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APLI-TSX

Rating:	**Speculative BUY**
Target:	**$2.75**
Price:	$1.00
Return:	175%
Valuation:	NPV, 20x EPS, 12.5x EV/EBITDA (F2027 ests)

Market Data

Basic Shares O/S (M)	61.8
FD Shares O/S (M)	82.1
Market capitalization ($M)	61.8
Enterprise Value ($M)	39.9
Cash ($M, most rec Q)	22.9
LT debt ($M, most rec Q)	1.0
52 Week Range	$0.50-$1.89
Avg. Weekly Volume (M)	0.7
Fiscal Year End	Mar-31

Key Milestones

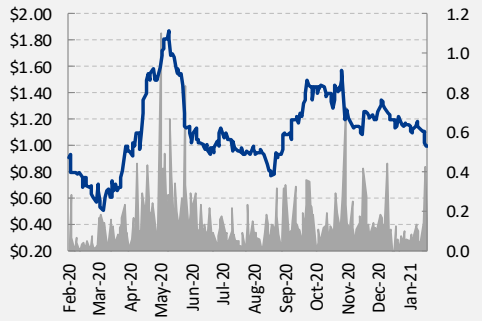
First revenue from ATI-1501	C2021
Commence favipiravir Phase III COVID-19 trial	CQ420
Phase II data, favipiravir Phase II COVID-19 trial	CQ121
Commence ATI-2307 CM trial	C2022

Financial Metrics

In C$	2021E	2022E	2023E
Total Revenue ($000)	0	88,946	39,260
EBITDA ($000)	(6,153)	82,143	32,118
Adj net inc ($000)	(6,483)	81,813	31,788
EPS (basic)	($0.10)	$1.32	$0.51
EPS (FD)	($0.08)	$1.00	$0.39
P/E	*NA*	*NA*	*NA*
EV/EBITDA	*NA*	*NA*	*NA*

Company Description

Appili Therapeutics is a Halifax-based infectious disease drug developer. The firm is presently assessing the FUJIFILM Toyama Chemical's drug favipiravir for the treatment of COVID-19 via a Phase II trial.



Source: Consensus Data - Refinitiv, Forecasts/Estimates - Leede Jones Gable

Initiating Coverage on Innovative Antifungal and Infectious Diseases Drug Developer with a Speculative BUY Rating

We are initiating coverage with a Speculative BUY rating and price target of $2.75 on Appili Therapeutics, a NS-based antifungal and infectious diseases drug developer with multiple clinical programs targeting bacterial, fungal, and virally-induced pathologies, and with flagship antiviral drug, the partnered pyrazine-based prodrug favipiravir, poised to imminently target COVID-19 infection based on already-published data and Phase III disease control data that Appili itself could generate before end-of-year.

Investment Thesis

COVID-19 antiviral could be first oral antiviral approved imminently in Canada with supranormal growth anticipated this year: Appili recently entered into a collaboration with partners Dr. Reddy's (RDY-NY, NR) and the international medical supply chain management organization Global Response Aid (GRA) to develop FUJIFILM Toyama Chemical's (4901-JP,NR) COVID-19-targeted small-molecule antiviral drug favipiravir, already approved since 2014 as an influenza therapy in Japan where it is branded as Avigan. Generic formulations of the drug are available in a few Asian geographies, but not yet in the US or Canada for any indication.

Originally developed by another Japan-based specialty firm Toyama Chemical Co, favipiravir is often called T-705 in some of the early literature describing the drug and it is the most active of several RNA polymerase-targeted pyrazinecarboxamide drugs that Toyama was characterizing back in 2002-2009. Almost without exception, favipiravir is detailed in recent review articles on the state of COVID-19 pharmacology as being one of the higher-profile antiviral therapies in formal clinical testing, and we agree with the status it has earned on that theme. As we show in Exhibit 11, the drug is in fact undergoing Phase II/III COVID-19 testing in multiple geographies, with most of these expected to generate infection-mitigating data within the next 3-4 quarters.

An application for favipiravir has since been filed under Health Canada's Interim Order, which could see favipiravir deployed for use under this expedited pathway as early as CQ121. Separately, this could represent the first oral antiviral targeting COVID-19 treatment in North America, and if approved, the drug's novel design/ administration could be competitive with Gilead's (GILD-Q,NR) IV-infused antiviral therapy Veklury, which as of this writing is the sole small-molecule antiviral drug approved for this condition. Our forecasts project that Appili could generate substantial favipiravir-driven top-line sales as early as next year (F2022 forecast of C$88.7M, Exhibit 1), with our model assuming lower-but-stable favipiravir sales in future years if/when global COVID-19 prevalence itself stabilizes at sub-pandemic levels.

Few players in the antifungal drug development space but with enticing partnership economics: Antifungal drug development has essentially declined in clinical initiatives over the years, despite rising global demand for antifungal therapies. Peak sales of other antifungal therapies also suggest potential in a medical market with high unmet need. As one of the few publicly-listed peers in the antifungal therapeutics space, Appili Therapeutics offers pure-play exposure to North America antifungal drug development alongside higher pricing power.

Antifungal therapy targeting a rare disease indication that could in turn yield a Priority Review Voucher: The firm's lead asset is the antifungal agent ATI-2307 acquired from FUJIFILM Toyama Chemical Co., LTD, slated to enter Phase II clinical trials by 2022. The two indications for which ATI-2307 will be targeting are cryptococcal meningitis (CM) and invasive candidiasis. We expect the firm to pursue CM first, given the rarity of this condition in North America. The firm could also be eligible for a Priority Review Voucher (PRV) upon approval, and a PRV once sold to other drug developers conventionally generates substantive cash for innovators. Our model expects that the asset can achieve approval and launch by H226, generating C$27.2M in revenue that year.

Exhibit 1. Income Statement & Financial Forecasts for Appili Therapeutics

Year-end March 31 (C$000, exc per share data)	2020A	2021E	2022E	2023E	2024E	2025E	2026E	2027E	2028E
ATI-1501 (metronidazole)	0	0	256	430	606	784	965	1,149	1,201
ATI-2307 (anti-fungal)	0	0	0	0	0	0	27,239	43,887	60,767
Favipiravir (COVID-19)	0	0	88,690	38,831	35,192	19,688	9,913	9,982	10,052
Total revenue	**$199**	**$0**	**$88,946**	**$39,260**	**$35,798**	**$20,472**	**$38,117**	**$55,018**	**$72,021**
Revenue growth (%)	*NA*	*NA*	*NA*	*44%*	*91%*	*57%*	*186%*	*144%*	*131%*
EBITDA	**($4,930)**	**($6,153)**	**$82,143**	**$32,118**	**$28,452**	**$12,895**	**$30,300**	**$46,954**	**$63,701**
EBITDA growth (%)	35%	25%	(1435%)	(61%)	(11%)	(55%)	135%	55%	36%
EBITDA margin (%)	*NA*	*NA*	*92%*	*82%*	*79%*	*63%*	*79%*	*85%*	*88%*
Non-operating expenses	$474	$318	$318	$318	$318	$318	$318	$318	$318
Net int expense (income)	$12	$12	$12	$12	$12	$12	$12	$12	$12
Net income, fully-taxed	($5,416)	($6,483)	$81,813	$31,788	$28,122	$12,565	$29,970	$46,624	$63,371
Fully-taxed EPS (basic)	($0.12)	($0.10)	$1.32	$0.51	$0.46	$0.20	$0.49	$0.75	$1.03
Fully-taxed EPS (fd)	**($0.09)**	**($0.08)**	**$1.00**	**$0.39**	**$0.34**	**$0.15**	**$0.37**	**$0.57**	**$0.77**
P/E (basic)	*NA*	*NA*	*1.0x*	*2.6x*	*2.9x*	*6.5x*	*2.7x*	*1.8x*	*1.3x*
EV/EBITDA	*NA*	*NA*	*NA*	*NA*	*NA*	*NA*	*NA*	*NA*	*NA*
S/O, basic (M)	*46.4*	*61.8*	*61.8*	*61.8*	*61.8*	*61.8*	*61.8*	*61.8*	*61.8*
S/O, fd (M)	*58.8*	*82.1*	*82.1*	*82.1*	*82.1*	*82.1*	*82.1*	*82.1*	*82.1*

Source: Historical Data – Appili Therapeutics; Forecasts/Estimates – Leede Jones Gable

Valuation

Our valuation is the average of three methodologies: NPV (30% discount rate), and multiples of our 2027 EPS and EBITDA forecasts. In F2027, we forecast EBITDA/EPS of $47.0M/$0.57 respectively. Our EV incorporates FQ221 cash of $22.9M and LT debt of $1.0M. The average of the three methodologies yields a price target of $2.69 (Exhibit 2), which we round to $2.75 and which corresponds to a one-year return of 175% when compared to APLI current price level.

On the milestone watch, we are clearly focused on favipiravir and its potential to generate positive interim Phase III data from the PRESECO trial before end-of-quarter (FQ421) and final data that we expect to be equally positive by end-of-FQ122. We are separately focused on timelines for Appili and its CRO partner CATO Research to commence a second and equally sizable 1,156-patient Phase III COVID-19 infection trial (the PEPCO trial), probably before end-of-FQ122, with PEPCO designed to assess favipiravir impact on vulnerable subjects (so elderly patients, or younger patients with at least one co-presenting pathology suggesting probability of developing severe symptoms) who have been exposed to a COVID-19-positive individual in recent days. We see upside to favipiravir's market prospects if it can demonstrate prophylactic activity in such patients in addition to demonstrating disease mitigation in already-symptomatic COVID-19 patients.

Exhibit 2. Valuation Summary for Appili Therapeutics

NPV, discount rate		20%	25%	30%	35%	40%	45%
Implied value per share		$4.35	$3.56	**$3.00**	$2.60	$2.30	$2.08
Price/earnings multiple, 2027E		**20%**	**25%**	**30%**	**35%**	**40%**	**45%**
Implied share price[1]	10	$2.28	$1.86	$1.53	$1.27	$1.06	$0.89
	20	$4.56	$3.72	**$3.06**	$2.54	$2.12	$1.78
	30	$6.84	$5.58	$4.59	$3.81	$3.18	$2.67
EV/EBITDA multiple, 2027E		**5x**	**10x**	**12.5x**	**15x**	**17.5x**	**20x**
Implied share price[1,2]		$0.70	$1.47	**$2.00**	$2.24	$2.62	$3.01
One-year Appili target price (C$) [1]				$2.69			

[1] *Based on F2027 fd fully-taxed EPS of $0.57; EBITDA of $47.0M, discounted at 30%, FD S/O of 82.1M*

[2] *Includes FQ221 cash of $22.9M and total debt of $1.0M*

Source: Historical Data – Appili Therapeutics; Forecasts/Estimates – Leede Jones Gable

Company History

Appili Therapeutics is relatively young on its capital markets profile. The firm was originally founded in 2015, and with shares initially listed on the TSX Venture exchange beginning in Jun/19, followed by up-listing to the main TSX exchange in Sept/20. Originally, the firm was headed by CEO Kevin Sullivan, with transition to current CEO Armand Balboni transpiring in Dec/19. Dr. Balboni was previously serving as Chief Scientific/Development Officer at Appili and thus had abundant knowledge of the firm's pipeline assets and their medical prospects.

Financings

Despite the relatively young age of the firm, the firm has executed on at least two sizable public financings valued at $27.2M in total including:

- **Jun. 4th 2020:** Appili raised $15.5M through the sale of 12.9 units at $1.20/Unit. Each unit consisted of one common share and one-half (1/2) of one common share purchase warrant, with each Warrant exercisable at C$1.50 and entitles the holder thereof to acquire one common share for a period of 3 years. A concurrent private placement was also announced, with the firm raising $1.4M in due process.

- **Feb. 20th 2020:** The firm raised $10.3M via the sale of 12.8M units valued at $0.80/unit. Each unit consisted of a common share and a one-half common share purchase warrant, with each warrant entitling the holder to acquire one common share at an exercise price of $1.10 each until Feb/23.

We estimate that the firm has raised ~$17.5M in various financing activities sans partnership activities prior to going public, and for a total of $42.7M in total financing mechanisms across its operating history.

Partnerships

Despite the firm's relatively young capital markets profile, the firm has achieved significant partnerships and contracts as reflected in a summary of tangible events below.

- **Oct. 30th 2020:** The firm announced its participation as part of a consortium (Dr. Reddy's and Global Response Aid) advancing favipiravir in the US, Canada and internationally. Appili will also be eligible for royalties on sales in Europe and Latin America.

- **Dec. 3rd 2019: ATI-1501.** Entered into a commercialization agreement with the NY-based specialty pharma firm Saptalis (Private) the manufacturing and commercialization of the taste-masked liquid oral suspension formulation of metronidazole (an antibiotic)/ATI-1501 in the US. While terms were undisclosed, the firm received an upfront payment of US$150,000 that was recognized in the firm's Q419 financial statements.

- **Nov. 21st 2019:** The firm acquired the small molecule antifungal ATI-2307 from FUJIFILM Toyama Chemical Co., LTD (4901-JP,NR).

- **Jul. 2nd 2019:** ATI-1503. The firm signed a contract with the United States Department of Defense, (DOD) Congressionally Directed Medical Research Programs, Peer Reviewed Medical Research Program (PRMRP). The contract saw Appili receive US$3M as a grant to develop the firm's Gram-negative targeting antibiotic ATI-1503.

Competitive Landscape

The competitive landscape for Appili can be segmented in a number of ways: antifungal drug developers, anti-infective drug developers, as well as COVID-19 drug developers. We provide a review of all three in our subsequent exhibits below. Notably, we observed that antifungal drug developer peers tend to be US-based peers, and the availability of public peers offering pure-play exposure within North America are few, if not rare.

Peer Commentary on the Antifungal Therapeutics Market and Outlook

Exhibit 3. Antifungal and Anti-Infectives Drug Development Peers

Company	Curr	Sym	Shares out (M)	Share price 31-Jan	Mkt cap ($M) (curr)	Mkt cap ($M) (C$)	Ent val ($M) (curr)	Ent val ($M) (C$)	Company description
Mayne Pharma Group Ltd	AUD	MYX	1,679.1	AUD 0.32	AUD 529	$516	AUD 794	$775	Mayne Pharma's formulation of itraconazole was FDA approved in 2018; itraconazole has been approved in the US since 1992.
Cidara Therapeutics Inc	USD	CDTX	43.9	$2.45	$108	$138	$70	$90	Cidara's rezafungin is now currently in Phase III trials for the treatment of candidemia and invasive candidiasis, and for the prevention of fungal infections.
SCYNEXIS Inc	USD	SCYX	19.1	$7.47	$143	$183	$127	$162	SCYNEXIS' lead is the ibrexafungerp/SCY-078, currently in Phase III trials for the treatment of vulvovaginal candidiasis.
Matinas BioPharma Holdings Inc	USD	MTNB	199.4	$1.46	$291	$372	$232	$297	Matinas Biopharma is currently developing the non-toxic encochleated form of amphotericin B/MAT2203, now in a 16-patient Phase II trial. Data by YE2021.
						$302		**$331**	
Other antifungal or antimicrobial drug developers									
BioCryst Pharmaceuticals Inc	USD	BCRX	176.6	$8.52	$1,504	$1,922	$1,437	$1,836	Antiviral drug RAPIVAB was FDA-approved in Dec/14 as influenza therapy, testing broad spectrum antiviral drug galidesivir (BCX4430) in a 132-patient Phase I COVID-19 trial.
Entasis Therapeutics Holdings Inc	USD	ETTX	35.5	$3.15	$112	$143	$51	$65	Two Phase III antibiotic assets under development: β-lactamases inhibitor durlobactam (for treating resistant *Acinetobacter* infections) and oral antibiotic zoliflodacin/ETX0914 for treating gonorrhea.
Iterum Therapeutics PLC	USD	ITRM	49.1	$1.41	$69	$88	$100	$127	Phase III results for UTI drug sulopenem reported in Jun/20; showed benefit in quinolone-resistant, but not quinolone-responsive, patients. Would be the first orally-active penem if approved
La Jolla Pharmaceutical Co	USD	LJPC	27.4	$6.12	$168	$214	$144	$184	La Jolla acquired Tetraphase in Jun/20 for US$59M, has one approved drug, fluorocycline antibiotic XERAVA/eravacycline for treating complicated intra-abdominal infections (cIAI).
Summit Therapeutics Inc	USD	SMMT	82.6	$6.96	$575	$734	$553	$706	Lead antibiotic ridinilazole/SMT19969 in two 680-patient Phase III trials for treating *C. difficile* infection, data in Q321
Spero Therapeutics Inc	USD	SPRO	27.2	$18.11	$493	$629	$366	$467	Lead drug is carbapenem drug tebipenem. Topline results in Sept/20 from 1,372-patient Phase III trial showed non-inferiority to IV ertapenem for treating complicated UTI & acute pyelonephritis.
Polyphor AG	CHF	POLN	11.2	$7.72	CHF 87	$0	$51	$0	POL7306 is a preclinical-stage outer membrane protein-targeted antibiotic (OMPTA) for treating difficult-to-treat Gram-negative bacteria (including multidrug resistant strains).
Average						**$533**		**$484**	
Appili Therapeutics Inc	**CAD**	**APLI**	**62.6**	**$1.00**	**$63**	**$63**	**$41**	**$41**	**The firm is currently assessing the Dr. Reddy's/GRA-partnered Favipiravir in mild-to-moderate COVID-19 patients in North America.**

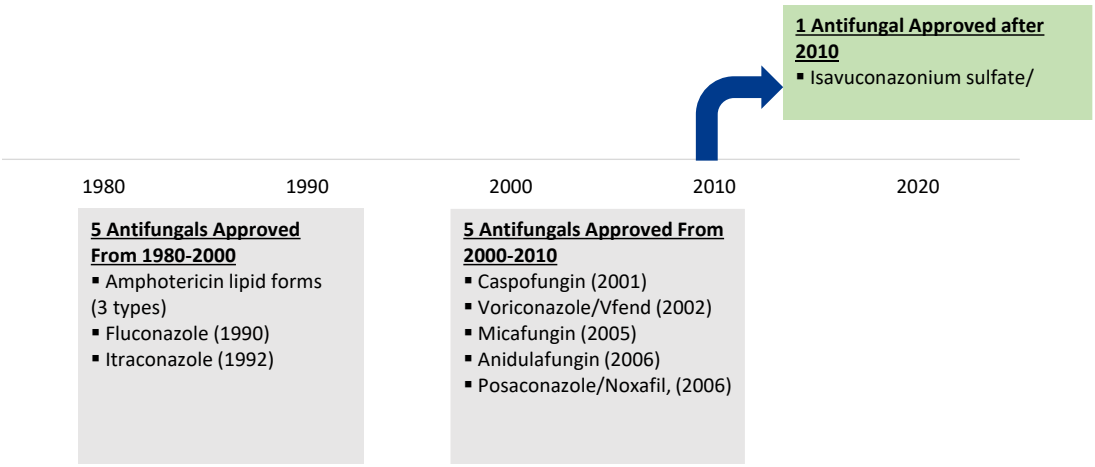
Source: Company filings, Refinitiv

As we will observe, antifungal drug development yields only a handful of peers. Before delving into each peer individually, we broadly assessed the broader antifungal drug development landscape for opportunities and potential valuations, where available.

Our key takeaway: High global market demand for antifungal drugs continues to persist. Although drug development has essentially dwindled in the field, deal value on partnerships within this field remain high alongside favourable regulatory environments to encourage development in the field.

Antifungal Drug Developers

Exhibit 4. Historical Approval of Antifungal Therapies (1980-Present)



Source: Chart created by Leede Jones Gable, Data from Cidara Therapeutics Investor Presentation (October 2020)

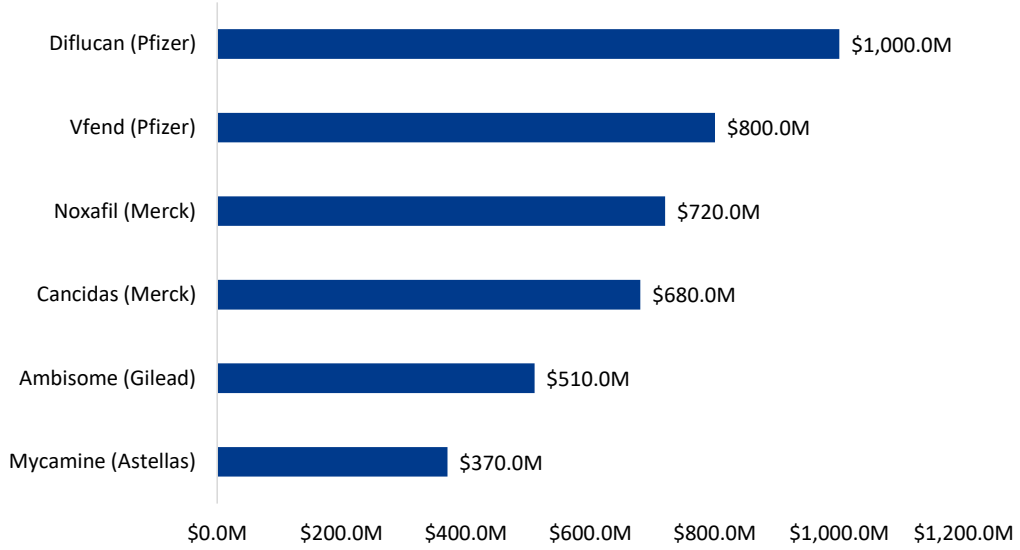
Since publicly available peers in the antifungal drug development space are sparse, we referred to a review by Gintjee and colleagues in the *Journal of Fungi* for a more recent update on the ongoing drug development initiatives in the space. Select commentary on both public and private peers are listed below.

Cidara Therapeutics

California-based Cidara Therapeutics (CDTX-Q, NR) is a drug developer focused on the development of therapies targeting fungal and viral infections. The firm's lead asset is the once-weekly echinocandin antifungal injection rezafungin, currently in two parallel Phase III trials. The 218-patient Phase III ReSTORE trial (aimed at the treatment of fungal infections caused by *Candida* spp., including candidemia and invasive candidiasis) and the 462-patient Phase III ReSPECT trial (aimed at the prevention of fungal infections, caused by *Candida*, *Aspergillus* and *Pneumocystis*, in patients undergoing allogeneic blood and marrow transplant) and is expected to generate data by mid-2021 and 2022 respectively. On the regulatory front, the asset has received three designations from the FDA: the QIDP designation, the Fast Track designation and the orphan drug designation. Considering the regulatory designations achieved, the firm anticipates twelves years of marketing exclusivity upon formal approval.

On the partnership front, Cidara entered into a partnership with Mundipharma in Sep/19 for the development and commercialization of rezafungin on a global basis (ex-US and ex-Japan basis). As part of the US$568M agreement, Cidara will receive US$30M in upfront payment, US$9M in an equity investment, US$42M in near-term funding (for the support of the firm's aforementioned Phase III trials), and the remaining US$529M in milestone payments. On peak sales estimates, the firm estimates that rezafungin's peak sales potential could be a US$750M opportunity if approved as both a treatment and as a preventative therapy for the indications in the aforementioned Phase III trial. More broadly, the firm estimates the current antifungal market is valued at US$4.2B globally.

Exhibit 5. Peak Annual Global Sales of Approved Antifungal Drugs Shows That This Infectious Disease Category Has Been Targeted by Several Therapies That Achieved Blockbuster or Near-Blockbuster Status



Source: Cidara Therapeutics Investor Presentation, October 2020

SCYNEXIS

SCYNEXIS (SCYX-Q, NR) is a NJ-based pure-play antifungal drug developer. The firm's lead asset is the glucan synthase inhibitor ibrexafungerp/SCY-078 (the drug was initially co-innovated under an agreement with Merck (MRK-NY, NR), though Merck's rights to the drug were returned to SCYNEXIS in 2013), aimed at the treatment of vulvovaginal candidiasis (VVC). The firm last presented data on its Phase III trials in Nov/19 and Apr/20 respectively. Presently, the firm has submitted the NDA to the FDA for ibrexafungerp, with the expectation that the FDA could provide a response to the NDA by Dec/20 (with response being the acceptance of the NDA and the provision of an anticipated PDUFA date). A separate Phase III CANDLE trial is currently ongoing as it relates to the prevention of recurrent VVC, with sNDA submission by H221.

Exhibit 6. SCYNEXIS Peak Net Sales Opportunity for Triterpenoid Anti-fungal Drug Ibrexafungerp Reflects Favorably on Projected Market Opportunity for Novel Anti-fungal Therapies in General

	Treatment Indication (First to Third episodes of VVC [1])	Prevention (4+ episodes of VVC [1])
US Prescriptions	13.4M	0.7M
Penetration Rates	3% - 18% (depending on # of VVC episodes)	25%
Pricing/Course of Therapy	US$300-US$400	US$1,800-US$2,400
Peak Net Sales Opporunity	US$220M-US$300M	US$210M-US$280M
Total Peak Sales: US$430M-US$580M		

[1] *VVC - vulvovaginal candidiasis*

Source: SCYNEXIS Investor Presentation, August 2020

Apart from VVC, the firm is exploring ibrexafungerp's utility for invasive fungal infections, with two open-label Phase III trials currently ongoing (the 30-patient CARES trial for patients with *C. Auris* infections and the 200-patient FURI trial for invasive fungal infections). Similar to Cidara Therapeutics, the asset has already garnered three regulatory designations from the FDA, the QIDP designation, Orphan Drug Designation and the Fast Track Designation. Together, the firm anticipates that it could enjoy 10-12 years of regulatory exclusivity in the US if approved (timelines expected for approval by mid-2021).

As for peak market sales projection, the firm projects a US$430-US$580M peak net sales opportunity in the US for the asset. On additional specifics, the firm expects to retail the therapy at US$300-400 on a wholesale acquisition cost (WAC) basis. On total addressable market, the firm used ~15.4M prescriptions as a gauge, with the prescriptions using fluconazole (an older antifungal drug that has since gone generic) as a proxy for their estimates. Using the WAC and the estimated market size, the firm projected a total addressable market of US$5.6B-US$6.2B.

Matinas Biopharma

Matinas BioPharma's (MTNB-NYSE AMERICAN, NR) lead antifungal candidate is the oral and non-toxic encochleated form of amphotericin B/MAT2203. Amphotericin B is not a new drug; the drug was first approved for visceral leishmaniasis in 1997. Despite its long approval history, the typically IV-infused drug is associated with renal toxicity. Matinas' formulation aims to reduce the risk of toxicity while maintaining the same level of fungicidal efficacy associated with the IV formulations of amphotericin B. The drug is currently undergoing a 16-patient Phase II trial for the treatment of patients with refractory mucocutaneous candidiasis, with completion targeted for YE2021. Separately, the firm is also exploring MAT2203's utility in a 176-patient Phase I/II trial for the treatment of cryptococcal meningitis; data from that trial is anticipated by YE2021.

Exhibit 7. Antifungal Drug Development Landscape – Publicly Traded

Innovator	*Ticker*	*Market Cap*	*Class*	*Agent*	*Mechanism of Action*	*Spectrum of Activity*	*Stage*
Publicly Listed Antifungal Drug Developers							
Mayne Pharma	MYX-AU	US$386.2M	Azole	SUBA-itraconazole	Interferes with cytochrome P450 activity, decreasing ergosterol synthesis, inhibiting cell membrane formation	Blastomycosis, histoplasmosis, and aspergillosis	FDA Approved
Cidara Therapeutics	CDTX-US	US$137.0M	Echinocandin	Rezafungin	Inhibition of 1,3-β-D-glucan synthesis	*Candida albicans, Candida auris Candida krusei, Candida tropicalis, Aspergillus* spp., *Pneumocystis* spp.	Phase III
SCYNEXIS	SCYX-US	US$63.7M	Terpenoid	Ibrexafungerp	Triterpenoid enfumafungin derivative that inhibits 1,3-β-D-glucan synthesis	*Candida* spp. including *Candida glabrata* and *Candida auris Aspergillus* spp.	Phase III
Matinas Biopharma	MTNB-US	US$170.9M	Polyene	Amphotericin B Cochleate	Cochleate are a multilayered lipid bilayers configured into a spiral. Drug encapsulated between the spiral layers gets released post-GI absorption when cochleate structure opens up in low Ca environment.	*Candida* spp.	Phase II
Toyama Chemical	FUJIY-US	US$25,331.5M	Arylamidine**	T-2307	Thought to inhibit fungal mitochondrial synthesis	*Candida* spp., *Aspergillus* and some hyaline moulds	Phase I
Vical/Brickell Biotech	BBI-US	US$30.7M	Siderophore	VL-2397	Uptake via siderophore iron transporter	*Aspergillus* , Some *Candida* spp. and *Aspergillus* spp., Mucorales	Terminated
Mirati Therapeutics	MRTX-US	US$8,057.0M	HDAC Inhibitor	MGCD290	Fungal histone deacetylase (HDAC) inhibitor	*Candida* spp. *Aspergillus* spp.	Failed Phase II/ Uncertain development

Abbreviations: Spp. = Species
***Drug development licensed to Appili Therapeutics*

Source: Table modified from *Journal of Fungi* (2020), Vol. 6, pp. 28; market capitalization data - Refinitiv

Private Antifungal Drug Developer Peers: Investment Interest from Large Pharma Players

F2G

F2G Ltd is a UK and Austria-based drug developer focused on the development of therapies targeting systemic fungal infections. The firm's most recent round of financing saw it secure US$60.8M in new financing from investors. Notable pharma investors in F2G include Novo Nordisk (NOVO.B-CPH, NR) and Novartis (NOVN-SW, NR). The firm's lead candidate is olorofim/F901318, currently being tested in a 100-patient Phase IIb trial in patients with invasive fungal infections. These infections include invasive aspergillosis (including azole-resistant strains), scedosporiosis, lomentosporiosis, fusariosis, scopulariopsosis, and coccidioidomycosis (Valley Fever). Data from the trial is expected by Feb/21.

On the regulatory front, olorofim was accorded with the Breakthrough Therapy Designation by the FDA in Nov/19 as it relates to the treatment of invasive mold infections in patients with limited or no treatment options. More recently, on June 10th 2020, olorofim was accorded with the QIDP designation for a number of invasive fungal infections including: invasive aspergillosis, invasive scedosporiosis, Invasive lomentosporiosis, Coccidioidomycosis, invasive disease due to *Scopulariopsis* species and invasive fusariosis.

Mycovia Pharmaceuticals

Mycovia Pharmaceuticals was formed following the acquisition of Viamet Pharmaceuticals by NovaQuest Capital Management in 2018. The firm's lead product is oral fungal CYP51 inhibitor oteseconazole/VT-1161, which is currently being assessed in two parallel Phase III trials for recurrent vulvovaginal candidiasis (RVVC)/chronic yeast infection. The 326-patient/180-patient Phase III trials are expected to be completed by FQ420 and mid-2021 respectively, with preliminary topline data which could be expected before that. Pending the outcome of the approval process, the firm expects to launch on the drug by next year.

On the partnership front, the firm has licensed the therapy to two firms – Jiangsu Hengrui Medicine (for rights in mainland China, Hong Kong, Macau and Taiwan) and Gedeon Richter Plc (RIG2-EU, NR; for rights in Europe, Russia, the Commonwealth of Independent States, Latin America and Australia). The drug has received the QIDP designation as well as Fast Track designation. If approved, it could represent the first ever treatment for RVVC.

Amplyx Pharmaceuticals

SD-based Amplyx Pharmaceuticals' (Private) lead asset is the broad-spectrum antifungal therapy fosmanogepix. On clinical development, the firm most recently reported topline data from its 21-patient Phase II trial as a first-line therapy in patients with invasive fungal infections caused by Candida. The trial met its primary endpoint, with a treatment success rate of 80%. Additional trials assessing fosmanogepix's utility in other fungal indications are also ongoing, including fosmanogepix as a treatment for *Aspergillus* and rare mold infections, as well as infections caused by drug-resistant *Candida auris*. On the regulatory front, the drug has received a trio of designations from the FDA, including the Fast Track designation, Orphan Drug Designation and QIDP designation. As for the firm's most recent round of financing, the firm last raised US$90M via a Series C financing round, of which Pfizer (PFE-NY, NR) counts among the firm's investors.

Exhibit 8. Antifungal drug development landscape – Private Peers

Innovator	*Last Raise*	*Notable Investors*	*Class*	*Agent*	*Mechanism of Action*	*Spectrum of Activity*	*Stage*
Private Antifungal Drug Developers							
Viamet Pharmaceuticals/ Mycovia Pharmaceuticals	US$25.0M	Owned by NovaQuest Capital Management (US$2.8B invested capital)	Tetrazole	VT-1161	Interferes with cytochrome P450 activity, decreasing ergosterol synthesis, inhibiting cell membrane formation	*Candida* spp., *Coccidioides* spp., *Rhizopus* spp.	Phase III
				VT-1598		*Candida* spp. including *C. auris*, *Aspergillus* spp., *Cryptococcus* spp.	Phase I
				VT-1129		*Cryptococcus* spp., *Candida* spp.	Pre-clinical
F2G Ltd.	US$60.8M	Novartis (NOVN-SW, NR), Novo Nordisk (NOVO.B-CPH)	Orotomides	Olorofim	Inhibition of dihydroorotate dehydrogenase, thereby inhibiting pyrimidine production which negatively affects fungal nucleic acid, cell wall, and phospholipid synthesis, as well as cell regulation and protein production	*Aspergillus fumigatus*, *Aspergillus nidulans*, *Aspergillus terreus*, *Aspergillus niger*, multidrug resistant strains of *Aspergillus* spp., uncommon moulds such as *Lomentospora prolificans* and *Scedosporium* spp., Endemic Fungi	Phase II
Amplyx Pharmaceuticals	US$90.0M	Pfizer (PFE-NY, NR)	Glycosyl-phosphatidylinositol inhibitor	Fosmanogepix (APX(	Inhibits fungal Gwt1 GPI anchor protein. Low affinity for human GPI anchor proteins	*Candida* spp. including *C. auris*, *Cryptococcus Coccidioides*, *Aspergillus* and hyaline moulds, Mucorales Not active against *C. krusei*	Phase II

Abbreviations: Spp. = Species

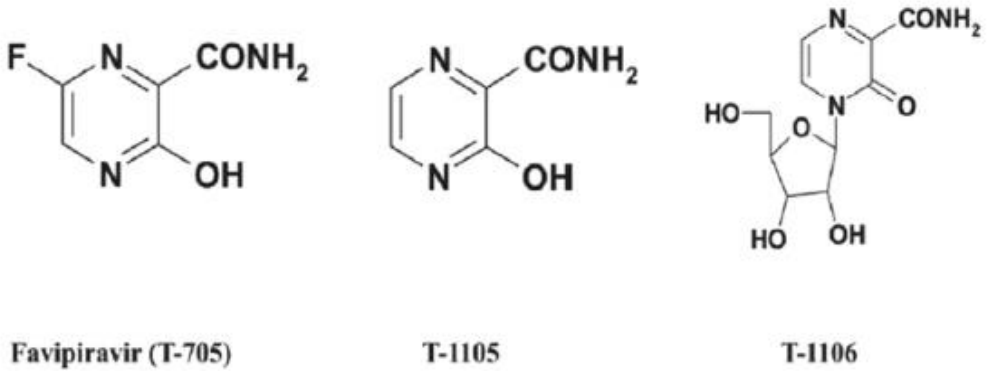
Source: Table modified from *Journal of Fungi* (2020). Vol. 6, pp. 28; market data sourced from Refinitiv

Favipiravir

Mechanism of Action - Oral Administration Route Offers Distinct Administration Advantages Over Other Approved Antiviral Therapies for COVID-19

Favipiravir (6-fluoro-3-hydroxy-2-pyrazinecarboxamide)/T-705 is a viral RNA polymerase inhibitor discovered by innovator and Appili's legacy partner FUJIFILM Toyama Chemical Co., Ltd. Favipiravir is taken orally as a tablet, offering it the distinct advantage over remdesivir (Gilead's FDA-approved Veklury), which is currently approved antiviral as it relates to COVID-19 (more on that below), and is infused intravenously. The drug first received approval in Japan in 2014 as an influenza viral drug.

Exhibit 9. Chemical Structure of Pyrazine-Based Prodrug Favipiravir and its Bioactive Derivatives



Favipiravir (T-705) **T-1105** **T-1106**

Source: *Antiviral Research* (2013). Vol. 100, pp. 446-454

The antiviral's initial use case was on the flu virus, specifically focused on the inhibition of RNA polymerase of the influenza virus. As observed via a 2013 review by Furuta and colleagues in *Antiviral Research* (Vol. 100, Issue 2, November 2013, Pages 446-454), the therapy has broad spectrum antiviral properties, and has been known to block the replication of other RNA viruses, including arenaviruses, phleboviruses, hantaviruses, flaviviruses (yellow fever and West Nile), enteroviruses (polio- and rhinoviruses), Western equine encephalitis virus, respiratory syncytial virus, and noroviruses.

The mechanism of action by which favipiravir exerts its antiviral effects is through the direct inhibition of viral replication and transcription. Specifically the drug targets the RNA-dependent RNA polymerase (RdRP) domains, which are conserved in RNA viruses.

Clinical Experience in COVID-19

Safety: As per a review on favipiravir, the adverse reaction rate was ~20% of treatment patients. The adverse effects were relatively minor and included hyperuricemia and diarrhea in 5% of the participants and reduced neutrophil count and transaminitis in 2% of the participants. One of the major risks with favipiravir is the potential for teratogenicity and embryotoxicity (destruction against embroyos and fetuses). As per Japanese approval protocol, the agency warned strongly against use in women of reproductive age.

Fujifilm: In Japan, FUJIFILM Toyama Chemical is currently testing favipiravir for the condition. On September 23rd 2020, the firm announced results from a Phase III trial testing the favipiravir (brand name: Avigan in Japan) in COVID-19 patients with non-severe pneumonia. Results indicated that the therapy met the primary endpoint, which was the time to negative conversion of detectable SARS-CoV 2 viral RNA (determined by RT-PCR assays) as well as the alleviation of symptoms. Data comes from 156 patients, for which the treatment arm achieved a shorter time to resolution at 11.9 days as compared to placebo at 14.7 days. Given a p value of 0.0136, the difference was considered statistically significant. Data for the trial has yet to be published at time of writing. For now, the Japanese Health Ministry has postponed a formal approval decision on the use of the drug for treatment of COVID-19.

Favipiravir Approvals for COVID-19

ChemRar: As of Jun/20, Russia's Ministry of Health issued a conditional marketing authorization for a generic formulation of favipiravir. The brand name for this generic formulation will be Avifavir, and represented the first global approval for the treatment of COVID-19. In Russia, Chromis (a JV between the Russian Direct Investment Fund (RDIF) and ChemRar (Private)) is overseeing the manufacturing and distribution of the Avifavir.

On clinical data for conditional approval, a preliminary manuscript has been accepted for publication in *Clinical Infectious Diseases* as of Aug/20. Data are focused on a 60-patient Phase II/III trial held testing Avifavir in patients with moderate COVID-19 pneumonia. The trial was split into a pilot trial portion and a pivotal trial portion. The latter portion of the trial would only proceed if data suggested that viral clearance in 80% of patients by day 10 was plausible and that response was greater than the presumed non-effective level of 50%.

Patients were administered one of two regimens: 1,600 mg BID on Day 1, followed by 600 mg BID on days 2-14 or 1,800 mg BID on day 1 and 800 mg for the remaining duration. In the pilot portion of the trial, the primary endpoint was the elimination of SARS-CoV-2 by Day 10 (defined as two negative PCR tests within a 24 hour interval). In both dosing groups, Afifavir demonstrated similar virologic response. Overall, viral clearance at day 5 was far higher at 62.5% of patients (25 of 40 patients) from the treatment arm as compared to 30% of patients on standard of care (6 of 20 patients). By day 10, viral clearance was achieved in 92.5% of treated patients (37 of 40 patients) as compared to 80% (16 of 20) of patients in the standard care arm. For now, the pivotal stage of the trial involving 330 patients remains ongoing.

Glenmark Pharmaceuticals: On June 20th 2020, Glenmark Pharmaceuticals (532296-BOM, NR) received approval for a generic version of favipiravir (to be sold under the brand name: FabiFlu) for the treatment of mild-to-moderate COVID-19 in India. Approval for the drug was based on a 150-patient Phase III clinical trial, where patients received Favipiravir tablets (3,600mg on day 1 and 1,600 mg on day 2 or later) for up to 14 days along with standard supportive care. Data indicated 28.6% faster viral clearance in the overall population, as compared to the control arm.

On secondary endpoints, the treated patients experienced 40% faster achievement of "clinical cure", with 69.8% of patients achieving this endpoint by day 4 (as compared to 44.9% in the control arm). In patients who had deteriorated and required oxygen support, those who received favipiravir had a longer median time to first time use of oxygen in 5 days as compared to 2 days in the control arm. On safety, 35.6% of patients experienced adverse events, though most were considered mild-to-moderate and did not lead to drug discontinuation or dosing adjustments. The most commonly observed AE was asymptomatic transient increases in uric acid which resolved by the first follow up. In India, the firm is retailing the drug for 75 rupees per tablet. At an estimated consumption of 122 tablets, this works out to 9,150 rupees or ~US$125 per treatment course.

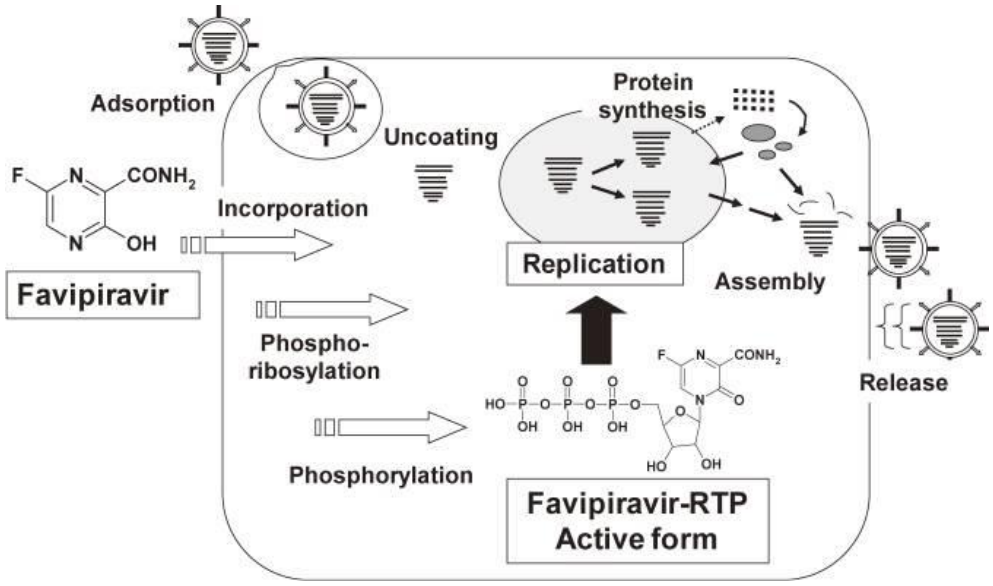
New Data from Partner Dr. Reddy's Laboratories was Mixed for Overall COVID-19 Patient Population, but Subgroup Analysis Reflects Favorably on Appili's PRESECO Trial

We of course know that Dr. Reddy's Laboratories terminated its own 353-patient Phase III COVID-19 trial in Kuwait last month. The trial tested moderate-to-severely symptomatic COVID-19-infected individuals and showed in an interim analysis that there was no statistically-significant difference in time to hypoxia resolution (so, restoration of normal serum oxygen levels, which we assume is a secondary consequence of resolving virus-induced respiratory distress) between favipiravir-treated and placebo-treated patients. Hypoxia resolution was slightly lower for drug-treated patients at seven days vs eight days, but not to a statistically-significant degree.

Interestingly, the broader update was actually quite positive to our investment thesis. Dr. Reddy's conducted a parallel subgroup analysis of 181 patients in the trial that presented with low NEWS scores at enrollment, and thus were less symptomatic than other severely-symptomatic patients who were allowed into the trial. For context, NEWS stands for National Early Warning Score, and is a multi-symptom scorecard system for assessing COVID-19-associated symptoms like respiratory rate, blood pressure/heart rate, fever, and blood oxygen saturation or requirements for supplemental oxygen support. In that patient subset, Dr. Reddy's found that favipiravir-treated subjects were discharged from hospital three days earlier than placebo patients (so, 8 days vs 11 days, with an extremely low p-value of 0.006, far below the 0.05/95% confidence interval normally deemed to be statistically significant).

We believe that this observation, taken together with the multiplicity of positive clinical signals already documented in the medical literature, gives us confidence in the drug's performance in the ongoing PRESECO and CONTROL trials, and the pending PEPCO trial described above. The drug is already approved for emergency use in mild-to-moderately symptomatic COVID-19-infected individuals in India (granted back in Q320), where various generic favipiravir formulations are separately approved for treating influenza infection and are marketed as such. Indeed, India-based generic drug developer Glenmark Pharmaceuticals is already marketing the drug (branded as FabiFlu) specifically as a therapy for mild-to-moderate disease.

Exhibit 10. Proposed Activation Mechanism for Favipiravir Involves Conversion of Administered Prodrug into a RNA Polymerase-Inhibiting Phosphorylated Derivative Called Favipiravir Ribofuranosyl-5'-Triphosphate, or Favipiravir-RTP



Source: *Proceedings of the Japan Academy, Ser. B, Physical and Biological Sciences* (2017). Vol. 93, pp. 449–463

Partnerships

In Jul/20, FUJIFILM announced a tripartite licensing agreement with generic drug manufacturer Dr. Reddy's Laboratories (RDY-NY, NR) and Global Response Aid (GRA) for the manufacture and sales of Avigan overseas (excluding Japan, China and Russia). As part of the deal, FUJIFILM will be receiving an undisclosed lump-sum license fee and royalties on sales.

Later in Oct/20, Appili's alliance with Dr. Reddy's and GRA was harmonized with the previously-announced alliance, with Appili's main role within this consortium of firms intended to design and implement global clinical programs (primarily multiple pivotal Phase III trials) for the use of favipiravir for the treatment or prevention of COVID-19. While Appili will be responsible for US and Canadian clinical trials, the firm will also be eligible for royalties in Europe and Latin America.

The core clinical development strategy will target early treatment and prevention, with the latter focusing on post-exposure prophylaxis in a community setting. Dr. Reddy's and GRA will likely be involved in other faucets of the agreement, including R&D, manufacturing, and commercialization. As an aside, we observed in a *Globe and Mail article* published in recent months that cited cost of production for favipiravir as being relatively low at $1.45 per pill (although with the qualification that dosing for COVID-19-infected patients is expected to be at or above 3x daily dosing for influenza patients), though cost-of-goods will undoubtedly be variable based on manufacturing requirements ascribed to specific geographies (likely higher in Canada/US-based facilities, for example)

Exhibit 11. Ongoing Clinical Studies Focused on Testing Favipiravir as a COVID-19-Mitigating Therapy

Therapy	Mechanism of Action	Phase	Main Sponsor/ Innovator	administered therapies, if	Patient number	Primary Endpoint(s)	Start Date	Data by	Comments/Clinical History
Active Clinical Studies Exploring Favipiravir Utility In COVID-19 Infection									
Favipiravir	RNA polymerase inhibition	II (CONTROL trial)	Appili Therapeutics, Sunnybrook, UHN, UT, Mount Sinai Hospital	None (placebo-controlled)	760	Control of out-break for 24d, to day 40	Oct-20	Q1-21	Long-term care patients, dosed at 1,600mg BID on day one, then 800mg BID on days 2-25; principal investigator AJ McGeer/Mt Sinai Hosp
Favipiravir	RNA polymerase inhibition	III (PRESECO trial)	Appili Therapeutics, Elixia Clinical Res Collaborative (FL)	None (placebo-controlled)	826	Time to clinical recovery, to day 21	Nov-20	Q2-21	Mild-to-moderate COVID-19 disease (symptomatic & rtPCR-positive, but minimal respiratory distress or hospitalization)
Favipiravir	RNA polymerase inhibition	III (PEPCO trial)	Appili Therapeutics, CATO Research	None (placebo-controlled)	1,156	Mitigation of COVID-19 infection post-exposure	TBD	TBD	Testing otherwise asymptomatic but vulnerable (elderly, or co-presenting pathologies) subjects after exposure to COVID-19-positive patient
Favipiravir	RNA polymerase inhibition	II/III (AviMild trial)	King Abdullah Intl Medical Research Center	None (placebo-controlled)	576	rtPCR-confirmed disease reversal at day 15	Jul-20	Q2-21	Mild-to-moderate disease; 1,800mg BID on day one, then 800mg BID on days 2-7
Favipiravir	RNA polymerase inhibition	III	Indonesia University	Oseltamivir (Tamiflu), plus background antibiotics	100	Radiol change in lung function, rtPCR conversion by day 14	Apr-20	Q4-20	Favipiravir/Avigan was approved in Indonesia in Sept-20 for COVID-19 infection; final data were expected last quarter
Favipiravir	RNA polymerase inhibition	III	Dr. Reddy's Laboratories (Kuwait)	None (placebo-controlled)	780	Time to hypoxia resolution by day 28	Aug-20	Q1-21	Moderate-to-severe disease; no benefit on time to hypoxia resolution (7d vs 8d) but 181 pts with low NEWS scores at enrollment perform better on time to hospital discharge (8d vs 11d)
Favipiravir (Favir 200)	RNA polymerase inhibition	III	Nepal Health Research Council	Remdesivir as co-therapy in one study arm	676	Time to clinical improvement	Jan-21	Q2-21	Mild-to-moderate disease; patient groups stratified by age and co-presenting morbidities
Favipiravir	RNA polymerase inhibition	III	Zhejiang Hisun Pharmaceutical	None (placebo-controlled)	256	Time to clin rec-overy, day 28	Jun-20	Q4-20	Moderate disease, 1,800mg BID on day one, then 600mg TID to day 14; final data expected last quarter
Favipiravir	RNA polymerase inhibition	II	Mexico General Hospital	Maraviroc (Cel-sentri) or enoxa-parin/dexameth-asone/antibiotics	100	Duration of ventilation avoidance or death, day 28	Jan-21	Q2-21	Severe but non-critical disease, hospitalized patients
Favipiravir	RNA polymerase inhibition	II	Medical University of Bahrain	Hydroxychloro-quine	150	Time to viral clear-ance, to day 14	Aug-20	Q2-21	Rationale is to compare antiviral activity and immuno-modulatory activity of two approved therapies
Favipiravir	RNA polymerase inhibition	II	Stanford University	Standard-of-care (not defined)	120	Time to cess-ation of viral shedding in oro-nasal mucus	Jul-20	Q3-21	Mild-to-asymptomatic disease, conventional dosing
Favipiravir	RNA polymerase inhibition	III	University of Pecs (Hungary)	None (placebo-controlled)	150	Time to symptom relief, to 9mo (O2 sat, CT, body temp, rtPCR)	Oct-20	Q2-21	COVID-19-infected patients with co-presenting mild pneumonia
Favipiravir	RNA polymerase inhibition	III	Ministry of Health, Turkey	Hydroxychloro-quine or azithro-mycin	1,000	Time to recovery or hospital discharge	May-20	Q4-20	Mild-to-moderate disease, with recently diagnosed COVID-19 infection, broad age stratification
Favipiravir	RNA polymerase inhibition	III (FIGHT-COVID-19 trial)	Rajavithi Hospital, Bangkok Thailand	Multiple (oselta-mivir, hydroxy-chloroquine)	320	COVID-19 eradi-cation, to 24 wks	Aug-20	Q4-21	Six-week prospective COVID-19 trial testing multiple antivirals including favipiravir plus hydroxychloroquine
Favipiravir	RNA polymerase inhibition	IIA (FLARE trial)	University College London, LifeArc (UK-based charity, was MRC Technology)	Lopinavir-Rito-navir (HIV1-pro-tease inhibitors)	240	Reduced in upper respiratory tract rtPCR-assessed viral load at day 5	Sep-20	Q1-21	Lopinavir-Ritonavir on their own did not eradicate COVID-19 infection in severe patients in a 199-pt study published in Mar/20 in *NEJM*
Favipiravir	RNA polymerase inhibition	III (PIO-NEER trial)	NHS Foundation Trust, Imperial College London, FujiFILM	Standard-of-care (not defined)	450	Hospitalization & time to discharge, O2 requirements, day 28	May-20	Q1-21	Two centers in London, conventional dosing, Pallav Shah as lead investigator (widely published specifically on lung pathology in COVID-19 infection)

Source: US National Institutes of Health clinical trials database, Health Canada

COVID-19 Disease

Pathology

We refer to a review by Cevik and colleagues in *Clinical Microbiology and Infection* (2020 Jul; 26(7): 842–847). The disease is relatively novel, with the first cases of atypical pneumonia reported in Dec/19. By Jan/20, the disease was formally identified as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), under the name COVID-19. The disease has since been considered a pandemic in almost every country.

ARDS is the key symptom that dictates disease severity: Symptoms typically include fever, cough, breathing difficulties, fatigue and loss of taste. According to Harenberg and colleagues in *Clinical Chemistry and Laboratory Medicine* (2020 May; 58(7)), the median time from onset of symptoms to first hospital admission was calculated at 7 days. Transfer to an intensive care unit (ICU) with mechanical ventilation was observed at 10.5 days mainly due to acute respiratory distress syndrome (ARDS). The median time from illness to discharge was ~22 days. ARDS is often the key symptom leading to severe disease progression. It is characterized by lung inflammation and fluid buildup in the lungs, which then lead to breathing difficulties.

Epidemiology

Given just how novel the disease is, studies on the prevalence and incidence rate of this condition have yet to be established, and thus information on the condition remains evolutionary at best.

Insofar, a preliminary collection of such information was published in a *JAMA* article by Drs. Wu and McGoogan (2020;323(13):1239-1242). Specifically, the article focuses on 72,314 cases (updated through February 11th 2020) that occurred in mainland China, as reported by the Chinese Center for Disease Control and Prevention. So on the case record, 44,672 cases of the 72,314 case records were confirmed cases of COVID-19 (representing 62% of all case records), with 1% of cases or 889 cases considered asymptomatic. In terms of the severity of the disease, a large majority of the 44,415 cases were reported as mild (36,160 cases or 81% of the cases), while severe/critical cases were 14%/5%, representing 6,168 cases/2,087 cases respectively. On fatalities, the fatality rate was 2.3% representing 1,023 of the 44,672 cases. The disease was observed to have higher fatality rates in elderly patients (14.8% in those aged 80 and above, and 8% in patients aged 70-79 years).

Treatment

For now, treatment guidance is still evolving as with knowledge on the condition. In the case of patients with mild-to-moderate disease, the current recommendation are identical by both the US (CDC) and Canada (the Canadian Critical Care Society and Association of Medical Microbiology and Infectious Disease (AMMI) Canada). Both types of guidance recommend patients to self-isolate at home, with no need for hospitalization unless there is a rapid deterioration in the condition.

Regulatory Interest in Accelerating Therapeutic Options for COVID-19

As such, there is currently no well-established standard of care for this condition yet, although as we will note below, Gilead's antiviral drug has since received full FDA approval for the treatment of COVID-19. In the US, the NIH is running four master protocol trials to test COVID-19 therapeutics (essentially adapts Phase II trials to seamlessly transition into Phase III trials). These four trials are collectively known as the Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV) trials. Of note, the 2,000-patient ACTIV-2 Phase II/III trial is currently assessing COVID-19 in an outpatient setting.

The only agent being tested in that trial for now is Eli Lilly's (LLY-NY, NR)/AbCellera Biologic's LY-CoV555, with a view of completion by Feb/21. The therapy is an IgG1 monoclonal antibody (mAb) directed against the spike protein of SARS-CoV-2. Apart from the ACTIV-trial, Lilly is also partnering with the NIAID for the 2,400-PATIENT Phase III BLAZE-2 trial, testing the therapy as a prophylactic treatment against SARS-CoV-2 infection and COVID-19 in residents and staff at long-term care facilities in the US. Trial design will assess the efficacy of a single dose of the therapy across 4 weeks, determining if the therapy can reduce the rate of infection in that timeframe.

Preliminary efficacy data from the firm's BLAZE-1 trial was released on September 16th, showing that one of the three dosing groups met the primary endpoint for viral load change at day 11 from baseline. The trial was focused on the treatment of patients with symptomatic COVID-19 on an outpatient setting basis, testing the mAb across four groups (placebo, 700 mg, 2800 mg, and 7000 mg). The 2,800 mg dose level met the aforementioned primary endpoint, although it was also observed that most patients (including those on placebo) had demonstrated near-complete viral clearance by day 11. The rate of hospitalization or ER visit was 1.7% in treated patients across all arms, as compared to 6% in the placebo arm, implying a 72% risk reduction. Additionally, on the safety front, no patients progressed to mechanical ventilation or died.

Exhibit 12. Publicly-Traded COVID-19 Drug Development Peers

Company	Curr	Sym	Shares out (M)	Share price 31-Jan	Mkt cap ($M) (curr)	Mkt cap ($M) (C$)	Ent val ($M) (curr)	Ent val ($M) (C$)	Company description
Canadian Peers Involved in COVID-19 Drug Development									
Arch Biopartners Inc	CAD	ARCH	61.2	$1.28	$78	$78	$81	$81	Arch's dipeptidase-1 LSALT sequence-based Metablok being tested in 60-patient Phase II trial, data on respiratory/kidney injury in COVID-19 patients expected by mid-2021
Algernon Pharmaceuticals Inc	CAD	AGN	142.6	$0.25	$36	$36	$29	$29	Algernon's lead N-methyl-D-aspartate (NMDA) receptor antagonist Ifenprodil/NP-120 is currently being tested in a 150-patient Phase II/III trial with data readout by Q420.
Cardiol Therapeutics Inc	CAD	CRDL	32.9	$3.16	$104	$104	$87	$87	High-purity cannabidiol (CardiolRx) in 422-patient Phase III COVID-19 trial, 28-day all-cause mortality & CV side effect data in H221
Ceapro Inc	CAD	CZO	77.6	$0.72	$56	$56	$53	$53	The firm is working alongside McMaster University for the development of an inalable formulation of yeast beta-glucan, aimed at the treatment of late-stage COVID-19 patients.
Edesa Biotech Inc	USD	EDSA	10.5	$5.76	$61	$77	$56	$71	The ON-based, US-listed Edesa Biotech testing TLR4 inhibitor EB05 in 865-patient Phase II/III moderate-to-severe COVID-19 pneumonia, data by Q221
Revive Therapeutics Ltd	CAD	RVV	189.4	$0.56	$106	$106	$103	$103	Small-molecule dithiol bucillamine in 1,000-patient Phase III COVID-19 trial, 28-day hospitalization/morality data by mid-2021
Mature Drug Developers Involved in COVID-19 Therapy Testing									
Gilead Sciences Inc	USD	GILD	1,253.5	$65.60	$82,231	$105,067	$87,572	$111,891	Gilead's antiviral remdesivir was approved in the US for the treatment of COVID-19 since August 31 2020.
Regeneron Pharmaceuticals Inc	USD	REGN	106.7	$503.84	$53,763	$68,693	$53,432	$68,270	Regeneron's/Sanofi's IL-6 inhibitor Kevzara (approved as a rheumatoid arthritis drug) was tested in a US Phase III trial on COVID-19 patients requiring mechanical ventilation. The trial failed to meet key primary/secondary endpoints.
Roche Holding AG	CHF	ROG	862.6	CHF 307	CHF 264,936	$338,509	CHF 278,220	$355,481	Roche's IL-6 inhibitor Actemra is currently approved for rheumatoid arthritis. The drug however failed to meet the primary endpoint in a Phase III COVACTA trial testing the therapy in severe COVID-19 associated pneumonia patients.
Merck & Co Inc	USD	MRK	2,530.0	$77.07	$194,990	$249,138	$216,459	$276,569	Molnupiravir/EIDD-2801/MK-4482 is N4-hydroxycytidine EIDD-1931 prodrug, partnered with Ridgeback, data from 1,300-pt COVID-19 (MK-4482-001) trial by end-of-2021
Abcellera Biologics Inc	USD	ABCL	265.6	$52.83	$14,030	$17,926	$14,023	$17,917	Bamlanivimab (LY-CoV555, targets surface spike protein epitope) is lead COVID-19 mAb, in the BLAZE-1-2-4 COVID-19 trials and NIH-sponsored ACTIV-2 trial, data in H221 or earlier
Alnylam Pharmaceuticals Inc	USD	ALNY	116.2	$150.48	$17,483	$22,338	$15,649	$19,995	The firm is working in partnership with Vir Biotechnology on the RNA-based therapeutic VIR-2703 (ALN-COV) targeting the SARS-CoV-2 genome; IND anticipated by YE2020.
Bausch Health Companies Inc	USD	BHC	355.2	$25.50	$9,056	$11,571	$32,504	$41,530	Bausch's Canadian arm Valeant Canada is currently testing the inhaled formulation of ribavorin in a 50-patient Phase I trial on hospitalized adult patients with Respiratory Distress due to COVID-19. Data expected by 2021.
						$67,802		**$74,333**	
Appili Therapeutics Inc	**CAD**	**APLI**	**62.6**	**$1.00**	**$63**	**$63**	**$41**	**$41**	**The firm is currently assessing the Dr. Reddy's/GRA-partnered Favipiravir in mild-to-moderate COVID-19 patients in North America.**

Source: Company filings, Refinitiv

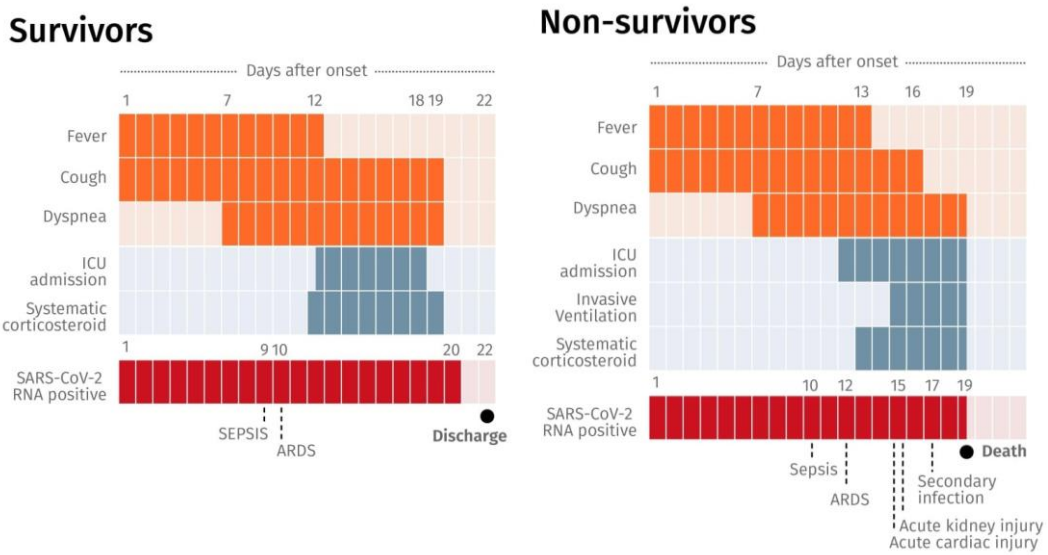
Antivirals used for treatment of COVID-19

Remdesivir: currently the only approved antiviral for COVID-19 treatment

Remdesivir (branded by Gilead as Veklury) is an intravenously-infused nucleotide analogue RNA polymerase inhibitor. The pro drug was first developed by Gilead Sciences (GILD-Q, NR) via a collaboration with the US Centers for Disease Control and Prevention (CDC) and the U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID). The prodrug had been initially deployed for testing in the 2014 Ebola outbreak but was considered inferior to other intervention therapies at that time as it relates to mortality data. The prodrug was formally approved under the FDA's emergency use authorization as of May 1st 2020 for the treatment of hospitalized COVID-19 patients with severe disease (defined as patients with low blood oxygen levels

or requiring breathing support). The approval was then expanded on August 28th for all hospitalized patients with suspected or laboratory-confirmed COVID-19, regardless of disease severity. Most recently, the FDA granted full approval of the antiviral drug in Oct/20 as the only treatment for COVID-19 patients, and separately for the treatment of patients with COVID-19 requiring hospitalization. In Canada, the drug was approved under Health Canada's Interim Order pathway as of July 27th 2020.

Exhibit 13. Differences in Disease Progression between COVID-19 Survivors and Non-Survivors.



Source: Canadian Broadcasting Company

According to a review by Singh and colleagues published in *Diabetes & Metabolic Syndrome* (2020 July-August; 14(4): 641–648.), the prodrug has established broad-spectrum antiviral properties against other viral conditions including respiratory syncytial virus (RSV), Nipah virus, Middle East respiratory syndrome (MERS-CoV), and Severe Acute respiratory Syndrome Coronavirus-1 (SARS-CoV-1). As it relates to the prodrug's efficacy in coronaviruses, the drug has been demonstrated via in vitro studies to inhibit all animal and human coronaviruses including MERS-CoV and SARS-CoV-1. This was also further demonstrated in animal models, and with the antiviral therapy demonstrating superiority over a different antiviral regimen (lopinavir-ritonavir). As it relates to SARS-CoV-2 (or currently, COVID-19), the drug was found to be a potent inhibitor of viral replication in human nasal and bronchial airway epithelial cells.

In terms of remdesivir's safety profile, the most common adverse events include rash, diarrhea, hypotension, abnormal liver function and renal impairment. Across the various trials reviewed by Singh and colleagues above, severe adverse events also included acute kidney injury, septic shock, and multi-organ failure. In one trial, it was reported that the treatment discontinuation rate was higher at 12% versus the control arm due to side effect profile.

Shifting to remdesivir's clinical history, approval for the prodrug in the US was based on data from two clinical trials listed below. The first clinical program was a NIAID-partnered 1,062-patient Phase III ACTT-1 trial assessing remdesivir in COVID-19 patients across different disease severities (mild, moderate and severe). Data indicated that the median time to recovery from COVID-19 was 10 days for the treatment arm, as compared to 15 days for placebo. Additionally, treatment with the prodrug also resulted in significantly higher clinical improvement at day 15 as compared to placebo. In patients with mild-to-moderate forms of the disease, the odds of improvement numerically favored the treatment arm over the placebo arm at Day 15.

In the second 1,113-patient Phase III GS-US-540-5774 trial, the prodrug was assessed against standard-of-care in hospitalized patients with moderate COVID-19 over the course of five days, and ten days. Results indicated that the odds of a patient's COVID-19 symptoms improving were statistically higher in the five-day treatment group at Day 11 as compared to those receiving only standard of care. The ten-day treatment group did not achieve statistical significance, although it did demonstrate numerically favourable results.

Exhibit 14. Selected COVID-19-Targeted Small-Molecule Antiviral Therapies in Development by Peer Firms

Innovator	Partner	Drug Name	Mechanism of Action	Mode of Admin	Number of patients	Disease Severity	Stage	Data expected by
Gilead	NA	Remdesivir/ Veklury	Viral RNA polymerase inhibitor	IV	1,230	Outpatient setting	FDA-approved but Phase III testing continues	Feb/21
Biocryst	NA	Galidesivir	Viral RNA polymerase inhibitor	IV	132	Moderate-severe (but not critical)	I	May/21
Ridgeback Biotherapeutics	Merck	Molnupiravir	Viral RNA polymerase inhibitor	Oral	1,450	Mild/ moderate (non-hospitalized)	II/III	Oct/21
Atea	Roche	AT-527	Viral RNA polymerase inhibitor	Oral	190	Moderate	II	Jan/21

Source: Clinicaltrials.gov, company filings

Remdesivir economics: As reported in a NPR article, Gilead formally announced the price of remdesivir for the treatment of COVID-19 in Jun/20. In the US, the firm intends to charge US$520/vial for patients with private insurance, although that cost will be lowered for those on government programs. The expected course of treatment is for 5 days, and with a double dose administered on the first day, and so the total cost per treatment course works out to be US$3,120. Gilead generated FQ320 remdesivir sales of US$873M and in a corporate update earlier this year, it projected full-year remdesivir sales of US$2.83B. We do expect remdesivir sales to equilibrate at a lower level by FH221 as impact from availability of novel vaccine formulations from Pfizer, Moderna and others is likely to soften COVID-19 prevalence in future periods.

As NPR reported as well, the HHS announced an agreement with Gilead in Jun/20 for 500,000 treatment courses to be distributed to hospitals in the US. At time of announcement, this represented the majority of Gilead's projected production schedule for remdesivir for July through to September: 94,200 treatment courses in July (100% of production schedule), 174,900 treatment courses for August (90% of production schedule), 232,800 treatment courses in September (90% of production schedule). Outside the US, governments in developed countries will pay US$390/vial or US$2,340 for a five-day course.

In Development: Oral Antiviral Therapies Aiming to Displace Gilead's Now Approved IV Antiviral

Roche/Atea: AT-527

Genentech/Roche (ROG-SW, NR) announced a partnership with Atea Pharmaceuticals (Private) for the development of an oral purine nucleotide prodrug AT-527. The focus is on the therapy being an oral antiviral, which could potentially offer advantages on the administration and compliance front over Gilead's infused antiviral form.

Presently, AT-527 is currently being studied in a 190-patient Phase II clinical trial for hospitalised patients with moderate COVID-19. Following the anticipated trial completion by Jan/21, the firm then plans to initiate a Phase III clinical trial for Q121, with the antiviral's utility to be studied in patients outside of the hospital setting. Separately, the two firms hope to develop AT-527 for the post-exposure prophylactic settings as well. Deal terms were not disclosed but will see Atea be in charge of the distribution in the US, while Roche will be involved in ex-US distribution.

Merck's/Ridgeback's Molnupiravir

Merck's (MRK-NY, NR)/Ridgeback Biotherapeutics' (Private) molnupiravir/EIDD-2801/MK-4482 has a similar mechanism of action to remdesivir in that it is a nucleoside analogue, but with the distinction that the drug can be administered in oral form instead of IV form as with remdesivir. The two firms announced the joint development of the drug back in May/20. Deal terms on the collaboration were not disclosed, but will see Merck receive global rights for EIDD-2801. Two Phase II/III trials assessing the vaccine began in Oct/20, and will see 1,300 to 1,450 COVID-19 patients assessed (two different patient groups will be assessed in the trial: hospitalized COVID-19 patients and non-hospitalized COVID-19 patients).

Biocryst's Galidesivir

Until recently, Biocryst was developing the nucleoside RNA polymerase inhibitor Galidesivir/BCX4430. The IV-infused drug is currently being assessed in a NIAID-partnered 132-patient Phase Ib trial for the treatment of COVID-19 patients. As part of its partnership with NIAID, the firm received US$44M; part of the funds received will be deployed towards a Phase II trial testing the drug in non-hospitalized COVID-19 patients at high risk for developing severe disease and complications of COVID-19. In late Dec/20, the firm announced that no clinical efficacy benefit was observed in the trial, and the firm would be discontinuing the pursuit of COVID-19 indication for galidesivir. Prior, the drug was assessed in partnership with US government agencies for other viral diseases including Marburg virus, and other filoviruses (including Ebola).

Exhibit 15. Applications Received Under Health Canada's Interim Order

Company	Drug	Application	Status	Filing date or review time
Applications Under Review				
AstraZeneca	Adenovirus vaccine vector (ChAdOx1)	Vaccine	Under review	1-Oct-20
Dr. Reddy's/Appili	Favipiravir	Antiviral	Under review	18-Dec-20
Janssen/J&J	JNJ-78436735/Ad26.COV2.S	Vaccine	Under review	30-Nov-20
Approved Applications				
Eli Lilly	Bamlanivimab/LY-CoV555	Immune sera and immunoglobulins	Authorized	39 days
Gilead	Remdesivir	Antiviral	Authorized	38 days
Moderna	mRNA-1273 SARS-CoV-2	Vaccine	Authorized	72 days
Pfizer/BioNTech	Tozinameran (mRNA vaccine, BNT162b2)	Vaccine	Authorized	61 days

Source: Health Canada

Current Clinical/Regulatory Status

Filing for Health Canada's Interim Order Now Pending Review

As of late December, Appili and partners Dr. Reddy's and Global Response Aid announced the submission of an application for favipiravir to Health Canada under the interim order pathway. The pathway was designed to allow for the expedited authorization for drugs deployed for the treatment of COVID-19, thereby allowing for the pre-positioning or placement of such drugs in Canadian facilities pending approval under the traditional drug approval pathway in Canada.

Under the Health Canada's Interim Order, applicants can pursue the expedited authorization pathway if the drug has already been authorized by a foreign regulatory authority. The pathway also diminishes the need to submit detailed reports on the clinical effectiveness of the drug as typically required under the traditional drug approval pathway, and instead only requires the submission of known information regarding the safety and efficacy of the drug. We believe that with favipiravir already approved for use in Russia and India, as well as history of safety and efficacy for other use cases (influenza), this should meet the requirements for approval under this pathway. At the same time we anticipate that new clinical data generated as part of the firm's ongoing clinical activities could be deployed for rolling review and subsequently expedite regulatory decisions under this pathway.

For now, there have been only seven applications under this expedited pathway, four of which have been approved. In the case of Gilead's remdesivir, the drug had a turnaround time of ~38 days from time of application submission. On average, the four approved applications had a turnaround time of ~52 days. Using this as a range for our estimates, it would be plausible to assume that approval could be forthcoming as early as end-January or by mid-February.

Ongoing studies being advanced in the US and Canada under Appili's oversight

Summary: Presently, the most advanced trial ongoing is the firm's 826-patient Phase III PRESECO trial testing favipiravir in early treatment outpatient care settings, and with data expected by late Q121 or by early Q221.

Timeline of clinical trial activities initiated in the US

Nov. 24th 2020: Appili announced the initiation of the Phase III PEPCO (Post Exposure Prophylaxis for COVID-19 (PEPCO)) trial testing favipiravir for the prevention of COVID-19. The trial will also be conducted in the US, with the FDA accepting a protocol amendment to do so. Enrolment and dosing in the trial is expected to begin before end-2021.

Sep. 11th 2020: The firm announced the submission of an IND with the FDA for an 826-patient Phase III PRESECO trial testing favipiravir as a treatment for mild-to-moderate COVID-19 infections. On trial design, the focus will be to determine if favipiravir can reduce the time to clinical recovery and prevent the progression of the infection into the severe or life-threatening forms of the disease. Trial design will see the recruitment of 826 outpatients who do not require hospitalization and have tested positive for COVID-19 (with mild-to-moderate disease). Patients in this trial will self administer the drug regimen at home, while being monitored by investigators remotely. The trial began in Nov/20, with a goal of data by Oct/21.

Along with this study, a 136-patient sub study will assess favipiravir's effect in viral shedding, and whether treatment can reduce this period of shedding and by implication diminish the period of infectivity and reducing the spread of the disease.

Aug. 10th 2020: Appili received clearance to proceed with the U.S. expansion of the 760-patient Phase II CONTROL clinical trial in LTC facilities. The trial was initiated in Canada (more on that below), with the focus on controlling outbreaks related to COVID-19 exposure in LTC facilities as well as other care settings.

Timeline of clinical trial activities initiated in Canada

Nov. 24th 2020: PEPCO study (see above)

May 21st 2020: Appili announced that regulatory clearance was granted by Health Canada to commence a 760-patient Phase II trial testing favipiravir as a preventative measure against COVID-19 outbreaks. The initial focus on the trial was on 16 long-term care (LTC) homes in Ontario, with the choice of doing so following observations of high COVID-19 mortality rates being associated with LTC facilities. The primary endpoint of the trial will be on outbreak control, which is defined as no new cases of COVID-19 in residents for 24 consecutive days up to Day 40 after the start of prophylaxis. Secondary endpoints will assess for safety, rates of infection, disease progression and fatality rates.

May 11th 2020: Appili submitted an IND to Health Canada for the first Phase II clinical trial to test favipiravir for the prevention of COVID-19. This was also the first announcement made by the firm regarding its clinical partnership with legacy partner FUJIFILM Toyama Chemical on Favipiravir.

Patent History

As disclosed in the firm's filings, the original composition of matter patents for favipiravir have since expired. However, the firm expects that with being first to secure regulatory approval, the drug might potentially enjoy data exclusivities, thereby providing a few years of runway before further generic entry.

ATI-2307

Presently, the firm's lead clinical asset is the FUJIFILM-acquired broad-spectrum antifungal agent ATI-2307 (previously known as T-2307), aimed at the treatment of two conditions – cryptococcal meningitis (CM) and invasive candidiasis. The asset has completed Phase I trials, and with a view of entering Phase II trials by 2022.

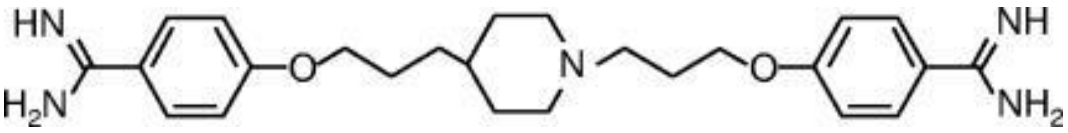
As noted above, the drug was originally developed by FUJIFILM Toyama Chemical, for which Appili acquired the ex-Japan rights in 2019. Prior to acquisition, FUJJIFILM completed three Phase I trials for the asset demonstrating that the drug was well-tolerated at the anticipated therapeutic doses.

Given that the drug is furthest advanced in CM, the context of our report is thus focused on this indication.

Chemical Structure and Early-Stage Studies to Date

ATI-2307 is an arylamidine derivative, with the specific structure 4-{3-[1-(3-{4-[amino(imino)methyl]phenoxy}propyl)piperidin-4-yl]propoxy}benzamidine. The agent belongs to a class of aromatic diamidines, which is similar to pentamidine (used in the treatment of pneumocystosis, leishmaniasis, and trypanosomiasis) and the furamidine prodrug pafuramidine (DB289, which has previously demonstrated efficacy in African trypanosomiasis, *Pneumocystis jirovecii* pneumonia, and malaria).

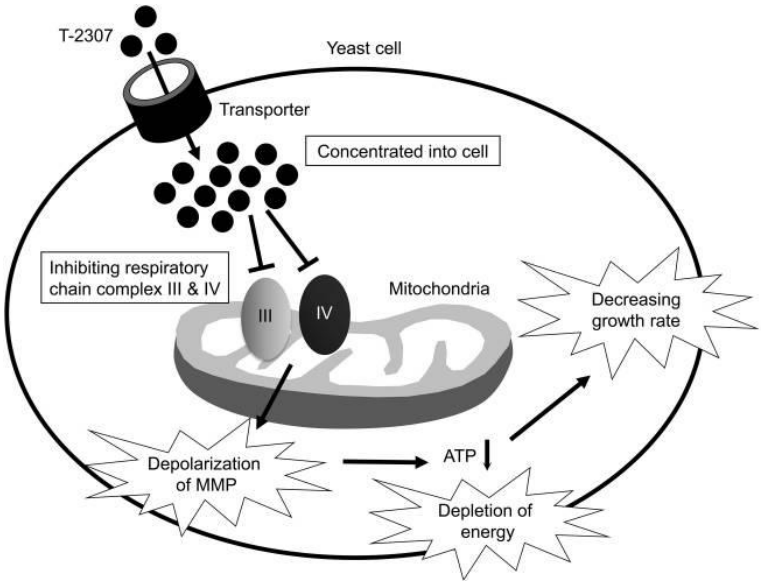
Exhibit 16. Chemical structure of ATI-2307/T-2307



Source: Antimicrobial *Agents and Chemotherapy* (2008). Vol. 52, pp. 1318–1324

However as a novel agent, its mechanism of action remains unknown, although it was hypothesized in later research by Mitsuyama and colleagues that was published in 2012 in the journal *Antimicrobial Agents and Chemotherapy* that the drug works by selectively disrupting yeast mitochondrial function. Also in more recent study published in *Antimicrobial Agents and Chemotherapy* last year by Yamashita and coworkers, researchers further explored how ATI-2307 selectively inhibits yeast mitochondrial function, noting that the inhibition of respiratory chain complexes III and IV were key factors for the disruption of mitochondrial function and antifungal activity. Specifically, researchers hypothesized that the drug works by interfering with ATP production since the respiratory chain is involved in ATP production. Of note, results also indicated that the drug did exert activity on yeast mitochrondrial respiratory chain complexes, it had little effect on mammalian mitochondrial respiratory chain complexes.

Exhibit 17. ATI-2307 is Thought to Exert Anti-Fungal Action Through Disrupting Yeast Mitochondrial Function



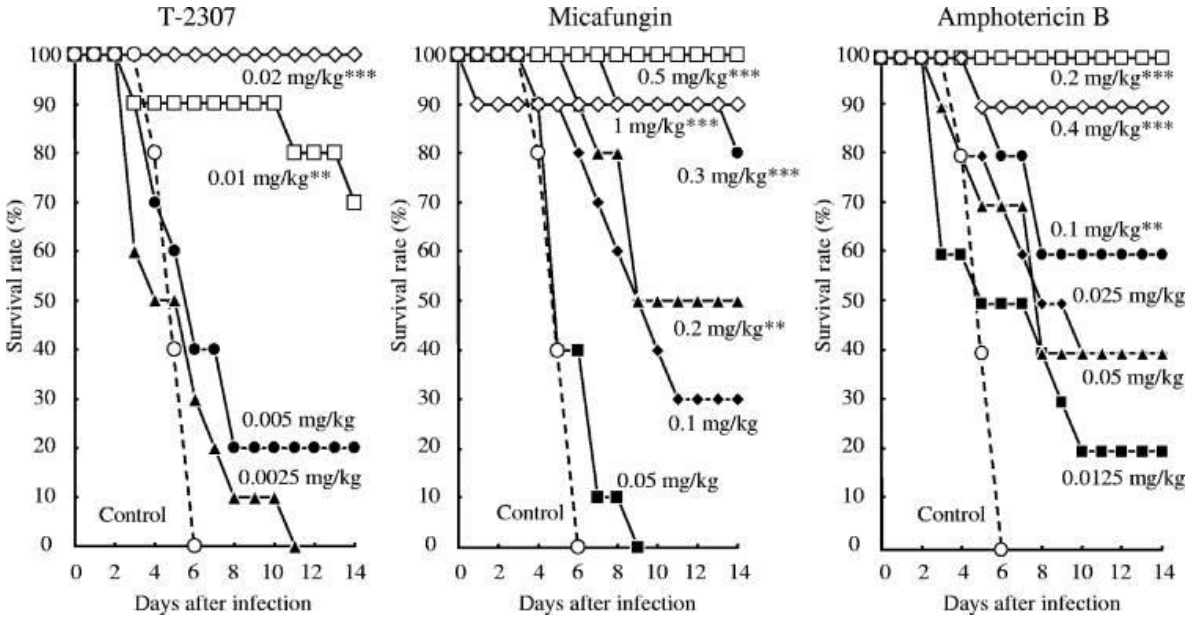
Source: *Antimicrobial Agents and Chemotherapy* (2019). Vol. 63, pp. e00374-19.

The efficacy of ATI-2307 were studied in an early murine model by researchers Mitsuyama and colleagues with results published in *Antimicrobial Agents and Chemotherapy* (2008 Apr; 52(4): 1318–1324). In that study, the agent was tested against three main fungal species: *Candida albicans*, *Aspergillus fumigatus* and *Cryptococcus neoformans*.

Overall, results indicated that the agent was able to significantly delay mortality in all three fungal species tested, however the agent's activity was more significant in systemic infections caused by *Candida albicans* and *Cryptococcus neoformans*.

In those two aforementioned species, the ATI-2307 doses deployed were lower than the doses of standard agents typically deployed in these conditions. For the treatment of *Candidas albicans*, the ATI-2307 dose was 0.01 $mg \cdot kg^{-1} \cdot dose^{-1}$ as compared to the standard agents micafungin and amphotericin B at 0.2 $mg \cdot kg^{-1} \cdot dose^{-1}$/0.1 $mg \cdot kg^{-1} \cdot dose^{-1}$ respectively.

Exhibit 18. Therapeutic Effects of T-2307, Micafungin, and Amphotericin B on Murine Systemic Candidiasis Caused by *Candida albicans*

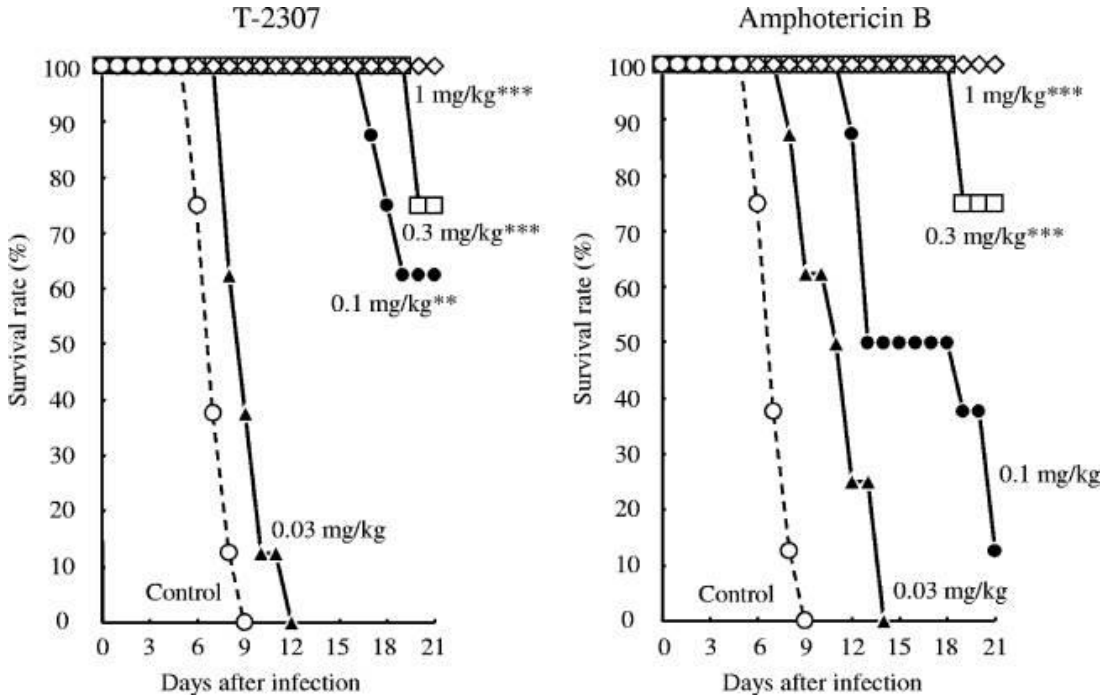


Source: *Antimicrobial Agents and Chemotherapy* (2008). Vol. 52, pp. 1318–1324

As it relates to the treatment of *Cryptococcus neoformans*, the dose of ATI-2307 administered was 0.1 $mg \cdot kg^{-1} \cdot dose^{-1}$ as compared to amphotericin B, which was administered at 0.3 $mg \cdot kg^{-1} \cdot dose^{-1}$. On systemic infections caused by *Aspergillus fumigatus*, ATI-2307 did extend the mortality in treated mice but was considered slightly less active than amphotericin B, although the agent did exhibit a superior therapeutic effect in contrast to micafungin.

Researchers thus concluded that the activity of ATI-2307 was demonstrably greater than other standard antifungal agents including micafungin and amphotericin B as it relates to candidiasis, and amphotericin B in cryptococcosis.

Exhibit 19. Therapeutic effects of T-2307, Micafungin, and Amphotericin B on Murine Systemic Candidiasis Caused by *Cryptococcus neoformans*



Source: *Antimicrobial Agents and Chemotherapy* (2008). Vol. 52, pp. 1318–1324

Current Clinical Development History

ATI-2307 has been evaluated in three Phase I trials consisting of 80 patients in total primarily assessing for dosing, safety and pharmacokinetics of the drug. The drug was deemed safe and well tolerated across all doses tested. Advancement into a Phase II trial is anticipated by 2022.

Patent History

The global dossier for ATI-2307 was initially published in 2003, and so the anticipated expiration of the global patent dossier will likely be expected by 2023. Despite just how near the dossier is to patent expiry, we anticipate actual patent life varying on a country-by-country basis.

As an example, we note that in North American markets:

US/Canada: In the US, the patent was formally published as of 2007, and so the anticipated expiration of said patent will be 2027. Additionally, upon formal FDA approval, the firm could enjoy up to seven years of regulatory exclusivity under the Orphan Drug Designation given its current focus on two orphan conditions (cryptococcal meningitis or invasive candidiasis). The firm could also tentatively speed up development of its asset under the Limited Population Pathway for Antibacterial and Antifungal Drugs pathway related to the 21st Century Cures Act. This allows for the accelerated clinical development of antibiotics and antifungals aimed at the treatment of serious or life-threatening conditions in a limited population. Under this pathway, smaller, shorter, or fewer clinical trials will be permitted. Canadian patents corresponding to the identical patent were issued in 2011, giving the firm abundant patent runway.

Exhibit 20. ATI-2307 Patent History (Global Patents Only)

Inventor(s)	Assignee	Issuance Date	Patent Number	Title	Description of Claims
ATI-2307					
Hayashi K., Ojima K., Hori K., Okujo H., Mitsuyama J., Kunitani K.,	Toyama Chemical Co Ltd.	Sep 12, 2003	WO 2003/074476	Novel Arylamidine Derivative or Salt Thereof	An arylamidine derivative with antifungal activity and with potential as a fungicide.
Hayashi K.	Toyama Chemical Co Ltd.	Jul 05, 2007	WO 2007/074868	Novel Arylamidine Derivative, Salt Thereof and Antifungal Agent Containing Those	Patent is similar to the one above, and with specificity on its use as an antifungal agent.
Hayashi K., Nomura, N.	Toyama Chemical Co Ltd.	Feb 02, 2006	WO 2006/011499	Novel Arylamidine Derivative, Salt Thereof, and Antifungal Agent Containing These	
Nomura, N., Nishikawa, H., Fujino, N.	Toyama Chemical Co Ltd.	Oct 19, 2006	WO 2006/109642	Pharmaceutical Composition and Method Using Antifungal Agent in Combination	A pharmaceutical composition containing the arylamidine derivative and an immunosuppressing agent has a strong antifungal activity and is useful for the treatment of fungal infection and a skin disease such as atopic dermatitis.

For brevity, we have not included all international patents, but other geographies where issued patents apply include: Australia, Canada, China, Europe, India, Portugal, Korea, Mexico, New Zealand, Russia, South Africa, US

Source: WIPO

Pathology

The disease is predominantly caused by an invasive fungal pathogen known as *Cryptococcus neoformans*. The fungus itself is typically not contagious, and is found in soil, decaying wood or bird droppings. Although not contagious, the disease tends to infect immunocompromised individuals via inhalation, entering the blood stream before affecting the central nervous system (CNS), for which CM is predicated on.

We observed that in North America, a separate fungal species known as *Cryptococcus gattii* was implicated in a cryptococcosis outbreak in 2004 (unlike *C. neoformans*, the fungus is not found in bird droppings but in eucalyptus trees). For now, the standard practice for treating CM due to *C. gattii* remains similar to the treatment of *C. neoformans*. It is also not routine for medical laboratories to identify the difference between the two at species level.

Epidemiology

Individuals most at risk of developing CM include those with HIV infections, immunosuppressed or immunocompromised individuals (solid organ transplant patients in particular). The disease tends more prevalent in countries outside North America and represents one of the leading causes of mortality in HIV/AIDS patients in sub-Saharan Africa. It is however rare for individuals who remain immunocompetent (that is, with healthy functioning immune systems) to be infected.

As it relates to HIV infection, routine screenings for cryptococcal infection are not strongly recommended by both the Department of Health and Human Services and the Infectious Diseases Society of America. This despite the cost of screening being far lower than the implied costs and length of hospitalization with this condition (ranging from US$50,000 to US$100,000 over an average 70-day stay).

We note the various epidemiological-related studies on this medical population:

- A study published in 2006 by Lortholary in AIDS (2006 Nov 14;20(17):2183-91) found dramatic improvements in overall survival in patients with cryptococcosis infections who have received combination antiretroviral therapy (also commonly known as highly active antiretroviral therapy/HAART) as compared to those who did not receive HAART.

- On more recent statistics, we reviewed an epidemiology study conducted by Rajasingham and colleagues and published in *The Lancet Infectious Diseases* (volume 17, issue 8, p.873-881, Aug 01, 2017). The study focused mainly on patients with HIV and who were on antiretroviral therapy. The study estimates an incidence of ~223,100 CM cases globally in 2014, out if which sub-Saharan Africa accounted for 73% of all estimated cases. On mortality statistics, CM is responsible for ~15% of AIDS-related deaths.

- In the US, prevalence data on the condition remains sparse. A study by McKenney and colleagues published in *Clinical Infectious Diseases* (2015 Mar 15; 60(6): 959–965) is one example of US-centric data, though focused on AIDS patients. On that study researchers assessed the prevalence of cryptococcal infection and outcomes in advanced AIDS patients from 1986 to 2012. Results indicated a 2.9% prevalence rate for AIDS patients who tested positive for Cryptococcal antigen (CrAg; or the presence of the antigen/foreign body in the blood stream). Out of that group of patients, 18% had a history of CM. As well, findings also indicated that CM was a higher possibility in patients with lower CD4 T cell counts due to patients having higher immunosuppression and thus are unable to control the infection.

- In non-HIV infected patients, a paper published by Singh and colleagues in Clinical Infectious Diseases (Volume 47, Issue 10, 15 November 2008, Pages 1321–1327) suggests that ~20%-60% of cryptococcosis infections in the US are related to non-HIV infected patients. In organ transplant recipients with cryptococcoal disease, CNS involvement is related to 53%-72% of the cases.

Standard of Care Consists of a Highly Toxic Regimen with Equally Harsh Side Effect Profile

At present, the standard of care for CM is amphotericin B in combination with flucytosine. However the combination regimen is known for its toxic side effect profile, and is often associated with high rates of renal failure.

Separately, another antifungal drug known as fluconazole (Pfizer's (PFE-NY, NR) Diflucan; FDA approved in 1990) is also typically deployed in the treatment of the condition. Fluconazole does not work by killing the yeast (*Cryptococcus neoformans*) per se but rather is involved in inhibiting its growth. The drug does exhibit several advantages over the amphotericin B/flucystosine regimen including oral availability as well as excellent central nervous system (CNS) penetration and few drug-drug interactions. However as observed by authors Hope and colleagues in the American Society for Microbiology's *mBio* Journal (Dec 2019), monotherapy alone with fluconazole is considered ineffective. On that, authors also noted that fluconazole monotherapy, even when administered at high doses of 800mg/day-1,200 mg/day, was associated with low rates of fungal clearance and suboptimal clinical outcomes as compared to amphotericin B-based therapy or in combination with flucytosine. Additionally, the monotherapy also puts patients at risk of developing resistance against the drug regimen.

Presently, the WHO recommends a 1-week regimen of the combination therapy during the induction phase, instead of two weeks previously; this was due to the regimen demonstrating a reduction in mortality by 38% over a shorter period and also to reduce the risk of developing anemia.

In contrast, current practice guidelines in the US are informed by the Infectious Diseases Society of America, which last provided an update in *Clinical Infectious Diseases* (Volume 50, Issue 3, 1 February 2010, Pages 291–322) call for a longer induction phase. The guidelines are split between treatment of individuals with HIV, organ transplant recipients and those who have neither of the conditions. Across all three conditions, it is recommended that individuals begin induction therapy with an amphotericin B formulation and flucytosine for two weeks, before transitioning into a fluconazole regimen for eight weeks or longer, depending on the condition. We provide the guidelines below for reference.

In HIV-infected patients, amphotericin B deoxycholate (0.7–1.0 mg/kg per day) and flucytosine (100 mg/ kg per day orally in 4 divided doses) are recommended for at least 2 weeks, followed by fluconazole (400 mg [6 mg/kg] per day orally) for a minimum of eight weeks.

In organ transplant recipients, induction therapy should begin with liposomal amphotericin B (3–4 mg/kg per day IV) or amphotericin B Lipid Complex (5 mg/kg per day IV) and flucytosine (100 mg/kg per day in 4 divided doses) for at least two weeks. This is then followed by a fluconazole regimen (400–800 mg [6–12 mg/kg] per day orally) for eight weeks and with the regimen then tapered down (200–400 mg per day orally) for 6–12 months. In those without HIV and are not an organ transplant recipient (with low risk of therapeutic failure), the guidelines call for induction therapy consisting of a combination of amphotericin B and flucytosine for two weeks, followed by fluconazole (800 mg [12 mg/kg] per day orally) for eight weeks.

Peak sales opportunity: a look at transactions driven by other antifungals

In one of the most recent reviews published on antifungals, Rauseo and colleagues in *Open Forum Infectious Diseases* noted of only one antifungal drug that has been approved and marketed over the last decade. The said drug is Basilea's (BSLN-SW, NR) azole antifungal isavuconazole (brand: Cresemba; FDA-approved in the US as of 2015), approved for the treatment of two invasive fungal conditions: invasive aspergillosis and invasive mucormycosis (interestingly, as an alternative treatment when amphotericin B is considered inadequate). The drug was initially partnered with Astellas in a global 2010 deal valuing the transaction at CHF553M (consisting of upfront payment of CHF78M and milestone payments of CHF478M.

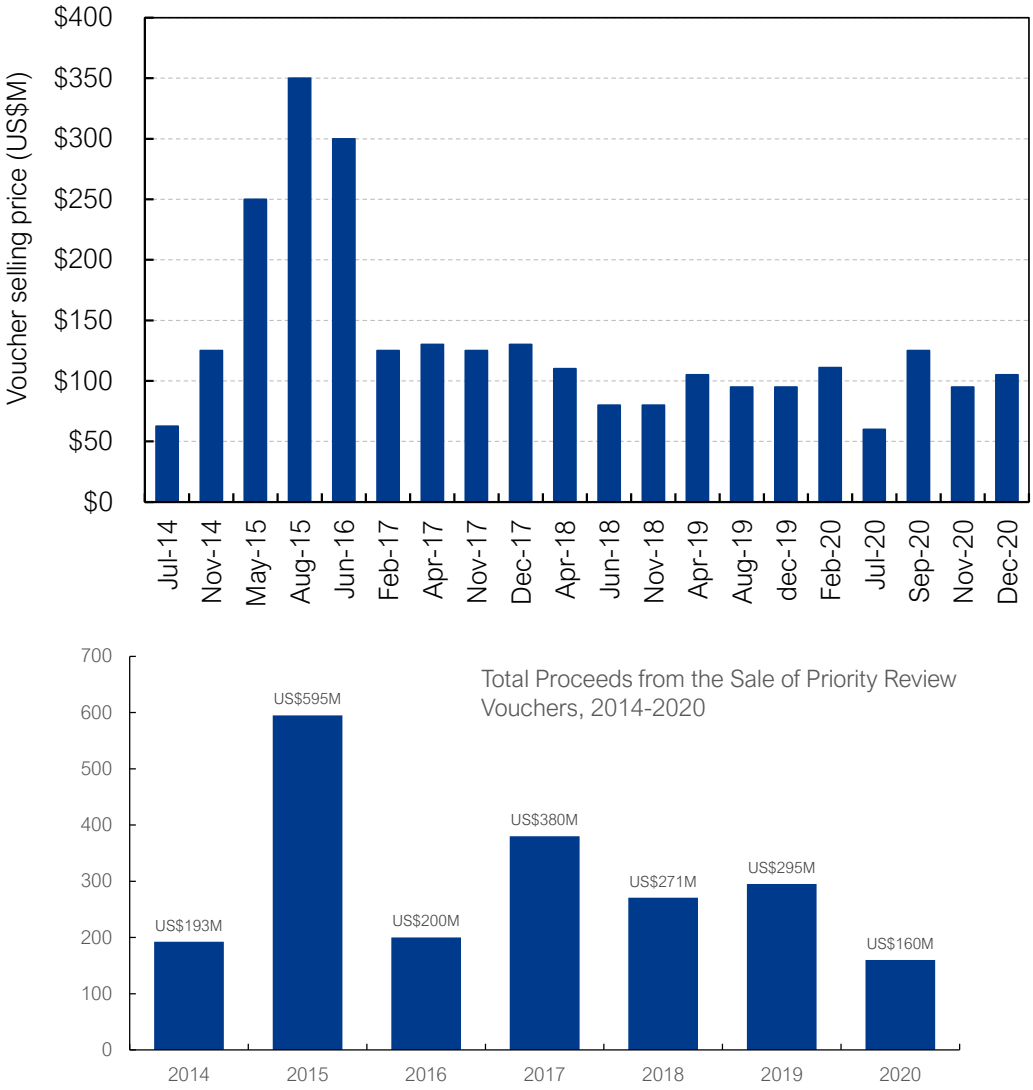
The deal was later amended in 2014, with Basilea taking back full rights outside of the US while retaining the potential of CHF374M in milestone payments. This then saw the licensing of rights to Europe, Russia, Turkey and Israel to Pfizer (PFE-NY, NR) in 2017. As part of the new deal with Pfizer, Basilea was eligible to receive CHF 70M in upfront payment, and up to US$427M in milestone payments. Regarding sales performance, Basilea estimated that global "in-market" sales of Cresemba by all of Basilea's partners, amounted to approximately US$180M over a 12-month period (Jul/18 to Jun/19), representing over 35% growth on a y/y basis.

Next, we refer to Pfizer's fluconazole, which was discussed in our review of standard practice treatments for CM. At its peak, fluconazole achieved peak sales of US$1.17B under Pfizer before genericization in 2004/2005. Following genericization, Pfizer went on to acquire Vicuron in 2005 via a US$1.9B transaction, adding Vicuron's antifungal agent anidulafungin (brand name: Eraxis) to Pfizer's antifungal portfolio; the drug was subsequently approved for candidemia in 2006.

Priority Review Voucher Potential with ATI-2307

If ATI-2307 receives formal FDA approval for cryptococcal meningitis, the firm will be eligible for a Priority Review Voucher (PRV) under the Neglected Tropical Disease pathway; CM was added as a qualifying disease for the tropical disease PRV in Aug/18. As we note in our exhibit below, it is indeed true that the sale prices of PRVs have been declining over time, with higher valuations last seen in 2015 than in more recent periods. Nonetheless, we remain of the view that any cash infusion (especially in the form of double-digit million range with recent voucher sales) represents upside to the firm's liquidity in the longer-term. A list of PRV sales can be viewed in our Appendix.

Exhibit 21. Pricing & Cumulative Revenue Dynamics for Sale of Priority Review Vouchers, 2014-Present



Source: Adapted from United States Government Accountability Office (Jan 2020, *FDA Priority Review Vouchers Program*)

ATI-1501

ATI-1501 is a taste-masked liquid suspension of metronidazole, which the firm aims to target patients who have difficulty swallowing. Metronidazole is a broad-spectrum antibiotic that is deployed for the treatment of parasitic and anaerobic bacterial infections. Over 10M prescriptions of the drug is estimated to be prescribed annually in the US. Despite its broad-spectrum efficacy, the drug is also typically associated with certain side effects including dry mouth, an unpleasant or sharp metallic taste, and a change in taste sensation. In patients who have difficulty swallowing metronidazole, the tablets are typically crushed and resuspended in liquid in order to ingest the drug. However, the strong metallic taste of the drug is enhanced when crushed, thereby exacerbating the issue and reducing patient compliance.

Since the drug is essentially a reformulation of an existing drug, Appili intends to target approval using the 505(b)(2) pathway. Presently, the drug is partnered with Saptalis for distribution in the US.

Financial Forecasts

ATI-2307: As for the Antifungal drug ATI-2307, our forecasts for now are only centered on initiatives related to cryptococcal meningitis. While invasive candidiasis is indeed another source of revenue opportunity for the firm, the firm is still not as advanced as it is in CM. As discussed before, the firm could still be eligible for a PRV, which could represent another source of upside for our forecasts. We will elect for now to wait until tangible progress has been made on the clinical and regulatory front before revisiting our forecasts for the potential of a PRV. On pricing, we model ATI-2307's cost after that of oral flucytosine therapy; and with our current estimate for a course of therapy in an average adult patient is ~US$67,200. Our forecasts anticipate launch and approval by 2026, with estimated net revenue in that year of C$27.2M.

ATI-1501: Given metronidazole's utility as a broad-spectrum antibiotic, it would be rather difficult to quantify the exact use cases in which patients will experience benefit from therapy. Instead, our forecasts focus on the number of antibiotic prescriptions annually, and then derives a proportion of these prescriptions for which metronidazole is then prescribed. Since the core selling point for ATI-1501 is the ability to mask the bitter taste of the drug, we believe its use case is best suited for patients which currently have difficulty with swallowing the tablet formulation of the drug. Two types of patients come to mind – pediatric and elderly patients with dysphagia (a condition where patients have trouble swallowing).

Since generic metronidazole is already available, our forecasts are a reflection of clawing market share away from the available oral metronidazole generic market instead of the drug being positioned as a market leader. As such, our pricing is more in line with generic pricing for metronidazole (we estimate US$20 per course of therapy), rather than being reflective of innovative drug pricing. The firm's only partnership is with Saptalis in the US, our forecasts anticipate that approval and launch of the product transpiring under best-case scenario by F2022, with estimated revenue of $0.3M in F2022, and increasing to >$1.0M by 2027.

Favipiravir: Given favipiravir's potential for reproductive harm, we have adjusted our estimates accordingly to exclude female cases in which the appropriate age groups correspond to ages of presumed reproductive age. For example in our Canadian forecasts, we exclude female cases between the ages of 20 to 49 from our COVID-19 case count. Since the use case for favipiravir will likely be in mild-to-moderate COVID-19 cases, we have adjusted our estimated case count accordingly to exclude hospitalization cases (wherein it is implied that the disease is advancing into more severe stages, for which other treatments will be required instead).

On the pathway towards drug approval, we believe the drug could receive approval under Health Canada's Interim Order pathway as soon as CQ121. With COVID-19 still an ongoing matter for which a second wave might soon be anticipated at time of writing (a province wide lockdown for Ontario began on December 26th 2020, with Southern Ontario expected to remain under lockdown until January 23rd 2021), our current forecasts estimate the heaviest demand for use in North America in F2022-F2024. As such, our revenue forecasts exhibit a period of supranormal growth in that time period. Post F2024, we expect a dramatic falloff in revenue, with minimal revenue reflecting government stockpiling initiatives than real world need.

On pricing, as we have noted earlier, core patents for favipiravir have essentially expired. But in the absence of generic drug developers, we anticipate pricing to reflect slightly below current COVID-19 branded therapeutics. In Canada, we anticipate a course of therapy to cost ~C$500. In the US, our pricing reflects the lack of patent protection on the drug but with costs lower than remdesivir, which is currently charged to government health programs at C$2,340 per course of therapy, and thus could be an attractive price point to consider over remdesivir. As such, we are of the view that favipiravir could indeed be charged at similar economics at ~US$500.

The firm is currently part of a consortium of companies (Dr. Reddy's and Global Response Aid) involved in the worldwide development, commercialization, and distribution of favipiravir. We model a 15% royalty rate from all profits received, and subsequently net revenue for favipiravir, less a 30% royalty rate back to FUJIFILM.

Exhibit 22. Revenue Forecasts for Appili Therapeutics

Year-end March 31 (C$, exc per share data)	2020A	2021E	2022E	2023E	2024E	2025E	2026E	2027E	2028E	2029E	2030E
ATI-1501 (Metronidazole Suspension)											
Current Population, United States (M)	330.3	332.6	335.0	337.3	339.7	342.0	344.4	346.9	349.3	351.7	354.2
Total Antibiotic Prescriptions (M)	253.3	255.1	256.9	258.7	260.5	262.3	264.1	266.0	267.8	269.7	271.6
Total Antibiotic Prescriptions, pediatric patients (M)	37.1	37.3	37.6	37.8	38.1	38.4	38.6	38.9	39.2	39.5	39.7
Estimated proportion of metronidazole in total antibiotic Rx (%)	*4.9%*	*4.9%*	*4.9%*	*4.9%*	*4.9%*	*4.9%*	*4.9%*	*4.9%*	*4.9%*	*4.9%*	*4.9%*
Proportion, estimated Metronidazole Rx, pediatric pts. (M)	1.8	1.8	1.8	1.9	1.9	1.9	1.9	1.9	1.9	1.9	1.9
Proportion, pediatric patients with swallowing issues (M)	*1.63%*	*1.65%*	*1.66%*	*1.67%*	*1.68%*	*1.69%*	*1.70%*	*1.72%*	*1.73%*	*1.74%*	*1.75%*
Total Antibiotic Prescriptions, elderly patients (M)	200.1	201.5	202.9	204.3	205.8	207.2	208.7	210.1	211.6	213.1	214.6
Proportion, estimated Metronidazole Rx, elderly pts. (M)	9.8	9.9	9.9	10.0	10.1	10.2	10.2	10.3	10.4	10.4	10.5
Proportion, elderly patients with swallowing issues (M)	*22%*	*22%*	*22%*	*22%*	*22%*	*22%*	*22%*	*22%*	*22%*	*22%*	*22%*
Proportion, elderly patients with swallowing issues (M)	2.2	2.2	2.2	2.2	2.2	2.2	2.3	2.3	2.3	2.3	2.3
Price per treatment, annually (US$)	$30.0	$30.0	$30.0	$30.0	$30.0	$30.0	$30.0	$30.0	$30.0	$30.0	$30.0
Est. value of target medical market (US$M)	$64.7	$65.2	$65.7	$66.1	$66.6	$67.0	$67.5	$68.0	$68.5	$68.9	$69.4
% Market Share	*0.0%*	*0.0%*	*3.0%*	*5.0%*	*7.0%*	*9.0%*	*11.0%*	*13.0%*	*13.5%*	*14.0%*	*14.5%*
Gross revenue, ATI-1501 (US$M)	$0.0	$0.0	$2.0	$3.3	$4.7	$6.0	$7.4	$8.8	$9.2	$9.7	$10.1
Gross revenue, ATI-1501 (C$M)	$0.0	$0.0	$2.6	$4.3	$6.1	$7.8	$9.7	$11.5	$12.0	$12.5	$13.1
Royalty rate on gross sales (%)	*10%*	*10%*	*10%*	*10%*	*10%*	*10%*	*10%*	*10%*	*10%*	*10%*	*10%*
ATI-1501 royalty revenue, US (C$M)	**$0.0**	**$0.0**	**$0.3**	**$0.4**	**$0.6**	**$0.8**	**$1.0**	**$1.1**	**$1.2**	**$1.3**	**$1.3**
ATI-2307											
Current Population, United States (M)	330.3	332.6	335.0	337.3	339.7	342.0	344.4	346.9	349.3	351.7	354.2
Proportion, HIV-1 infection (M)	43.9	44.2	44.5	44.9	45.2	45.5	45.8	46.1	46.5	46.8	47.1
Proportion, low CD-4 count (M)	15.9	16.1	16.2	16.3	16.4	16.5	16.6	16.7	16.9	17.0	17.1
Proportion, estimated cryptococcal infection rate	*0.6%*	*0.6%*	*0.6%*	*0.6%*	*0.6%*	*0.6%*	*0.6%*	*0.6%*	*0.6%*	*0.6%*	*0.6%*
Proportion, specific to cryptococcal meningitis	*5.0%*	*5.0%*	*5.0%*	*5.0%*	*5.0%*	*5.0%*	*5.0%*	*5.0%*	*5.0%*	*5.0%*	*5.0%*
Target Medical Population	4,784	4,818	4,851	4,885	4,920	4,954	4,989	5,024	5,059	5,094	5,130
Price per treatment, annually (US$)	$67,200	$67,200	$67,200	$67,200	$67,200	$67,200	$67,200	$67,200	$67,200	$67,200	$67,200
Est. value of target medical market (US$M)	$321.5	$323.8	$326.0	$328.3	$330.6	$332.9	$335.2	$337.6	$340.0	$342.3	$344.7
% Market Share	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*25.0%*	*40.0%*	*55.0%*	*70.0%*	*70.0%*
Gross revenue, ATI-2307 (US$M)	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$83.8	$135.0	$187.0	$239.6	$241.3
Gross revenue, ATI-2307 (C$M)	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$109.0	$175.5	$243.1	$311.5	$313.7
Royalty rate on gross sales (%)	*25%*	*25%*	*25%*	*25%*	*25%*	*25%*	*25%*	*25%*	*25%*	*25%*	*25%*
ATI-2307 royalty revenue (C$M)	**$0.0**	**$0.0**	**$0.0**	**$0.0**	**$0.0**	**$0.0**	**$27.2**	**$43.9**	**$60.8**	**$77.9**	**$78.4**

Year-end March 31 (C$, exc per share data)	2020A	2021E	2022E	2023E	2024E	2025E	2026E	2027E	2028E	2029E	2030E
Favipiravir - pending deal economics											
Canada											
Current Population, Canada (000)	37,971	38,503	39,042	39,588	40,142	40,704	41,274	41,852	42,438	43,032	43,635
Proportion, tested for COVID-19 (000)	6,767	6,861	6,957	7,055	7,154	7,254	7,355	7,458	7,563	7,669	7,776
Proportion, COVID-19 positive rate (000)	142.1	144.1	146.1	148.2	150.2	152.3	154.5	156.6	158.8	161.0	163.3
Proportion, adj. for female cases, reproductive age (000)	116.5	118.1	119.8	121.4	123.1	124.9	126.6	128.4	130.2	132.0	133.8
Less: Hospitalized cases (indicating severity of condition)	13.9	14.1	14.3	14.5	14.7	14.9	15.1	15.3	15.5	15.7	15.9
Target Medical Population, Mild-to-Moderate COVID-19 (000)	102.6	104.0	105.5	107.0	108.5	110.0	111.5	113.1	114.7	116.3	117.9
Price per treatment, annually (C$)	$500	$500	$500	$500	$500	$500	$500	$500	$500	$500	$500
Est. value of target medical market (C$M)	$51.3	$52.0	$52.8	$53.5	$54.2	$55.0	$55.8	$56.6	$57.3	$58.1	$59.0
% Market Share	*0.0%*	*35.0%*	*25.0%*	*20.0%*	*10.0%*	*2.5%*	*2.5%*	*2.5%*	*2.5%*	*2.5%*	*2.5%*
Gross revenue, Favipiravir (C$M)	$0.0	$18.2	$13.2	$10.7	$5.4	$1.4	$1.4	$1.4	$1.4	$1.5	$1.5
Royalty rate on gross sales (%)	*15.0%*	*15.0%*	*15.0%*	*15.0%*	*15.0%*	*15.0%*	*15.0%*	*15.0%*	*15.0%*	*15.0%*	*15.0%*
Favipiravir, royalty revenue, Canada (C$M)	**$0.0**	**$2.7**	**$2.0**	**$1.6**	**$0.8**	**$0.2**	**$0.2**	**$0.2**	**$0.2**	**$0.2**	**$0.2**
United States											
Current Population, United States (M)	330,321.1	332,633.4	334,961.8	337,306.6	339,667.7	342,045.4	344,439.7	346,850.8	349,278.7	351,723.7	354,185.7
Proportion, tested for COVID-19 (M)	105,140.0	105,876.0	106,617.1	107,363.4	108,115.0	108,871.8	109,633.9	110,401.3	111,174.1	111,952.4	112,736.0
Proportion, COVID-19 positive rate	8,411.2	8,470.1	8,529.4	8,589.1	8,649.2	8,709.7	8,770.7	8,832.1	8,893.9	8,956.2	9,018.9
Proportion, adj. for female cases, reproductive age	6,789.1	6,836.6	6,884.5	6,932.7	6,981.2	7,030.1	7,079.3	7,128.8	7,178.7	7,229.0	7,279.6
Less: Hospitalized cases (indicating severity of condition)	1,217.4	1,226.0	1,234.5	1,243.2	1,251.9	1,260.6	1,269.5	1,278.4	1,287.3	1,296.3	1,305.4
Target Medical Population, Mild-to-Moderate COVID-19 (000)	5,571.6	5,610.7	5,649.9	5,689.5	5,729.3	5,769.4	5,809.8	5,850.5	5,891.4	5,932.7	5,974.2
Price per treatment, annually (US$)	$500.0	$500.0	$500.0	$500.0	$500.0	$500.0	$500.0	$500.0	$500.0	$500.0	$500.0
Est. value of target medical market (US$M)	$2,785.8	$2,805.3	$2,825.0	$2,844.7	$2,864.7	$2,884.7	$2,904.9	$2,925.2	$2,945.7	$2,966.3	$2,987.1
% Market Share	*0.0%*	*0.0%*	*23.0%*	*10.0%*	*9.0%*	*5.0%*	*2.5%*	*2.5%*	*2.5%*	*2.5%*	*2.5%*
Gross revenue, Favipiravir (US$M)	$0.0	$0.0	$649.7	$284.5	$257.8	$144.2	$72.6	$73.1	$73.6	$74.2	$74.7
Gross revenue, Favipiravir (C$M)	$0.0	$0.0	$844.7	$369.8	$335.2	$187.5	$94.4	$95.1	$95.7	$96.4	$97.1
Royalty rate on gross sales (%)	*15.0%*	*15.0%*	*15.0%*	*15.0%*	*15.0%*	*15.0%*	*15.0%*	*15.0%*	*15.0%*	*15.0%*	*15.0%*
Favipiravir gross royalty revenue (C$M)	**$0.0**	**$0.0**	**$126.7**	**$55.5**	**$50.3**	**$28.1**	**$14.2**	**$14.3**	**$14.4**	**$14.5**	**$14.6**
Less: Fujifilm proportion of favipiravir economics	*30%*	*30%*	*30%*	*30%*	*30%*	*30%*	*30%*	*30%*	*30%*	*30%*	*30%*
Favipiravir net royalty revenue (C$M)	**$0.0**	**$0.0**	**$88.7**	**$38.8**	**$35.2**	**$19.7**	**$9.9**	**$10.0**	**$10.1**	**$10.1**	**$10.2**
Total product royalty revenue (C$M)	$0.0	$0.0	$88.9	$39.3	$35.8	$20.5	$38.1	$55.0	$72.0	$89.3	$89.9

Source: Appili Therapeutics, Leede Jones Gable

Exhibit 23. Income Statement & Financial Forecast Data for Appili Therapeutics

Year-end March 31 (C$000, except per share data)	2020A	2021E	2022E	2023E	2024E	2025E	2026E	2027E	2028E	2029E	2030E
Revenue											
Licensed revenue	199	0	0	0	0	0	0	0	0	0	0
Pipeline revenue											
ATI-1501 (metronidazole)	0	0	256	430	606	784	965	1,149	1,201	1,255	1,309
ATI-2307 (anti-fungal)	0	0	0	0	0	0	27,239	43,887	60,767	77,881	78,426
Favipiravir (COVID-19)	0	0	88,690	38,831	35,192	19,688	9,913	9,982	10,052	10,123	10,193
Total revenue	**199**	**0**	**88,946**	**39,260**	**35,798**	**20,472**	**38,117**	**55,018**	**72,021**	**89,258**	**89,928**
Y/Y revenue growth(%)	*NA*	*NA*	*NA*	*44.1%*	*91.2%*	*57.2%*	*186.2%*	*144.3%*	*130.9%*	*123.9%*	*100.8%*
Operating Expenses											
R&D Expense, net of govt assistance	1,391	1,669	1,919	2,015	2,065	2,115	2,167	2,220	2,275	2,330	2,387
G&A expense, net of non-opex	2,796	3,495	3,844	4,036	4,158	4,282	4,411	4,543	4,679	4,820	4,964
Business Development Expense	942	990	1,039	1,091	1,124	1,180	1,239	1,301	1,366	1,434	1,506
Other	0	0	0	0	0	0	0	0	0	0	0
Total operating expenses	**5,129**	**6,153**	**6,803**	**7,143**	**7,346**	**7,577**	**7,817**	**8,064**	**8,320**	**8,584**	**8,858**
EBITDA	**(4,930)**	**(6,153)**	**82,143**	**32,118**	**28,452**	**12,895**	**30,300**	**46,954**	**63,701**	**80,674**	**81,071**
EBITDA margin (%)	*NA*	*NA*	*92.4%*	*81.8%*	*79.5%*	*63.0%*	*79.5%*	*85.3%*	*88.4%*	*90.4%*	*90.2%*
Non-Operating Expenses											
Amort expense, PP&E	18	18	18	18	18	18	18	18	18	18	18
Amort expense, Intangible Assets	0	0	0	0	0	0	0	0	0	0	0
Stock option expense	457	300	300	300	300	300	300	300	300	300	300
Loss (gain) on one-time items	0	0	0	0	0	0	0	0	0	0	0
EBIT	**(5,404)**	**(6,471)**	**81,825**	**31,800**	**28,134**	**12,577**	**29,983**	**46,636**	**63,383**	**80,356**	**80,753**
Adjusted EBIT margin (%)											
Interest expense/accreted interest	12	12	12	12	12	12	12	12	12	12	12
Effective interest rate (%)	*NA*	*NA*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*(0.0%)*	*(0.0%)*	*(0.0%)*	*(0.0%)*
EBT	**(5,416)**	**(6,483)**	**81,813**	**31,788**	**28,122**	**12,565**	**29,970**	**46,624**	**63,371**	**80,344**	**80,741**
Tax expense	0	0	0	0	0	0	0	0	0	0	0
Less: Income Tax Recovery	0	0	0	0	0	0	0	0	0	0	0
Effective tax rate (%)	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*
Net income, fully-taxed	**(5,416)**	**(6,483)**	**81,813**	**31,788**	**28,122**	**12,565**	**29,970**	**46,624**	**63,371**	**80,344**	**80,741**
EPS (basic, fully-taxed)	($0.12)	($0.10)	$1.32	$0.51	$0.46	$0.20	$0.49	$0.75	$1.03	$1.30	$1.31
Adjusted EPS (fd, fully-taxed)	**($0.09)**	**($0.08)**	**$1.00**	**$0.39**	**$0.34**	**$0.15**	**$0.37**	**$0.57**	**$0.77**	**$0.98**	**$0.98**
Shares out (basic, 000)	*46,401*	*61,774*	*61,774*	*61,774*	*61,774*	*61,774*	*61,774*	*61,774*	*61,774*	*61,774*	*61,774*
Shares out (fd, 000)	*58,848*	*82,067*	*82,067*	*82,067*	*82,067*	*82,067*	*82,067*	*82,067*	*82,067*	*82,067*	*82,067*

Source: Appili Therapeutics, Leede Jones Gable

Valuation

As noted above, our valuation is the average of three methodologies: NPV (30% discount rate), and multiples of our 2027 EPS and EBITDA forecasts. In F2027, we forecast EBITDA/EPS of $47.0M/$0.57 respectively. Our EV incorporates Q221 cash of $22.9M and LT debt of $1.0M. The average of the three methodologies yields a price target of $2.69, which we round to $2.75 and the PT of that magnitude implies 175% upside from our forecasts, as we described above.

Appendix I: Failed Antiviral Trials That Reflect Favorably on Favipiravir Competitive Landscape – Abbott's Lopinavir–Ritonavir

Abbott Labs' (ABT-NY, NR) lopinaivir-ritonavir (brand names: Kaletra/Aluvia) is a combination of two protease inhibitors (lopinavir: a human immunodeficiency virus (HIV) type 1 aspartate protease inhibitor) indicated for the treatment of HIV-1 infection (FDA approval since Sep/00). Ritonavir works by inhibiting cytochrome P450, thereby increasing the plasma half-life of the drug.

The choice to use this drug was based on prior testing in other related coronavirus conditions. Beginning in 2003, lopinavir was identified via drug screening as a potential treatment for severe acute respiratory syndrome (SARS). In further testing that took place in 2004 (Chu et al, *Thorax*; 2004 Mar; 59(3): 252–256.), results indicated a potential treatment effect when lopinavir was added to ribavirin, suggesting a significant reduction in adverse outcomes (of which acute respiratory distress syndrome (ARDS) is included in that definition) at 2.4% versus 28.8% in the control arm, although exact efficacy was difficult to pin down. Separately the drug was also tested in Middle East respiratory syndrome coronavirus (MERS-CoV), with preclinical data suggesting efficacy against the virus.

As it relates to its track record in COVID-19, results have not been as positive. A 199-patient randomized, controlled, open-label trial by Cao and colleagues assessed lopinavir-ritonavir against standard care in hospitalized patients with severe SARS-CoV-2 infection and with results published last year in the *New England Journal of Medicine*. The primary endpoint of the trial was time to clinical improvement, defined as an improvement of two points on a seven-category ordinal scale or discharge from the hospital, whichever came first. The trial failed to demonstrate difference from standard care in time to clinical improvement, while also demonstrating similar mortality rates to the standard-care group at 28 days (19.2% vs. 25.0%). In the modified intent-to-treat analysis, treatment with lopinavir-ritonavir led to a median time to clinical improvement by only one day less than standard of care. On safety, gastrointestinal events were more common in the treatment arm although serious adverse events were more common in the standard-care group. 13 patients in the treatment group discontinued treatment due to adverse events, representing a 13.8% treatment discontinuation rate. As such, researchers concluded no benefit using this regimen beyond standard of care.

Likewise, the World Health Organization (WHO) announced that the lopinavir/ritonavir treatment arms from its COVID-19 treatment-focused Solidarity Trial was discontinued as of July 4th 2020 following recommendations from the International Steering Committee. The recommendation to discontinue treatment was based on interim trial results which showed lopinavir/ritonavir had little or no reduction in the mortality of hospitalized COVID-19 patients as compared to standard of care, although no solid evidence of increased mortality was observed.

Appendix II: Sales Prices of Priority Review Vouchers (PRV) as of 2019

PRV Recipient	Voucher Type	Year of Sale	Buyer(s)	Price	Subsequent Use
BioMarin	Rare Pediatric Disease	2014	Sanofi/ Regeneron	US$67.5M	Used to accelerate approval of PCSK9 inhibitor Praluent.
Knight Therapeutics	Tropical Disease	2014	Gilead	US$125M	For the approval of HIV triple-drug combination therapy Odefsey; FDA approval in Mar/16.
United Therapeutics	Rare Pediatric Disease	2015	AbbVie	US$350M	For the accelerated approval of upadacitinib for the treatment of adult patients with moderate to severe rheumatoid arthritis; FDA approval as of Aug/19.
Asklepion Pharma	Rare Pediatric Disease	2015	Sanofi	US$245M	Was redeemed to support the approval of Soliqua, a fixed-ratio combination of basal insulin glargine and the GLP-1 receptor agonist lixisenatide (ann. in Feb/16); FDA approval granted in Nov/16
PaxVax Bermuda	Tropical Disease	2016	Gilead	~US$200M	Unconfirmed sale to Gilead; was used to accelerate approval for Descovy (emtricitabine and tenofovir alafenamide) as a re-exposure prophylaxis (PrEP) to reduce the risk of sexually acquired HIV-1 infection among individuals who are HIV-negative and at risk for HIV. Approval in 2019.
Sarepta Therapeutics	Rare Pediatric Disease	2017	Gilead	US$125M	Used to accelerate approval of Biktarvy (Bictegravir, Emtricitabine, Tenofovir Alafenamide) for treatment of HIV-1 infection.
BioMarin	Rare Pediatric Disease	2017	Undisclosed	US$125M	NA
Ultragenyx	Rare Pediatric Disease	2017	Novartis	US$130M	Voucher was used to accelerate the review of the sphingosine 1-phosphate receptor modulator Mayzent (siponimod) for the treatment of secondary progressive multiple sclerosis (SPMS) in adults. FDA approval in 2019.
Spark Therapeutics	Rare Pediatric Disease	2018	Jazz Therapeutics	US$110M	Voucher was used to speed up review of the oxybate product Xywav/JZP-258 for the treatment of cataplexy and excessive daytime sleepiness (EDS) in adults with narcolepsy. Approval granted in Jul/20.
Ultragenyx	Rare Pediatric Disease	2018	Gilead	US$80.6M	Was used to speed the review of the oral JAK1 inhibitor filgotinib in patients with moderate-to-severe rheumatoid arthritis (RA); CRL issued in Aug/20.
SIGA Technologies	Material Threat Medical Countermeasure	2018	Eli Lilly	US$80M	NA
Medicines Development for Global Health	Tropical Disease	2019	Novo Nordisk	NA	Was used for the review of oral semaglutide, approved in Sep/19.
GW Pharma	Rare Pediatric Disease	2019	Biohaven Pharmaceutical	US$105M	Biohaven intends to employ the voucher towards the calcitonin gene-related peptide (CGRP) receptor antagonist Rimegepant Zydis.
Sobi and Novimmune	Rare Pediatric Disease	2019	AstraZeneca	US$95M	Plans have yet to be disclosed.
Bavarian Nordic	Material Threat	2019	Undisclosed	US$95M	NA
Sarepta Pharmaceuticals	Rare Pediatric Disease	2020	Vifor Pharma	US$100M	Firm intends to use the voucher for the approval of the oral hypoxia-inducible factor prolyl hydroxylase inhibitor vadadustat, aimed as a treatment for anemia due to chronic kidney disease.
Lumos Pharma (formerly NewLink Genetics)	Material Threat	2020	Merck	US$60M	Voucher was originally valued at US$100M, but was sold based on % ownership (60%); Merck was a co-partner with Lumos for the development of the Ebola vaccine

Source: Regulatory Focus, "Regulatory Explainer: Everything You Need to Know About FDA's Priority Review Vouchers", February 2020

Disclosures none

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Speculative Buy	8	53.3%
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Sell	-	-
Tender	-	-
Under Review	-	-