	0.0625/>64	>64/>64	2/4
Aspergillus flavus NBRC 6343	0.5/8	>64/>64	0.5/1	0.0625/>64	2/2
Aspergillus fumigatus ATCC 16424	0.125/>64	>64/>64	0.25/32	0.0313/>64	1/2
Aspergillus fumigatus IFM 46895	0.0625/>64	>64/>64	0.5/4	0.0313/>64	2/2
Aspergillus fumigatus IFM 49895	0.5/>64	>64/>64	2/8	0.0313/>64	2/2
Aspergillus fumigatus TIMM 0063	1/>64	>64/>64	1/1	0.0156/>64	2/2
Aspergillus nidulans NBRC 33017	0.0156/0.0313	64/>64	0.125/0.25	0.0313/>64	2/2
Aspergillus niger NBRC 33023	0.0625/0.0625	>64/>64	0.5/16	0.0313/>64	2/2
Aspergillus terreus NBRC 33026	0.125/4	>64/>64	0.5/32	0.0313/>64	2/>64
Fusarium solani IFO 31093[d]	0.125/>64	>64/>64	8/8	>64/>64	2/2
Pseudallescheria boydii NBRC 32229[b]	4/>64	16/>64	1/>64	0.5/>64	>64/>64
Rhizopus oryzae NBRC 31005[e]	>64/>64	>64/>64	8/32	>64/>64	1/1
Absidia corymbifera NBRC4009[e]	0.5/>64	>64/>64	32/>64	32/>64	2/>64
Mucor racemosus NBRC5403[d,e]	2/>64	>64/>64	>64/>64	32/>64	1/2
Trichophyton rubrum NBRC 5467[b]	2/>64	0.25/>64	0.0313/>64	0.0313/>64	1/1

[a] Unless indicated otherwise, RPMI 1640-MOPS medium was used, the inoculum sizes were 0.65×10^3 to 2.5×10^3 CFU/ml for the yeasts and 0.87×10^4 to 3.8×10^4 CFU/ml for the filamentous fungi, and incubation was at 35°C for approximately 48 h.
[b] Incubation was for 72 h.
[c] Modified RPMI 1640-MOPS medium was used.
[d] Incubation was at 30°C.
[e] Incubation was for 24 h.

Source: Mitsuyama *et al.*, 2008

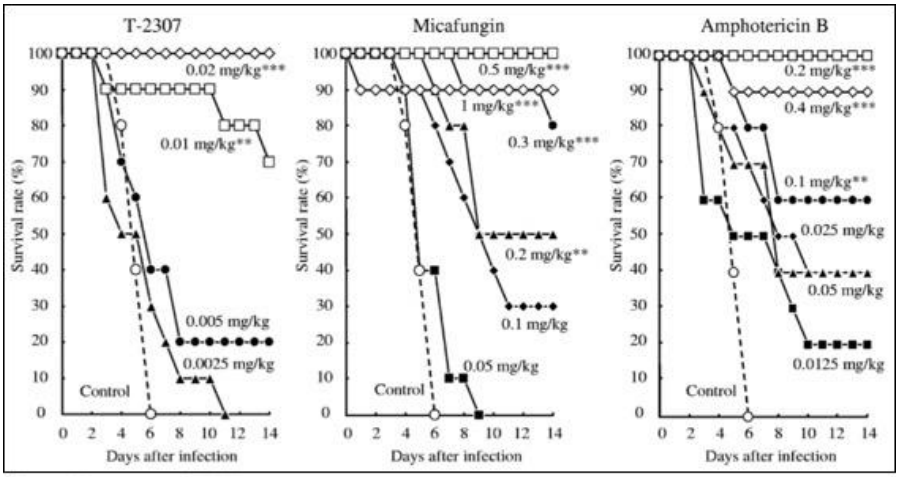
ATI-2307 showed no cross-resistance against fluconazole-resistant and fluconazole-susceptible-dose-dependent *C. albicans* strains, as shown in the following table.

Strain	MIC (μg/ml)				
	T-2307	Fluconazole	Voriconazole	Micafungin	Amphotericin B
ATCC 64124	0.001	>64	16	0.0625	2
ATCC 64550	0.0005	16	0.25	0.0625	1
ATCC 96901	0.001	>64	0.5	0.125	1
ATCC MYA-573	0.001	>64	0.25	0.0625	2
ATCC MYA-574	0.001	64	0.25	0.0625	1
ATCC MYA-575	0.001	16	0.0625	0.125	2
ATCC MYA-1003	0.001	64	0.5	0.125	2
ATCC MYA-2732	0.001	16	0.25	0.125	2

[a] RPMI 1640-MOPS medium was used, the inoculum size was 1.1×10^3 to 1.5×10^3 CFU/ml, and incubation was at 35°C for approximately 47 h.

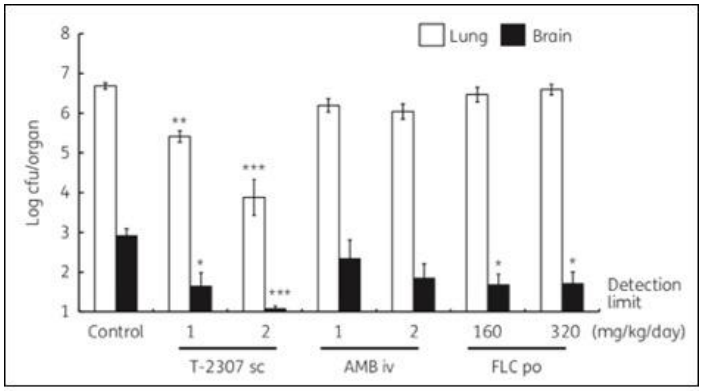
Source: Mitsuyama *et al.*, 2008

ATI-2307 showed a superior protective effect over that of micafungin and amphotericin B in a murine model of systemic candidiasis caused by *C. albicans*. The following graphs show survival curves for mice infected intravenously with *C. albicans* and then treated with varying doses of T-2307, micafungin, or amphotericin B. The ED_{50} of ATI-2307, micafungin, and amphotericin B were 0.00755, 0.182, and 0.0466 mg/kg/dose, respectively. Similar results were seen in murine models of cryptococcosis caused by *C. neoformans*.



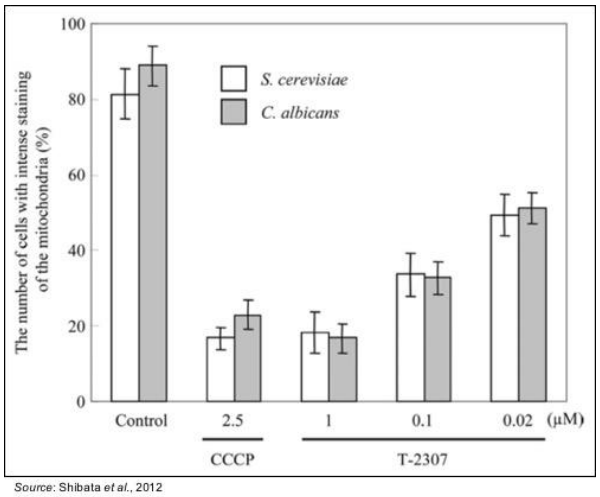
Source: Mitsuyama *et al.*, 2008

Nishikawa *et al.*, 2017: This study tested the efficacy of ATI-2307 in an *in vivo* model of cryptococcosis caused by *C. gattii*. The following graph shows the viable counts of *C. gattii* following treatment with 1 or 2 mg/kg/day ATI-2307, 1 or 2 mg/kg/day AmpB, or 160 or 320 mg/kg/day fluconazole starting on Day 14 post-infection and continuing for seven days. While ATI-2307 significantly decreased the viable counts of *C. gattii*, AmpB was ineffective even at a dose of 2 mg/kg/day, which was the maximum tolerated dose for the mice. These data show the potential for treating *C. gattii* infection with ATI-2307.



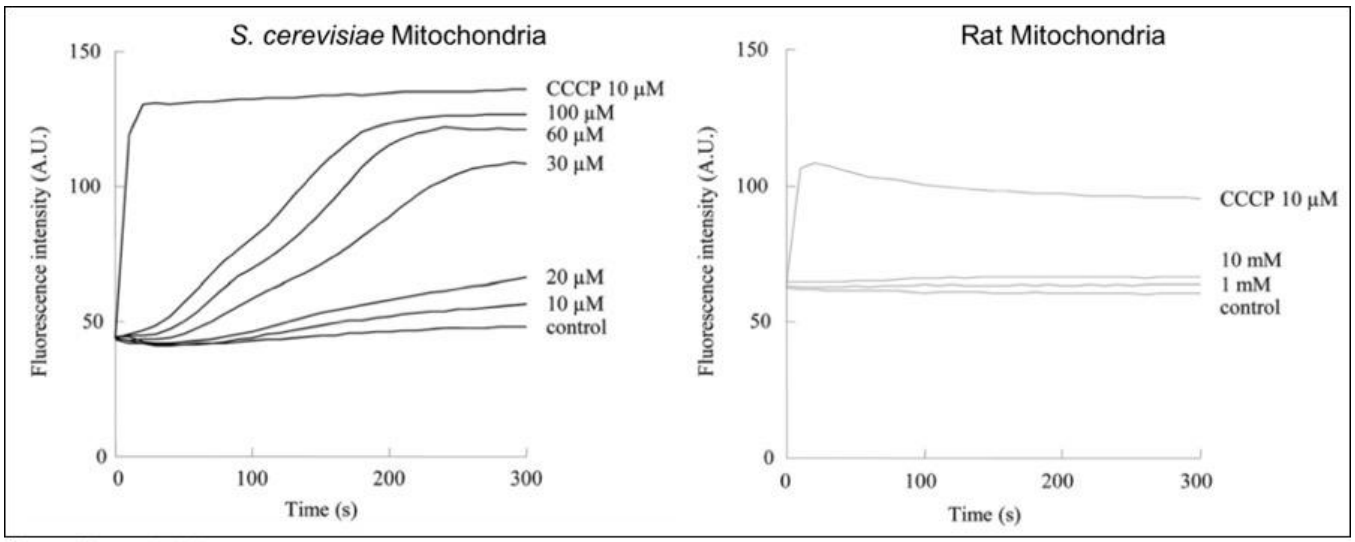
Source: Nishikawa *et al.*, 2017

Shibata *et al.*, 2012: This study sought to determine the mechanism of action for ATI-2307 by examining its effect on mitochondrial function. The following graph shows that treatment of *S. cerevisiae* cells with ATI-2307 for 24 hours prior to staining for mitochondrial function results in a significant decrease in mitochondrial staining. M-chlorophenylhydrazone (CCCP) served as a positive control.



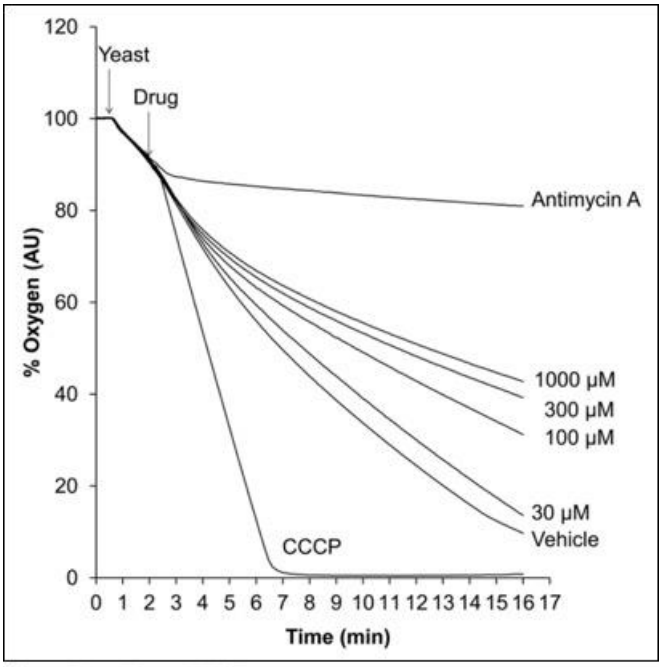
Source: Shibata *et al.*, 2012

In addition to inhibiting uptake of a mitochondrial-specific staining compound, the following graph on the left shows that ATI-2307 disrupts the membrane potential of isolated *S. cerevisiae* mitochondria, further supporting its role as a mitochondria-inhibiting agent. Dicarbocyanine iodide (diS-C_3) is a fluorescence marker that shows mitochondrial depolarization (increased fluorescence intensity) or polarization (decreased fluorescence intensity). Increasing concentrations of ATI-2307 lead to an increase in fluorescence, which is indicative of mitochondrial depolarization (i.e., lack of mitochondrial function). This is in contrast to the effect of ATI-2307 on rat mitochondria, in which there does not appear to be any sign of depolarization (bottom right). In both experiments, CCCP was utilized as a mitochondrial inhibiting positive control.



Source: Shibata *et al.*, 2012

Yamashita *et al.*, 2019: This study aimed to determine how ATI-2307 inhibits mitochondrial function and shows selectivity for yeast mitochondria over mammalian. The following figure shows the effect of ATI-2307 on oxygen consumption in yeast cells. CCCP is an uncoupling agent that dissociates ATP generation from the electron transport chain (i.e., oxygen gets continuously utilized via the electron transport chain since it is no longer tied to production of ATP). Antimycin A is an inhibitor of oxidative phosphorylation, thus little to no oxygen is consumed in its presence. Increasing concentrations of ATI-2307 lead to decreased respiration in a dose-dependent fashion showing that it is an inhibitor of yeast mitochondrial respiration.



Source: Yamashita *et al.*, 2019

The mitochondrial respiratory chain in eukaryotes is composed of four enzymatic complexes (complexes I to IV), however *S. cerevisiae* lacks complex I (Matus-Ortega *et al*., 2015). ATI-2307 was tested against each complex in yeast, with results shown in the following table. The compound inhibited all complexes, except for complex II in *C. albicans*, with the IC_{50} values being lowest for complexes III and IV. ATI-2307 shows IC_{50} values of > 3,000 μM against mitochondrial complexes purified from bovine heart, thus showing little to no activity against mammalian mitochondria.

TABLE 1 The 50% inhibitory concentration values of T-2307 against respiratory chain complexes in *Saccharomyces cerevisiae*, *Candida albicans*, and bovine heart mitochondria[a]

	IC_{50} (μM) ± SD		
Source	***S. cerevisiae***	***C. albicans***	**Bovine heart**
Complex I	Nonexistence	344 ± 32	>3,000
Complex II	755 ± 73	>3,000	Not determined
Complex II + III	271 ± 37	220 ± 55	>3,000
Complex IV	149 ± 23	225 ± 23	>3,000

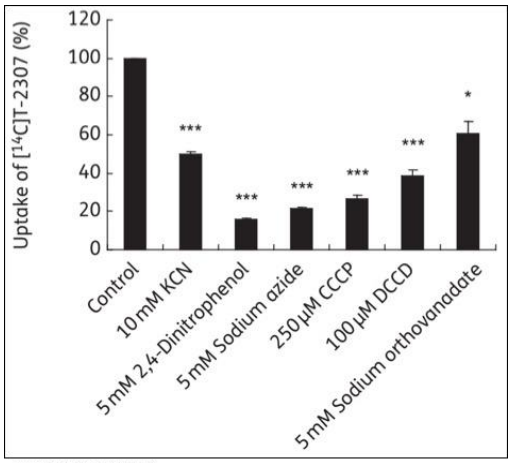
Source: Yamashita *et al*., 2019

Nishikawa *et al*., 2010: This study was performed to identify if ATI-2307 uptake into *C. albicans* was transporter-mediated. Radioactively labeled ATI-2307 was incubated with *C. albicans* at a concentration of 0.02 μM, which has no effect on cell viability in the time frame examined (30 min). The following table shows the intracellular concentration in different species of *C. albicans* ranged from approximately 2200 to 5100-fold higher than the starting extracellular concentration. This is in contrast to rat hepatocytes, in which the intracellular concentration after incubation with the same extracellular concentration of ATI-2307 as used for *C. albicans* was only 35-fold higher.

	Uptake of [^{14}C]T-2307 (pmol/10^7 cells)	Intracellular concentration (μM)[a]	C/E ratio[b]	MIC of T-2307 (mg/L)[c]	MIC of fluconazole (mg/L)[c]
C. albicans TIMM 1623	27.33 ± 1.07 (PB)	43.7	2200	0.001	0.125
	57.54 ± 2.71 (PBG)	92.1	4600		
C. albicans ATCC 90028	40.08 ± 3.42	64.1	3200	0.001	0.125
C. albicans ATCC 10261	57.23 ± 1.51	91.6	4600	0.001	0.125
C. albicans ATCC 64550	44.72 ± 1.86	71.6	3600	0.0005	16
C. albicans ATCC MYA-574	63.00 ± 1.73	101	5100	0.001	64
Rat hepatocytes	27.64 ± 0.91	0.691	35	—	—

Source: Nishikawa *et al*., 2010

To determine what is driving the uptake of ATI-2307, various uptake inhibitors were tested with the same concentration of ATI-2307. The following table shows that inhibitors of mitochondrial respiration, including both KCN (10 mM) and sodium azide (5 mM), significantly decreased ATI-2307 along with 2,4-dinitrophenol (5 mM), an inhibitor of oxidative phosphorylation.



Source: Nishikawa *et al*., 2010

Nishikawa *et al*., 2016: This study was undertaken to better characterize the specificity and kinetic features of the high-affinity carrier of ATI-2307 in *C. albicans* and *S. cerevisiae*. The following table shows the uptake of radioactively labeled ATI-2307 in the presence of varying concentrations of different potential inhibitors. Only spermine and spermidine, which belong to the same class of compounds as ATI-2307, showed the ability to inhibit its uptake.

		C. albicans TIMM 1623		*S. cerevisiae* BY4741	
	Substrate (μM)	uptake (pmol/10^7 cells)	statistics[a]	uptake (pmol/10^7 cells)	statistics[a]
None (control)	—	20.2 ± 1.4	—	28.9 ± 0.3	—
Spermine	0.1	8.8 ± 1.0	***	12.0 ± 0.3	***
	1	4.7 ± 0.6	***	4.4 ± 0.3	***
	10	2.5 ± 0.4	***	1.8 ± 0.04	***
Spermidine	0.1	13.2 ± 0.9	**	26.1 ± 1.4	*
	1	9.1 ± 0.9	***	20.0 ± 0.3	***
	10	5.4 ± 0.3	***	6.4 ± 0.3	***
Putrescine	0.1	21.1 ± 2.6	NS	30.0 ± 0.3	NS
	1	18.7 ± 2.9	NS	29.5 ± 0.5	NS
	10	20.1 ± 2.9	NS	28.2 ± 0.3	NS
Adenine	0.1	18.9 ± 1.0	NS	29.6 ± 0.4	NS
	1	19.8 ± 0.2	NS	29.3 ± 0.4	NS
	10	18.8 ± 1.0	NS	29.3 ± 0.9	NS
Adenosine	0.1	20.1 ± 1.9	NS	29.3 ± 0.5	NS
	1	19.4 ± 0.9	NS	30.2 ± 0.5	NS
	10	18.3 ± 1.0	NS	29.9 ± 0.4	NS
Arginine	0.1	18.4 ± 1.0	NS	29.9 ± 0.3	NS
	1	20.4 ± 3.0	NS	29.5 ± 0.4	NS
	10	20.0 ± 0.4	NS	28.5 ± 0.2	NS

Uptake of 0.02 μM [^{14}C]T-2307 in *C. albicans* TIMM 1623 and *S. cerevisiae* BY4741 was measured for 5 min at 30°C in PBG in the absence and presence of 0.1, 1 and 10 μM of a potential competitive substrate. The results are expressed as the mean ± SE of triplicate experiments.
[a]Statistical analysis was performed with the parametric Dunnett's multiple comparison test. Asterisks indicate a significant difference from the control (*, $P<0.05$; **, $P<0.01$; ***, $P<0.001$; NS, not significant).

Source: Nishikawa *et al*., 2016

The identities of polyamine transporter proteins are fairly well characterized in *S. cerevisiae*, thus a collection of strains with various deletions of those polyamine transporters were tested to determine which may be involved in ATI-2307 uptake. The following table shows that the Δ*agp2* strain showed a significantly increased MIC for ATI-2307 while deletion mutants for other polyamine transporters showed little effect on the activity of ATI-2307, thus showing that *Agp2* regulates the transport system of ATI-2307.

Strain	MIC (mg/L)[a]	Uptake (pmol/10^7 cells)[b]	Statistics[c]
BY4741 (control)	0.00012	35.1 ± 0.7	—
Δgap1	0.00012	35.2 ± 0.7	NS
Δagp2	>8	11.4 ± 0.1	***
Δdur3	0.00012	34.4 ± 1.0	NS
Δsam3	0.00012	34.9 ± 1.1	NS
Δptk2	0.0005	14.5 ± 0.2	***
Δsky1	0.0005	11.8 ± 0.3	***

Source: Nishikawa *et al*., 2016

In summary: the data presented here show that ATI-2307 is a potent inhibitor of a wide range of fungal species, including pathogenic organisms, and this activity is due to the presence of an active transporter that moves ATI-2307 into fungal cells where it inhibits the production of ATP through inhibition of the mitochondrial respiratory complexes III and IV. Concurrently, ATI-2307 shows little to no activity against mammalian mitochondrial complexes, thus it is highly specific to fungal species.

ATI-2307 Development Plan

ATI-2307 has been successfully tested in multiple Phase 1 clinical trials, including a Phase 1 clinical trial in healthy volunteers in Japan that showed the drug was safe and well tolerated (NCT02289599). We believe Appili will need to perform additional pre-clinical work before clinical trials can commence, including a rigorous PK/PD workup along with manufacturing of the drug product. We anticipate an IND being filed with the FDA in 2021 with a Phase 2 clinical trial initiating shortly thereafter.

ATI-2307 Market Opportunity in CM

As mentioned previously, we believe Appili will initially be targeting ATI-2307 for the treatment of CM. While the majority of CM cases occur in sub-Saharan Africa, we estimate there are approximately 3,000 to 5,000 cases each year in the U.S., with one study finding the 90-day all-cause mortality in patients with CM being 21% (Brizendine *et al*., 2013). This level of mortality supports the urgent necessity for more effective treatment options, particularly those with better tolerance than the current standard of care AmB. In addition to the high mortality, typical hospital stays for patients with CM are approximately 15 days and total costs to treat CM have been estimated at approximately $75,000 (Merry *et al*., 2016). This cost is driven in part due to the fact that up until 2017 there was only one manufacturer of flucytosine, thus the daily cost of flucytosine to treat CM had risen to approximately $2,000 per day. However, the FDA has approved three additional ANDA's for flucytosine over the past two years, and the wholesale cost has dropped to approximately $400-$500 per day (GoodRx).

The costs listed above do not take into consideration potential side effects of using AmB, of which approximately 15-30% of patients will suffer from some form of renal failure, which typically increases the length of stay in the hospital. Thus, a treatment that is more effective than AmB and does not carry the potential for adverse renal effects would likely command premium pricing, and we estimate that for a course of treatment with ATI-2307 for CM in the U.S. Appili could charge $70,000, thus making it a potential $350 million opportunity.

Potential for Priority Review Voucher

In addition to the potential $350 million market opportunity in CM, ATI-2307 may also be eligible for a priority review voucher (PRV) as CM has been designated a tropical disease under the PRV system. A PRV allows the holder of the voucher to receive an expedited six-month review from the FDA for an NDA or biologics license application (BLA) instead of the usual ten-month review. The Food and Drug Administration Amendments Act created the neglected tropical disease priority review voucher system in 2007 to spur the development of new therapies for rare tropical diseases, with CM added as a disease to the PRV program by the FDA in August 2018. Priority review vouchers are also awarded for the development of treatments for rare pediatric diseases and medical countermeasures.

Priority review vouchers are fully transferrable, and a number of companies that have been issued the vouchers in the past have sold them, including one that was sold to AbbVie (ABBV) in Aug. 2015 for $350 million. The four most recent purchases are by Eli Lilly (LLY) for $80 million in Nov. 2018, Biohaven Pharmaceutical Holding Company for $105 million in Mar. 2019, AstraZeneca (AZN) for $95 million in Aug. 2019, and an undisclosed buy for $95 million in Dec. 2019. While prices for PRVs have come down since AbbVie purchased one for $350 million in 2015, the price for them appears to have settled in the $80-$100 million range. The following table shows how many PRVs have been issued along with the current status of the voucher, if known.

Priority Review Vouchers			
Voucher Award Date	Voucher Type	Voucher Awardee	Voucher Status
2009	Tropical Disease	Novartis	Used for BLA for canakinumab
2012	Tropical Disease	Janssen	Used to accelerate approval of Tremfya (guselkumab) for plaque psoriasis
2014	Rare Pediatric Disease	BioMarin	Sold to Sanofi for $67.5M in Jul 2014; used for approval of Praluent
2014	Tropical Disease	Knight Therapeutics	Sold to Gilead for $125M in Nov 2014; used for approval of Odefsey
2015	Rare Pediatric Disease	United Therapeutics	Sold to AbbVie for $350M in Aug 2015
2015	Rare Pediatric Disease	Asklepion Pharmaceuticals	Transferred to Retrophin and sold to Sanofi for $245M in May 2015
2015	Rare Pediatric Disease	Wellstat Therapeutics	Transferred to AstraZeneca
2015	Rare Pediatric Disease	Alexion Pharmaceuticals	Used for approval of ALXN1210
2015	Rare Pediatric Disease	Alexion Pharmaceuticals	Not used
2016	Tropical Disease	PaxVax Bermuda	Not used (possibly sold to Gilead for ~$200M in 2Q16)
2016	Rare Pediatric Disease	Sarepta Therapeutics	Sold to Gilead for $125M in Feb 2017; used for approval of HIV treatment
2016	Rare Pediatric Disease	Ionis Pharmaceuticals	Not used
2017	Rare Pediatric Disease	Marathon Pharmaceuticals	Not used
2017	Rare Pediatric Disease	BioMarin	Sold for $125 million in Nov 2017
2017	Tropical Disease	Chemo Research, S.L.	Not used
2017	Rare Pediatric Disease	Novartis	Used for brolucizumab for wetAMD
2017	Rare Pediatric Disease	Ultragenyx Pharmaceutical	Sold to Novartis for $130 million in Dec. 2017; used for approval of siponimod
2017	Rare Pediatric Disease	Spark Therapeutics	Sold to Jazz Pharmaceuticals for $110 million in Apr 2018
2018	Rare Pediatric Disease	Ultragenyx Pharmaceutical	Sold to undisclosed buyer for $80.6 million in Aug. 2018
2018	Rare Pediatric Disease	Medicines Development	Sold to Novo Nordisk for undisclosed amt
2018	Rare Pediatric Disease	GW Pharma	Sold to Biohaven for $105 million on Mar. 18, 2019
2018	Material Threat Medical Countermeasure	SIGA Technologies	Sold to Eli Lilly for $80 million on Nov. 1, 2018
2018	Tropical Disease	GlaxoSmithKline	Used by ViiV Healthcare for NDA for HIV-1 infection
2018	Rare Pediatric Disease	Leadiant Bioscience Inc	Not used
2018	Rare Pediatric Disease	Sobi and Novimmune	Sold to AZN for $95 million in Aug 2019
2019	Tropical Disease	Novartis	Not used
2019	Rare Pediatric Disease	Vertex	Not used
2019	Rare Pediatric Disease	Alexion Pharmaceuticals	Not used
2019	Tropical Disease	Sanofi	Not used
2019	Rare Pediatric Disease	Novartis	Not used
2019	Tropical Disease	TB Alliance	Not used
2019	Material Threat Medical Countermeasure	Bavarian Nordic	Sold to undisclosed buyer for $95 million in Dec. 2019
2019	Rare Pediatric Disease	Vertex	Not used
2019	Rare Pediatric Disease	Sarepta Therapeutics	Not used
2019	Tropical Disease	Merck	Not used

Source: raps.org / Zacks SCR

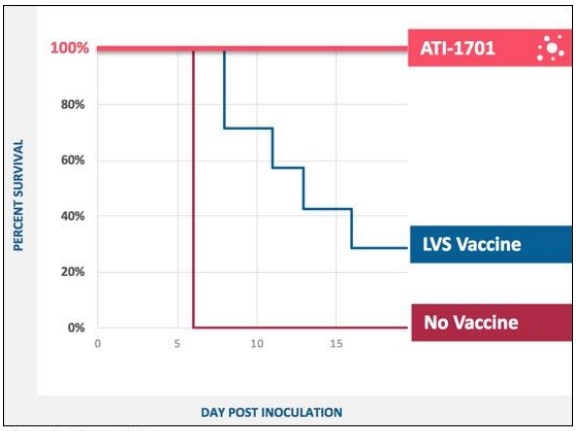
ATI-1701

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. It is an intracellular bacterium that primarily infects macrophages (Clemens *et al*., 2007). Symptoms typically occur three to five days following exposure and include sudden chills, fever, headaches, diarrhea, muscle aches, and progressive weakness (CDC). Streptomycin is the standard of care for tularemia, although gentamicin is an acceptable alternative, and treatment typically lasts for 10 days. Tetracyclines may also be used in place of aminoglycosides, but treatment with those agents is done for 14 days. Ciproflaxin and other fluoroquinolones are not FDA-approved to treat tularemia, but they have shown good efficacy *in vitro* and i*n vivo*.

The U.S. Army developed a live vaccine strain, *F. tularensis* LVS, from an attenuated strain derived from the less virulent subspecies *holarctica* (Sjostedt, 2007). Human volunteer studies showed this vaccine to be approximately 25-100% effective against aerosol challenge and 66-90% effective against intradermal challenge with *F. tularensis* strain SCHU S4 (Saslaw *et al*., 1961). However, an absence of correlation between antibody titer and protection from disease symptoms (Saslaw *et al*., 1961) along with concerns regarding its manufacture and attenuation has prevented the approval of LVS. Thus, scientists at the Canadian National Research Council set out to develop an improved tularemia vaccine based on the SCHU S4 strain.

Targeted deletion mutants of SCHU S4 were developed and tested for their efficacy against an aerosol challenge of *F. tularensis* in mice (Conlan *et al*., 2010). Mice immunized with the SCHU S4 mutant missing the heat shock protein *clpB* (ATI-1701) were significantly better protected against an aerosol challenge with wild-type SCHU S4 than mice immunized with LVS. In addition, vaccination with ATI-1701 resulted in a significantly

higher production of IL-17 and fewer bacteria in the lungs than in mice immunized with LVS, with no other cytokine showing the same inverse correlation (Shen *et al*., 2010). Lastly, the following graph shows that ATI-1701 shows enhanced efficacy compared to LVS with 100% of mice surviving a lethal challenge of *F. tularensis* and only 1/3rd of mice being protected by LVS.



Source: Appili Therapeutics Inc.

ATI-1701 Development Plan

Since it is no longer acceptable 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. The company recently presented data showing 100% protection in non-human primates 90 days after vaccination with ATI-1701 and we anticipate data on the efficacy of the vaccine up to 365 days in the first half of 2020. We anticipate the vaccine entering clinical trials in healthy volunteers in the first half of 2022. Appili has received approximately $6 million in funding to support ATI-1701 from the US Department of Defense (DoD) Defense Threat Reduction Agency (DTRA).

ATI-1701 Market Opportunity

There are three potential market opportunities for ATI-1701:

Civilian Stockpiling: The U.S government's Strategic National Stockpile (SNS) could store ATI-1701 in the event of a bioterror attack. The SNS is managed by the CDC and the U.S. Department of Health and Human Services (HHS) and is tasked with keeping the nation's largest supply of potentially life-saving pharmaceuticals and medical supplies for use in a public health emergency. There are many examples of companies selling products to be stored in the SNS, including:

- SIGA Technologies Inc. (2011): received a contract for up to $472 million for two million units of smallpox antiviral ST-246.
- Emergent BioSolutions (2011): received a contract for up to $1.25 billion for 44.75 million units of the anthrax vaccine BioThrax®.
- Emergent BioSolutions (2016): received a contract for up to $1.6 billion for 52 million units of the anthrax vaccine NuThrax®
- Bavarian Nordic (2017): received a contract for up to $539 million for the smallpox vaccine Imvamune®

The HHS also has the authority to procure products in advance of an FDA approval, which was done previously when 20,000 doses of Abthrax™ was purchased from Human Genome Sciences, Inc. for $165 million.

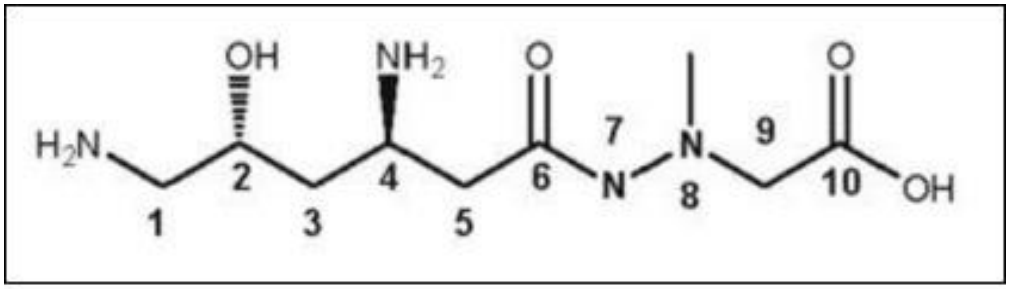
Military Use: *F. tularensis* is thought to have been weaponized since World War II and more recently by hostile actors on the world stage, including Iran, North Korea, and Russia. The potential deployment of troops to various "hot zones" around the world may involve their immunization to tularemia were a vaccine available. In addition, there are a number of countries with standing armies that are located near potential adversaries

(e.g., Israel, South Korea) that may wish to immunize their troops to protect against a potential tularemia attack.

PRV: ATI-1701 would qualify for a PRV based on it being a "medical countermeasure", which was included in the PRV program with the signing of the 21st Century Cares Act in 2016. As discussed previously, a PRV could potentially be sold for approximately $100 million.

ATI-1503

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. The structure of negamycin is shown below.



Source: Olivier *et al.*, 2014

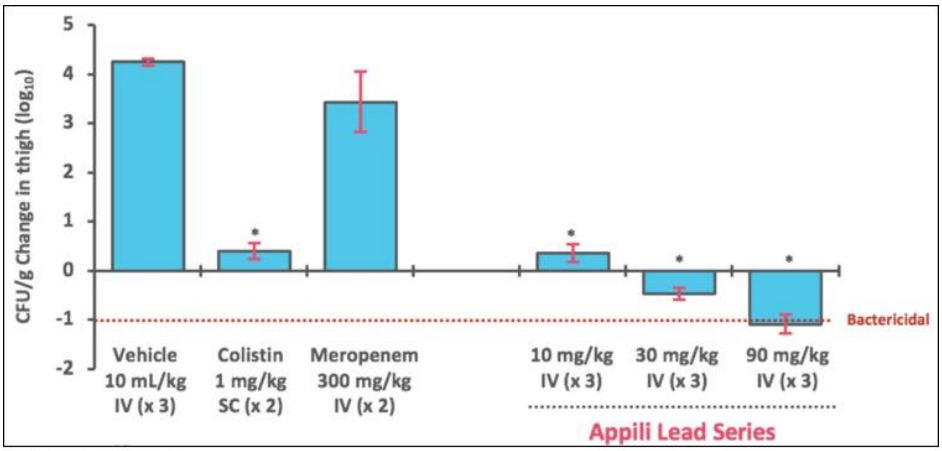
Negamycin was originally isolated from cultures of *Streptomyces purpeofuscus* where it showed activity in immunocompetent mouse models of sepsis caused by Gram-negative pathogens such as *P. aeruginosa* and *Klebsiella Pneumoniae* (Hamada *et al*., 1970). It exerts its antibiotic effect by targeting 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 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 been awarded multiple non-dilutive grants to continue research into developing negamycin analogues:

- In November 2017, Appili was awarded a $1.2 million grant by the U.S. Department of Defense, Congressionally Directed Medical Research Programs, Peer Reviewed Medical Research Program
- In April 2017, Appili was awarded an additional $400,000 from the National Research Council of Canada Industrial Research Assistance Program, bringing the total support for the project up to $759,000
- In July 2019, Appili was awarded a $3.0 million grant from the U.S. Department of Defense, Congressionally Directed Medical Research Programs, Peer Reviewed Medical Research Program

ATI-1503 Development Plan

The company is currently evaluating multiple lead candidates through *in vivo* testing to determine which is the most promising compound(s) to take into clinical testing. The focus now is to do a full characterization of the PK/PD profile along with a thorough analysis of safety and toxicity. The following graph shows promising *in vivo* results for a lead candidate with a nice dose response that is able to reach bactericidal levels at the highest dose. The company hopes to select a lead development candidate to advance into clinical testing in 2020.



Source: Appili Therapeutics Inc.

ATI-1503 Market Opportunity

Infections caused by Gram-negative bacteria, particularly those that are resistant to one or more approved antibiotics, are a serious public health issue. The CDC's *Antibiotic Resistance Threats in the United States, 2019* includes data on multiple species of antibiotic-resistant bacteria and fungi categorized by the level of concern to human health (urgent, serious, and concerning). Included in the "urgent" category are the Gram-negative bacteria *Acinetobacter* and *Enterobacteriaceae*, which are responsible for hospitalizing thousands of patients each year.

Given the ever increasing incidence of antibiotic-resistant infections, and the need for more effective antibiotics, particularly those with novel mechanisms of action, antibiotic development continues to generate sizeable deals, particularly from regional pharmaceutical companies that are interested in securing commercial rights to drugs even if still in clinical development, as shown in the following chart.

Company	Type	Acquirer/Partner	Stage	Territory	Transaction Value (excl. royalties)
Warp Drive	License	Roche	Discovery / Preclinical	Global	**$387M** (Oct 2017)
iNtRON	License	Roivant	Phase 2	Global	**$668M** (Nov 2018)
Entasis	License	Zai Labs	Phase 2	Asia-Pacific	**$104M** (Apr 2018)
VenatoRx	License	Everest Medicines	Pre-Phase 3	Asia-Pacific	**$114M** (Sep 2018)
Basilea	License	CR Gosun	Marketed	China	**$152M** (Sep 2017)
Medicines Co	Asset Purchase	Melinta Therapeutics	Marketed	-	**$270M** (Nov 2017)
AstraZeneca	License	Pfizer	Marketed	Ex-US	**$1.6B** (Aug 2016)

Source: Appili Therapeutics Inc.

ATI-1501

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).

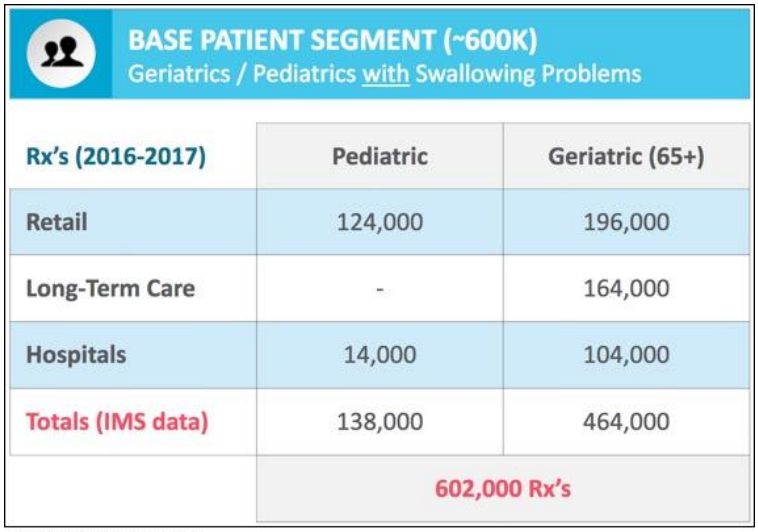
Unfortunately, many young and elderly patients have a hard time swallowing metronidazole tablets. These patients are then forced to crush or re-suspend the medicine, which exacerbates its already bitter and unpleasant taste (the taste is so pronounced it is listed as an adverse event on the drug label). To help patients who have difficultly swallowing metronidazole tablets, Appili developed a proprietary taste-masked orally-administered refrigerated formulation with excipients to sequester metronidazole and limit taste bud interaction while also including flavoring agents to limit the potential for a bad after-taste.

In July 2018, the company announced the results of a pivotal relative bioavailability study evaluating ATI-1501 in healthy adults. The data showed that a single 500 mg dose of ATI-1501 achieved equivalent systemic drug levels as a 500 mg metronidazole tablet under both fasted and fed conditions. In addition, study subjects found the liquid formulation to be more palatable than metronidazole tablets.

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. Saptalis is currently evaluating formulation options to maximize product stability and we anticipate an NDA being filed in the next 18 months.

ATI-1501 Market Opportunity

The following chart shows the number of metronidazole prescriptions written in 2016/2017 for pediatric and geriatric patients, which are the initial target populations for ATI-1501. A course of metronidazole costs approximately $25, thus with similar pricing the initial market opportunity for ATI-1501 is approximately $15 million.



Source: Appili Therapeutics Inc.

Future market expansion for ATI-1501 is based on targeting non-elderly patients with swallowing issues or taste sensitivities, creating taste-masked formulations for other antibiotics (e.g., clindamycin), and treating patients with NG tubes.

Financials and Capital Structure

On November 27, 2019, Appili announced financial results for the second quarter of fiscal year 2020 that ended September 30, 2019. The company reported a net loss of CAD$1.2 million for the three months ending Sep. 30, 2019 compared to a net loss of CAD$1.3 million for the three months ending Sep. 30, 2018. R&D expenses for the second quarter of fiscal year 2020 were CAD$0.6 million compared to CAD$1.0 million for the second quarter of fiscal year 2019. The decrease was mainly attributable to decreased spending for the ATI-1501 and ATI-1503 programs. G&A expenses for the second quarter of fiscal year 2020 were CAD$0.7 million compared to CAD$0.6 million in the second quarter of fiscal year 2019. The increase was primarily due to increased G&A expenses, excluding salaries, and an increase in salary and benefits partially offset by a decrease in stock-based compensation.

As of September 30, 2019, Appili had approximately CAD$3.1 million in cash, cash equivalents, and short-term investments. In addition, the company has only drawn down approximately $0.1 million of the $3.0 million US PRMRP grant for the development of ATI-1503. We estimate that the company currently has sufficient capital to fund operations for the next two quarters.

As of November 27, 2019, Appili had approximately 33.6 million shares outstanding and when including the approximately 2.7 million stock options and 0.9 million warrants a fully diluted share count of approximately 37.2 million.

Risks to Consider

Development Risk: Appili is in the very early stages of development for ATI-2307, thus there is still a substantial amount of work that is necessary before clinical trials can be initiated. ATI-1701 is currently in animal testing and will be the first tularemia vaccine to test out to 365 days for efficacy, thus there is no guarantee that the positive 90-day results will be confirmed for the longer time frame. A lead candidate for the ATI-1503 program has not yet been selected, thus there is no guarantee that the selected compound will show efficacy in clinical testing or have a favorable safety or tolerability profile. In addition, other antibiotics that have greater efficacy and/or fewer side effects than ATI-1503 may be developed. ATI-1501 has been out-licensed to Saptalis Pharmaceuticals, however there is no guarantee that Saptalis will be able to secure approval for ATI-1501 or, if approved, will be able to successfully market the drug.

Clinical Risks: ATI-1701 will not be entering Phase 1 safety studies until 2022, and there is no guarantee that the drug will be safe and well tolerated in that trial. While ATI-2307 has been tested in three Phase 1 studies and was shown to be safe and well-tolerated in healthy volunteers, there is no guarantee that those results will be seen when Appili begins clinical testing in critically ill patients suffering from *cryptococcal* or *candida* infections. Pre-clinical results for ATI-2307 show the drug to be active in multiple animal models, however there is no guarantee that same level of activity will be seen in clinical trials. The ATI-1503 program is years away from entering the clinic, and there is no guarantee that the compound selected for clinical testing will lead to positive results.

Financing Risk: Appili has less than 12 months of cash, thus the company will need to obtain additional funding to continue the development of its pipeline candidates. There is no guarantee that the company will be able to raise sufficient capital to develop each of the product candidates to commercialization, and raising additional funds may cause significant dilution for existing shareholders.

MANAGEMENT PROFILES

Armand Balboni, MD, PhD – Chief Executive Officer

Dr. Balboni's career includes medical research and drug development experience in civilian, academic, and military organizations, most recently as a partner at Bloom Burton & Co. where he was the firm's senior advisor for regulatory and medical affairs. As an active duty military officer, Dr. Balboni served as a staff officer at the U.S. Army Research Institute of Infectious Diseases (USAMRIID). He completed a military staff fellowship at the U.S. Food and Drug Administration and went on to serve as the deputy director of clinical and regulatory affairs for the U.S. Army. Armand completed his doctoral work in the MD/PhD program at the Icahn School of Medicine at Mount Sinai and earned his law degree at Brooklyn Law School.

Kimberly Stephens – Chief Financial Officer

Ms. Stephens brings nearly 20 years of financial management experience at public and private companies to her role at Appili. Most recently Ms. Stephens served as CFO of IMV Inc. (formerly Immunovaccine) (Nasdaq: IMV; TSX: IMV), where she raised more than $40 million in equity financing and government grants. She was instrumental in IMV's graduation from the TSX Venture Exchange to the TSX and listing on the OTCQX in the USA. Ms. Stephens began her career as an audit manager at PwC and has extensive experience across multiple industries in addition to the life science sector, including financial services, software, and oil and gas.

Myriam Triest, PhD – Senior Director, Product Development

Dr. Triest brings over 15 years of experience as a drug development professional and chemist to her role as Director of Manufacturing and Pharmaceutical Development. She manages the chemical, regulatory, and quality aspects of Appili's drug development pipeline. In her previous role as Director of Product Development at Locemia Solutions (Montreal), Dr. Triest supported the development of a combination drug candidate from discovery through a successful phase 3 clinical program that was ultimately licensed to Eli Lilly for $150M USD upfront plus milestones. In addition, she brings to Appili experience as a vice president of a clinical research organization with a wide range of drug development programs, including small molecules, peptides, and medical devices. She earned her PhD from Katholieke Universiteit Leuven, Belgium and completed her post-doctorate fellowship at Université de Montréal.

Stephane Paquette, PhD – Director, Business Development

As Director, Business Development, Stéphane Paquette directs evaluation and licensing activities for Appili, as well as key stakeholder and partner management. Dr. Paquette brings extensive infectious disease and R&D experience to his role at Appili, with over 10 years in industry and leading academic institutions. Prior to joining Appili, Dr. Paquette was a researcher at the University Health Network / University of Toronto studying emerging viral pathogens, immune responses to infection and vaccination, and novel antiviral compounds. Previously, Dr. Paquette was Associate Scientist at Abbott Point of Care where he conducted exploratory R&D on novel diagnostic assays. He is author on 14 peer-reviewed publications in the fields of infectious disease and biochemistry, and holds a PhD from the University of Toronto with a BSc in Microbiology & Immunology from McGill University.

VALUATION

We are initiating coverage of Appili Therapeutics Inc. (APLI.V) with a valuation of CAD$4.00. Appili is a biopharmaceutical company focused on the acquisition and development of novel treatments for infectious diseases. The company's pipeline includes four programs: ATI-2307 for the treatment of invasive fungal infections; ATI-1701 for protection against *Francisella tularensis*, a Category A pathogen and potential biological weapons threat; ATI-1503 for development of new Gram-negative antibiotics; and ATI-1501 is a taste-masked liquid suspension reformulation of metronidazole.

ATI-2307

ATI-2307 is a broad-spectrum, novel antifungal agent with 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*. The company is currently performing preclinical evaluations to determine the optimal Phase 2 development plan, with an initial target indication likely being the treatment of cryptococcal meningitis.

Amphotericin B (AmB) is the current gold standard for systemic antifungal drugs with a 50+ year history of intravenous (IV) therapy. No oral formulations of AmB are currently commercially available given the poor bioavailability of the drug. Although some patients are able to tolerate the IV injection, many experience localized and systemic side effects associated with IV administration of the drug, with the most serious being renal impairment. Despite these risks, worldwide sales of the perceived "least toxic" formulation of AmB, AmBisome®, were $597 million in 2018, up 13% from 2017.

While AmB is effective in treating cryptococcosis its use is associated with a number of potentially serious side effects, particularly renal impairment. Thus, what would be most beneficial is a broad-spectrum antifungal agent that did not carry the risk of serious side effects, and we believe that ATI-2307 may prove to be that drug.

ATI-1701

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. 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.

Since it is no longer acceptable 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. The company recently presented data showing 100% protection in non-human primates 90 days after vaccination with ATI-1701 and we anticipate data on the efficacy of the vaccine up to 365 days in the first half of 2020.

ATI-1503

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*. Negamycin has a number of positive attributes, however the compound itself is not potent enough for development as an antibiotic, with MIC values of 16-64 μg/mL. Thus, the company is currently evaluating multiple lead candidates that are derivatives of negamycin through *in vivo* testing to

determine which is the most promising compound(s) to take into clinical testing. The focus now is to do a full characterization of the PK/PD profile along with a thorough analysis of safety and toxicity. The company hopes to select a lead development candidate to advance into clinical testing in 2020.

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ATI-1501 is a taste-masked liquid oral suspension formulation of the antibiotic metronidazole, an antibiotic used to treat various protozoan and anaerobic bacterial infections, including giardiasis, trichomoniasis, and amebiasis. It is a widely used antibiotic, with more than 10 million oral prescriptions written each year.

Unfortunately, many young and elderly patients have a hard time swallowing metronidazole tablets. These patients are then forced to crush or re-suspend the medicine, which exacerbates its already bitter and unpleasant taste (the taste is so pronounced it is listed as an adverse event on the drug label). To help patients who have difficulty swallowing metronidazole tablets, Appili developed a proprietary taste-masked orally-administered refrigerated formulation with excipients to sequester metronidazole and limit taste bud interaction while also including flavoring agents to limit the potential for a bad after-taste.

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. Saptalis is currently evaluating formulation options to maximize product stability and we anticipate an NDA being filed in the next 18 months.

Valuation

We value Appili using a probability adjusted discounted cash flow model that takes into account potential future revenues for ATI-2307, ATI-1701, and ATI-1501. We are not including ATI-1503 yet as a lead compound for that program has yet to be identified. In addition, all values below are in USD, since the U.S. market is the primary one that Appili will be targeting for each of their development candidates.

For ATI-2307, we anticipate Phase 1 studies will initiate in 2021 that will eventually lead to a Phase 3 trial in 2024, an NDA filing in 2026, and approval in 2027. We currently forecast for Appili to form a partnership(s) for commercialization and receive a 15% royalty on net sales. Our model calls for treatment of cryptococcal meningitis with ATI-2307 to cost $70,000 and we forecast peak sales of approximately $250 million. In addition, we model for the company to be issued a PRV in 2027 that we estimate will be sold for $90 million. Using a 15% discount rate and a 25% probability of approval leads to a net present value for ATI-2307 of $14 million. We note that potential upside to this valuation exists through expansion of the drug's use to include infections caused by various *Candida* species.

For ATI-1701, we forecast for an NDA filing in 2023 and approval in 2024. Our model currently incorporates the potential sale of ATI-1701 as a stockpiled treatment in the event of a bioterror attack using *F. tularensis*. Based on other stockpile contracts, including a $472 million contract to stockpile a smallpox vaccine in 2011 and a $539 million contract for a smallpox vaccine in 2017, our model includes a $500 million, five-year contract signed in 2024. In addition, we forecast for a PRV to be issued upon approval of ATI-1701, and for it to be sold that same year for $90 million. Using a 15% discount rate and a 50% probability of approval leads to a net present value for ATI-1701 of $124 million.

For ATI-1501, we forecast that a filing for approval will be made in 2021 and that the drug will be approved in 2022. Based on its ability to be utilized by patients that would otherwise not be able to receive the drug, we estimate for each treatment with ATI-1501 to cost $100 and for peak sales of $30 million. Using a 15% discount rate and a 75% probability of approval leads to a net present value for ATI-1501 of $5 million.

Combining the net present values for each of the company's assets along with the current cash balance leads to a net present value for the company of $147 million. We divide this by an estimated fully diluted share count of 49.2 million, which includes the current fully diluted share count of 37.2 million plus an additional 12 million shares to account for future financings, which leads to a valuation of approximately $3.00 per share, or CAD$4.00 per share.

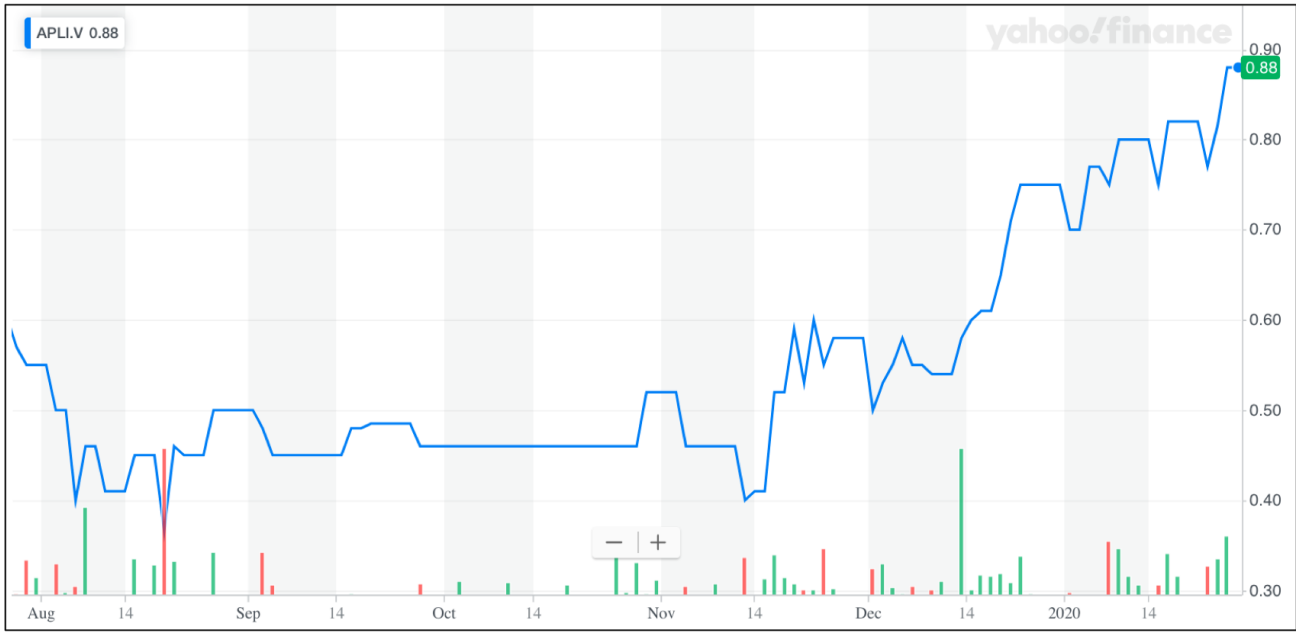
PROJECTED FINANCIALS

Appili Therapeutics Inc. Fiscal Year Ends Mar. 31 / in Canadian dollars	FY2019 A	Q1FY20 A	Q2FY20 A	Q3FY20 E	Q4FY20 E	FY2020 E	FY2021 E	FY2022 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	$0.1	$0.0	$0.1	$0.9	$0.0
Other Income	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0
Total Revenues	**$0.0**	**$0.0**	**$0.0**	**$0.1**	**$0.0**	**$0.1**	**$0.9**	**$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	$3.3	$0.6	$0.6	$0.6	$0.6	$2.3	$7.7	$10.0
General & Administrative	$2.4	$0.9	$0.7	$0.8	$0.8	$3.1	$3.2	$3.3
Business Development	$0.9	$0.5	$0.1	$0.2	$0.2	$1.0	$1.0	$1.0
Other (Income) Expense	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0
Operating Income	($6.5)	($1.9)	($1.4)	($1.5)	($1.6)	($6.4)	($11.0)	($14.3)
Operating Margin	-	-	-	-	-	-	-	-
Non-Operating Expenses (Net)	$2.2	$0.1	$0.2	$0.1	$0.1	$0.6	$0.0	$0.0
Pre-Tax Income	($4.3)	($1.8)	($1.1)	($1.4)	($1.5)	($5.8)	($11.0)	($14.3)
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	**($4.3)**	**($1.8)**	**($1.1)**	**($1.4)**	**($1.5)**	**($5.8)**	**($11.0)**	**($14.3)**
Net Margin	-	-	-	-	-	-	-	-
Reported EPS	**($0.14)**	**($0.06)**	**($0.03)**	**($0.04)**	**($0.04)**	**($0.18)**	**($0.28)**	**($0.32)**
YOY Growth	-	-	-	-	-	-	-	-
Basic Shares Outstanding	30.3	30.3	33.6	33.6	33.7	32.8	40.0	45.0

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

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HISTORICAL STOCK PRICE



Source: Yahoo Finance

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