EQUITY RESEARCH INITIATION

RBC Capital Markets

RBC Capital Markets, LLC
Adnan Butt (Analyst)
(415) 633-8588
adnan.butt@rbccm.com

John Chung (Associate)
(415) 633-8620
john.chung@rbccm.com

May 29, 2014

SCYNEXIS Inc.

Targeting systemic fungal infections with a novel mechanism of action

Our view: Initiating coverage with Outperform, Speculative Risk and a $17 price target. Scynexis is targeting systemic fungal infections where patient mortality is high and resistance growing with SCY-078. Given SCY-078's novel mechanism, efficacy, safety and convenience, we believe it could see broad use. Phase I/II results in 2015, FDA sign off on QIDP and pivotal plans, and Phase II/III data in 2017 could all rapidly enhance value.

Key points:

New mechanism of action against a validated target. SCY-078 attacks the fungal cell wall, a target validated by the echinocandins, but has activity against echinocandin resistant organisms, which demonstrates its unique mechanism of action.

Prior Phase Is and preclinical data lower clinical risk. SCY-078 demonstrated potent killing activity in in vitro models of wild-type Candida and Aspergillus and in organisms with resistance against azoles and echinocandins, the leading anti-fungal drug classes. Phase I safety data also appears clean. In vitro and in vivo data is important and animal models meaningful in demonstrating potential effectiveness in human patients.

SCY-078 addresses the limitations of current drugs. Since SCY-078 shows potential activity against organisms resistant to currently available drugs, has a wider therapeutic window, and a convenient intravenous-to-oral switch for step down therapy, it addresses nearly all the limitations of the current drug classes.

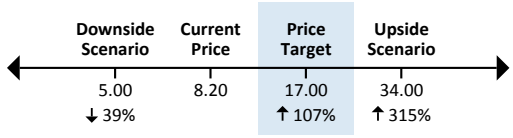
Market is attractive and resistance is increasing. Globally there are roughly 600,000 confirmed cases of invasive fungal infections. However, many more patients are treated given the heavy reliance on empiric therapy. Overall market dynamics are favorable as the rates of resistance are increasing as is the patient population where risk factors increase vulnerability to systemic fungal infections. We forecast peak sales of SCY-078 could be ~$1B+ worldwide.

Limited competition on the horizon. There are few companies targeting systemic anti-fungal infections despite the FDA's cooperative stance on advancing anti-fungal drugs with the GAIN Act for serious, life threatening infections where resistance is increasing or need is high.

Wholly owned rights in all major markets and long patent life. The composition of matter patent on SCY-078 expires in 2030 with potential for additional term extension.

Upside is news flow driven. Oral Phase II and intravenous Phase I data for SCY-078 is expected in 2015, as are plans for a potentially pivotal Phase II/III study, which could start in 2016 and readout by YE:17/early 2018.

Outperform
Speculative Risk
NASDAQ: SCYX; USD 8.20
Price Target USD 17.00
Scenario Analysis*



*Implied Total Returns

Key Statistics

Shares O/S (MM):	9.7	Market Cap (MM):	80
Dividend:	0.00	Yield:	0.0%

RBC Estimates

FY Dec	2013A	2014E	2015E
Revenue	16.9	17.0	17.1
EPS, Ops Diluted	(6.84)	(1.69)	(2.05)
P/E	NM	NM	NM

Revenue	Q1	Q2	Q3	Q4
2014	4.3E	4.3E	4.3E	4.3E
2015	4.3E	4.3E	4.3E	4.3E
EPS, Ops Diluted				
2014	(0.48)E	(0.37)E	(0.42)E	(0.44)E
2015	(0.47)E	(0.49)E	(0.51)E	(0.58)E

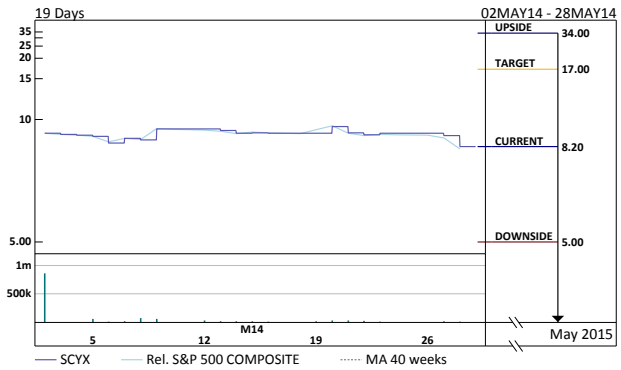
EPS, Ops Diluted: Basic shares used when EPS are negative.
All values in USD unless otherwise noted.

Priced as of prior trading day's market close, EST (unless otherwise noted).

For Required Conflicts Disclosures, see Page 43

Target/Upside/Downside Scenarios

Exhibit 1: SCYNEXIS Inc.



Source: Bloomberg and RBC Capital Markets estimates for Upside/Downside/Target

Target price/ base case

We value SCYX at $17 per share, which includes US and ROW sales of SCY-078. We assign a probability of success of 60% and a value of ~$10 per share to the US and $7 per share to the ROW opportunity. We assume a US launch in 2019 and an ROW launch in 2020. Currently, we assume that SCYX will sell SCY-078 in the US and a partner will commercialize these compounds outside the US. We forecast peak SCY-078 sales of $300-400MM in the US and $1.0-1.4B in the ROW.

Upside scenario

Our upside scenario includes ~$18 per share in value for the US opportunity and ~$16 per share in value for the ROW opportunity. We forecast peak SCY-078 sales of $600-700MM in the US and $1.7B-$2B in the ROW. We assign SCY-078 a 60% probability of success, a discount rate of 15%, and use a terminal growth rate of -50%.

Downside scenario

Our downside scenario assumes that SCY-078 may not be successful clinically or commercially either because efficacy against resistant organisms was not borne out or it was not long lasting or an unexpected adverse event was seen. Under such a scenario shares would trade at roughly cash per share which is currently ~$5.

Investment summary

Scynexis' (SCYX) SCY-078 treats systemic fungal infections via a new mechanism of action that attacks the fungal cell wall, a validated target. These infections are serious, have high rates of mortality, and rates of resistance to current drugs are rising. All currently available drugs have limitations, which allow SCY-078 to generate an attractive value proposition. The worldwide market for systemic anti-fungals is nearly $4B. Roughly 600,000 patients are identified with invasive fungal infections and an even higher number is treated. Phase I studies are completed for the oral version and in vitro and in vivo data shows activity in organisms both susceptible and resistant to currently approved drugs. Next up is a Phase II for the oral and a Phase I for the intravenous form with data in 2015. A Phase II/III study in resistant patients could start in 2016 and potentially provide a more rapid path to the market. SCYX essentially owns all rights to SCY-078, which is patent protected through 2030, as well as to its anti-fungal pipeline. This leaves SCYX free to commercialize the products itself, partner on a global or regional basis, and/or sell the company.

Potential catalysts for SCYX shares

- **Phase II data for oral SCY-078 in 2015.** Important catalyst as this will be the first time SCY-078 will be used in human patients.
- **Phase I data for intravenous SCY-078 in 2015.** Important as an intravenous does not yet exist and is needed to maximize the value of SCY-078 franchise.
- **Phase II/III trial design in 2015/2016.** A sign off from the FDA could determine the pace and potential path to the market.
- **Phase II/III trial start in 2016 and data by YE:17/ early 2018.** A Phase II/III study in drug resistant patients could be the first proof that SCY-078 can achieve in patients what it is designed to do and has shown in in vitro and in vivo models.
- **Business development activities in 2014/2015.** Non-core pipeline assets and even SCY-078 could be partnered opportunistically raising non-dilutive capital.

Risks to our investment thesis

- **Clinical studies for oral and intravenous SCY-078 could fail**. Expectations are based on pre-clinical and Phase I data and human studies could show a lack of efficacy or emergence of resistance.
- **Merck returned rights for SCY-078 back to SCYX**. This raises the question of whether MRK saw anything in SCY-078's clinical or commercial profile that was lacking.
- **Sales ramp of SCY-078 could lag expectations** unless rates of resistance continue to rise.
- **SCYX could fail to find a partner** outside the US for SCY-078.
- **Timelines are rapid and any delays could disappoint investors**.

Key questions for Scynexis

		Our view
1.	**Why did Merck return SCY-078 (previously called MK-3118) to SCYX**?	Merck (MRK) conducted a thorough pre-clinical in vitro and in vivo program as well as seven Phase I studies prior to returning all rights to SCYX. Since the rights were returned in 2013, when MRK was in the process of re-prioritizing its R&D pipeline and commercialization objectives, we believe the decision was based more on internal criteria and commitments to a disease areas rather than on SCY-078. MRK is still eligible to receive milestone payments upon progress as well as royalties on sales of SCY-078.
2.	**What evidence is there that SCY-078 could work in patients with systemic fungal infections?**	In addition to generating in vitro data in organisms both responsive to and with resistance to currently available drugs, SCY-078 has also been tested in vivo, i.e., in animal models of systemic fungal infections that have historically been very predictive of clinical success. Finally, although SCY-078 possesses a novel mechanism of action its target is similar to that of the echinocandin class of drugs which gives further validation to the therapeutic target for SCY-078.
3.	**What evidence is there that SCY-078 could work in resistant organisms?**	Several in vitro studies in organisms with resistance against Candida or Aspergillus show that SCY-078 has efficacy against them. This is very similar to the development of antibiotics for serious infections where efficacy is initially proven in the test tube before being evaluated in patients with disease. The main goal there is to demonstrate safety and durability as the efficacy and potency has already been seen in vitro.
4.	**Are there any concerns regarding the development of an intravenous form of SCY-078?**	An oral form of SCY-078 is available. The development of an intravenous form for SCY-078 has not been pursued before either by SCYX or MRK. While it appears that an intravenous dosage form should be feasible, data will not be available until 2015. Historically, the challenge for companies has been to turn an intravenous into an oral and not the other way around so we believe the technical hurdle is lower.
5.	**Is there a role for SCY-078 in a market that could be dominated by generics**?	The key initial value proposition for SCY-078 is its ability to work in patients where current drugs are not succeeding, i.e., organisms have developed resistance to them. In such a scenario, SCY-078 will retain its importance as a therapeutic alternative based on efficacy to the azole and echinocandin classes of drugs and on safety to the azole and polyenes. SCY-078 also presents a convenient step-down therapy option from the echinocandin class, which is something lacking with the echinocandin class as they are only available in intravenous forms.
6.	**How sufficient is news flow near-term to create value?**	SCYX could report on a Phase II study showing a switch from an intravenous anti-fungal to oral SCY-078 in 2015. The Phase I trial of intravenous SCY-078 should also read out in 2015. These are important events as they could show that the SCY-078 value proposition, availability of a convenient oral form and feasibility of an intravenous to maximize the opportunity, is intact and progressing. Furthermore, SCYX could announce plans for and initiate a Phase II/III study in patients with resistant infections to currently marketed anti-fungals in 2016, which will be important as it could potentially represent a faster path to market assuming FDA 's sign off.

Table of contents

Portfolio manager's summary

Scynexis (SCYX) SCY-078 treats systemic fungal infections via a new mechanism of action that attacks the fungal cell wall, a validated target. These infections are serious, have high rates of mortality associated with them, and rates of resistance to currently available drugs are rising. All currently available drugs have their limitations, which is for a weakness SCY-078 has been designed to address. SCYX estimates that the worldwide market for systemic anti-fungals is nearly $4B. Approximately 600,000 patients are identified with invasive fungal infections and an even higher number is treated annually. Phase I studies are completed for the oral version and in vitro and in vivo data shows activity in organisms both susceptible and resistant to currently approved drugs. Next up is a Phase II for the oral and a Phase I for the intravenous forms with data in 2015. A Phase II/III study in resistant patients could start in 2016 and potentially provide a more rapid path to the market especially if it shows efficacy in drug resistant patients. SCYX essentially owns all rights to SCY-078, which is patent protected through 2030, as well as to its anti-fungal portfolio. This leaves SCYX free to commercialize the products itself, partner on a global or regional basis, and/or sell the company.

Key selling points

New mechanism of action against a validated target. SCY-078 targets the biosynthesis of fungal cell walls by inhibiting a glucan synthase enzyme, the same enzyme targeted by the echinocandin class of drugs. However, SCY-078 is an enfumafungin derivative and works independently of how the echinocandins exert their influence. This is evident from its activity in echinocandin resistant strains of fungi. A new mechanism of action is almost always welcomed into the anti-infectious armamentarium as a therapeutic alternative or a replacement for the standard of care, especially if it is accompanied by safety, efficacy and convenience.

Previously conducted Phase Is and preclinical data lowers clinical and development risk. SCY-078 has demonstrated potent killing activity in in vitro models of wild-type Candida and Aspergillus, two clinically relevant fungi. Importantly, it has also demonstrated strong activity in organisms that had developed resistance to azoles and echinocandins, the leading classes of anti-fungal drugs. The drug has been dosed in over 100 healthy volunteers and to date has a clean safety profile. Together these attributes lower clinical development risk for SCY-078.

In vitro activity against drug resistant organisms. The prevalence of drug resistant organisms, both against the azole class of drugs and even for the echinocandins, which are newer is increasing and likely to continue to rise. Patent expirations for many of these branded drugs is likely to accelerate this trend as is the increasing number of immune compromised patients. SCY-078 has demonstrated potent killing power against drug resistant fungi making it a potentially important new addition to the therapeutic paradigm.

Convenient i.v. to oral switch would be good for patients and the healthcare system. A key limitation of the echinocandin class of drugs is the lack of an oral dosage form. SCY-078 is available orally and could be used for patients on echinocandins as a step-down therapy. Furthermore, SCYX is developing an intravenous form of SCY-078. This would allow physicians to transition patients to an oral from the i.v. form. Right now the only option is a switch to oral azoles, which risks the reemergence of disease. The availability of an i.v. and oral form of SCY-078 could also result in cost savings to the overall system with sooner patient discharges.

FDA has designated SCY-078 a qualified infectious disease product (QIDP). Anti-fungal agents, similar to the FDA's cooperative approach towards the development of antibiotics, can be deemed a QIDP, which signifies several positive developments including a potentially

serious infectious disease, an important, possibly unmet clinical need, and benefits such as greater interaction with the FDA, accelerated review times and longer exclusivity periods. The oral form of SCY-078 already has this designation and the intravenous form is likely to receive the same once SCYX applies for it.

Clinical development path could be rapid. SCYX could initially target patients with drug resistant Candida or Aspergillus in a potentially pivotal Phase II/III study. Should it receive FDA sign off on such a strategy, SCY-078 development is likely to be more rapid as patients who have developed resistance to the two drug classes of azoles and echinocandins may not have any good therapeutic alternatives available to them.

Market is attractive and SCY-078 could become a first-line therapy. Globally there are roughly 400,000 confirmed cases of invasive Candida infections and another 200,000 confirmed cases of Aspergillus. Likely more patients receive empiric therapy without a confirmation of their infection. SCYX estimates the annual market for systemic anti-fungals to be ~$3.6B. Invasive fungal infections have significant morbidity and mortality associated with and tailwinds include increasing rates of resistance to available drugs and an increase in vulnerable, at-risk patient populations. SCY-078, which has been shown to work against resistant organisms, could see initial use in the treatment failure setting and then be accepted as a first-line agent given its safe, potent and convenient i.v. to oral switch profile, which addresses all the limitations of existing anti-fungal drugs.

Limited competition on the horizon. The number of companies targeting systemic anti-fungal infections is few compared to the relatively larger number of companies developing antibiotics, with which anti-fungals share similar clinical, regulatory and commercial hurdles and opportunities. Successful development of an anti-fungal drug with a new mechanism of action, which works against resistant organisms and faces little to no competitor development programs, would make it a more valuable asset.

Wholly owned rights in all major markets and long patent life. The composition of matter patent on SCY-078 will expire in 2030 and there is potential for additional term extension. SCYX owns essentially worldwide rights to SCY-078 except for Russia and select regions in Asia, Europe and Africa that have been out licensed to R-Pharm.

Meaningful news flow starting 2015 and through 2017. Oral SCY-078 will be evaluated in an i.v. to oral step down Phase II trial and intravenous SCY-078 will be entering a Phase I study. Results from both are expected in 2015 and will produce the first efficacy and feasibility data for both. Plans for potentially pivotal Phase II/III studies or a Phase II study in drug-resistant patients are expected in 2015/ 2016 with the trial starting in 2016. This trial could have data by the end of 2017. Finally, Phase III trials in a broader patient population could begin in 2016 as well. Assuming FDA's sign off on clinical trials plans and positive results, there is a chance for investigating a more rapid path to an NDA based on studies starting in 2016/2017 with approval potentially around 2018/2019 under the most optimistic scenario.

Anti-infective seasoned management team and advisors. SCYX's Chief Executive and Chief Medical officers as well as senior advisors all have significant experience developing drugs for various infectious diseases, including systemic fungal infections. SCYX's CMO was previously responsible for Merck's anti-bacterial, anti-fungal and vaccine development programs, including the clinical development of Cancidas, the leading anti-fungal from the echinocandin class of drugs.

Risk factors

Merck returned rights for SCY-078 back to SCYX. SCY-078 was discovered by SCYX in a collaboration with MRK that has an important presence in the anti-fungal space. However, MRK returned all rights back to SCY-078 and retained milestones and royalties in return. This raises the question of whether MRK saw anything in SCY-078's clinical or commercial profile that was questionable or whether the decision was a part of Merck's internal pipeline prioritizations.

Limited data set available at this time. Oral SCY-078 has been thoroughly tested in pre-clinical and Phase I studies. The data set is also limited because intravenous SCY-078 has yet to enter the clinic and oral SCY-078 has not been tested in patients suffering from invasive fungal infections to date.

Clinical studies for oral and intravenous SCY-078 could fail. SCY-078 is SCYX's primary value driver and the Phase I intravenous and Phase II oral study are planned based largely on pre-clinical data. However, Phase I safety data is available. This raises the risk that the intravenous form may not be able to reliably deliver therapeutic quantities of SCY-078 or that the oral form prove ineffective in human patients.

Development of intravenous SCY-078 could be delayed or suffer setbacks. The ideal anti-fungal drug would be available in both oral and intravenous forms so patients can transition from the intravenous to the oral. While SCY-078 is available in the oral form for trials, the intravenous form is still underdevelopment. Should the intravenous form suffer from development delays or fail in the clinic, SCYX would not be able to optimize the value of its anti-fungal franchise.

Anti-fungal market is seeing and will continue to see entry of generics. A number of drugs from the azole class have already become genericized and other drugs and drug classes will also lose exclusivity protection as patents expire. This could mean that SCYX cannot compete on price and must differentiate SCY-078 on efficacy, safety and/or convenience.

Sales ramp of SCY-078 could lag expectations. We assume SCY-078 will see usage because of increasing rates of resistance and physicians could be attracted to using a safe, effective and convenient alternative with a new mechanism of action, especially in patients failing current therapy. However, a new mechanism of action could also lead to more cautious uptake initially inside and outside the US. Furthermore, the availability of cheaper generic drugs could blunt adoption in the first-line setting.

SCYX must find a partner outside the US and commercialize itself in the US. Most companies competing in the anti-fungal space are far larger in size and could have greater financial capabilities than SCYX. SCYX must also find a partner to commercialize SCY-078 outside the US in major regions such as Western Europe, South American and large portions of Asia. A timing of such a deal and financial terms are indeterminate at this time.

Timelines are rapid and delays could disappoint investors. SCYX will initiate a Phase II study for oral SCY-078 by year end 2014 and a Phase I study of intravenous SCY-078 in 2015. Assuming success and FDA sign off a Phase II/III study in patients with resistant disease could begin in 2016 along with a standard Phase III study in systemic fungal infections. SCYX could also undertake opportunistic business development by partnering non-core pipeline assets and even SCY-078 regionally or globally. Maintaining this pace and schedule requires flawless execution, cooperation from the FDA, and positive clinical data and any delay could disappoint investors and increase caution regarding execution.

Limited trading volumes. SCYX is a recent IPO. Therefore, trading volumes are low which means liquidity and the ability to enter or exit an investment on a timely basis and favorable terms could be risky.

Exhibit 2: Forecast news flow

Timing	Expected News Flow	Program
4Q:14/ YE:14	Initiate Phase II with oral SCY-078	SCY-078
Late 2014/ early 2015	Request QIDP designation for i.v. SCY-078	SCY-078
2014/2015	Potential pipeline related business development	
Early 2015	Initiate Phase I study with i.v. SCY-078	SCY-078
Mid-/2H:15	Phase I intravenous SCY-078 results	SCY-078
YE:15	Phase II results from oral SCY-078 step down study	SCY-078
2016	Initiate Phase II/III i.v. to oral SCY-078 in relapsed/ refractory patients	SCY-078
YE:2016/ early 2017	Initiate Phase III study for i.v. to oral SCY-078 in 1st line patients	SCY-078
Late 2017/ early 2018	Phase II/III i.v. to oral data	SCY-078
2018	Potential NDA for SCY-078	SCY-078
YE:18/ 2019	Potential accelerated approval	SCY-078

Source: Company reports and RBC Capital Markets estimates

Exhibit 3: Pipeline

Product	Mechanism	Stage	Indication
SCY-078	1,3 beta – glucan synthesis inhibitor	Phase II anticipated with oral; Phase I with intravenous anticipated	Invasive fungal infections caused by Candida and Aspergillus species
SCY-635	Cyclophilin inhibitor	Phase IIa	Hepatitis C Virus (HCV)
SCYX-7158	Anti-parasitic	Phase I	Human African Trypanosomiasis (Sleeping sickness)
SCY-641	Cyclophilin inhibitor	Pre-Clinical	Dry Eye disease

Source: Company reports

Recently completed initial public offering

Scynexis, Inc. (SCYX) completed its US initial public offering (IPO) on May 2, 2014. The company raised approximately $62MM (gross) at a price of $10 per share with 6.2MM shares offered. The overallotment was 930,000 shares, which at $10 per share would result in gross proceeds of $9.3MM. The company ended December 2013 with approximately $1.4MM in cash. Therefore, pro forma net cash balance after the IPO is roughly $40-45MM without the overallotment being exercised and $50-55MM with it. SCYX raised capital to fund clinical trials for the oral and intravenous forms of SCY-078 and to pay down the outstanding loan of $15MM. Estimates for clinical development costs are roughly $30MM for clinical and pre-clinical costs associated with the completion of Phase II studies and the initiation of a Phase III trial for SCY-078.

Invasive fungal infections: Serious, potentially lethal and with increasing resistance

Invasive fungal infections have high morbidity and mortality

Systemic fungal infections have high rates of morbidity and mortality despite treatment. Resistance to currently available drugs is on the rise requiring the development of a convenient, safe and effective anti-fungal with a new mechanism of action.

Invasive or systemic fungal infections (IFIs) are a heterogeneous group of infections caused by different species of fungi that mainly affect individuals whose immune function is compromised. These infections have been on the rise over the last few decades because of the wider use of new medical techniques as well as an increase in the number of susceptible patients whose immune system is weakened. These include patients with serious infections, AIDS, and other causes of immunosuppression such as solid organ and bone marrow transplantation, cancer and autoimmune diseases, and the use of drugs that generally reduce the competence of the immune system. In addition, being neutropenic, having had abdominal surgery, being in the intensive care unit, receiving parenteral nutrition, or the presence of a central line and use of invasive devices in the hospital are all risk factors for IFIs as well.

A survey of 25 US hospitals shows the seriousness of systemic fungal infections. In patients with systemic fungal infections, the 12-week survival rate ranged from 37.5% for hematopoietic stem cell transplant recipients to ~75.0% for those with HIV/AIDS. Invasive fungal infections are a problem that has been increasing over the last 20-30 years and will continue to gain momentum especially with the emergence of resistant strains of various fungi.

Many more systemic fungal infection patients are treated than diagnosed because treatment delays increase mortality.

Nearly 85% of all invasive fungal infections in the US and EU are caused by Candida and Aspergillus. The number of confirmed cases of invasive Candida worldwide is 400,000 and that of invasive Aspergillus is 200,000. However, many more patients are treated empirically since the rates of mortality can be so high in patients with systemic fungal infections. An improper diagnosis or a treatment delay raises mortality significantly. SCYX estimates that confirmed cases of Candida blood infections account for only 25-33% of all Candida treatments.

Exhibit 4: Estimated incidence of serious fungal infections

Body location	Pathogen type	Organ	Most frequent genus	Est. incidence of infection
Superficial	Primary	Skin and hair	Malassezia Trichophyton	~140,000,000 cases/year
Cutaneous	Primary	Skin and nails	Epiderophyton Microsporum	~1,500,000,000 cases/year
Mucosal	Opportunistic	Vagina, digestive tract, urinary tract, and eye	Candida Aspergillus, Fusarium	~75,000,000 cases/year ~9,500,000 cases/year ~1,000,000 cases/year
Systemic	Opportunistic	Any organ	Candida Aspergillus Cryptococcus Histoplasma Pneumocystis Coccidioidomyces	~300,000 cases/year ~350,000 cases/year ~1,000,000 cases/year ~500,000 cases/year >200,000 cases/year up to 300,000 cases year

Source: Int J Microbiol. 2012;2012:713687. doi: 10.1155/2012/713687.

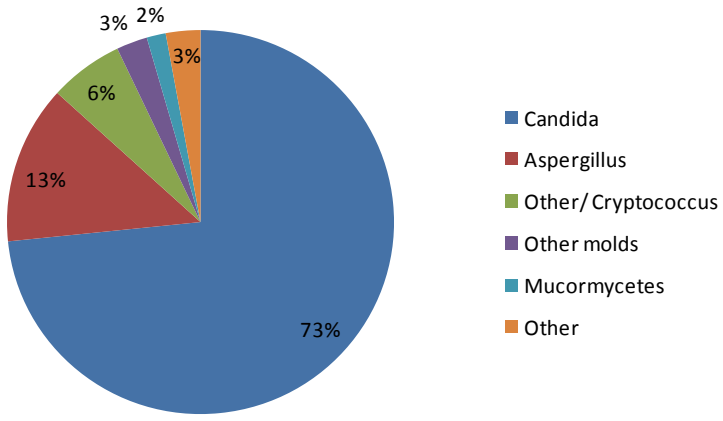
Common fungal infections: Candida and Aspergillus are the focus

Invasive fungal infections can affect all types of tissue from the blood to the brain.

There are several different species of fungi; however, not all cause invasive fungal infections. Candidiasis, aspergillosis and cryptococcosis are some of the most common systemic fungal infections that are caused by Candida, Aspergillus and Cryptococcus, respectively. If any of these fungi enter the bloodstream, they can attack internal organs, lead to serious infection, and cause death, especially in immune compromised patients. Candida spp. are the most common pathogen (73.4%) followed by Aspergillus spp. (13.3%) and then other yeasts (6.2%). However, the presence or absence of different fungi is usually region and hospital specific.

Support for the need for new agents comes from the fact that even successful treatment can shift the balance of organisms present. For example, there has been a shift in the distribution of Candida spp. from Candida albicans to non-albicans Candida spp. This has been observed in various parts of the hospital, including the ICU and oncology units of the last 20 years.

Exhibit 5: Distribution of organisms causing fungal infections



Source: ARTEMIS DISK global anti-fungal surveillance project.

Candida is a fungus that lives within the human body but under certain circumstances starts multiplying and affecting organs. While candidemia (bloodstream infection with Candida) is extremely rare in individuals without risk factors, it is the fourth most common bloodstream infection among hospitalized patients in the US and can result in high mortality (~40%), prolonged hospital stays (~1 month longer), and increased costs (~$40-50,000 more). Invasive candidiasis necessitates treatment with intravenous and oral anti-fungal mediation for several weeks. The overall mortality rate of invasive candidiasis remains over 30% despite the availability of drugs to treat it.

Exhibit 6: Length of stay and costs with Candidemia

Variable	Early Evidence of Candidemia			Late Evidence of Candidemia*		
	C glabrata (n = 45)	*C albicans* (n = 80)	*P*†	*C glabrata* (n = 186)	*C albicans* (n = 289)	*P*†
Length of stay, d			.05			.31
No.	44	80		185	285	
Mean (SD)	19.7 (19.0)	14.5 (13.3)		21.9 (21.8)	20.0 (23.8)	
Median (IQR)	13.5 (8.5–25.0)	11.5 (6.0–19.0)		17.0 (7.0–29.0)	12.0 (6.0–24.0)	
Costs, $			.04			.09
No.	25	30		76	96	
Mean (SD)	56,026 (56,186)	32,810 (34,947)		67793 (80421)	52112 (74044)	
Median (IQR)	31,782 (17325–88586)	20501 (8252–39252)		39865 (19629–93429)	25324 (10567–64323)	
Mortality, No. (%)			.96			.36
No.	45	80		186	289	
Deaths, No. (%)	15 (33.3)	27 (33.8)		89 (47.8)	126 (43.6)	

Abbreviation: IQR, interquartile range.

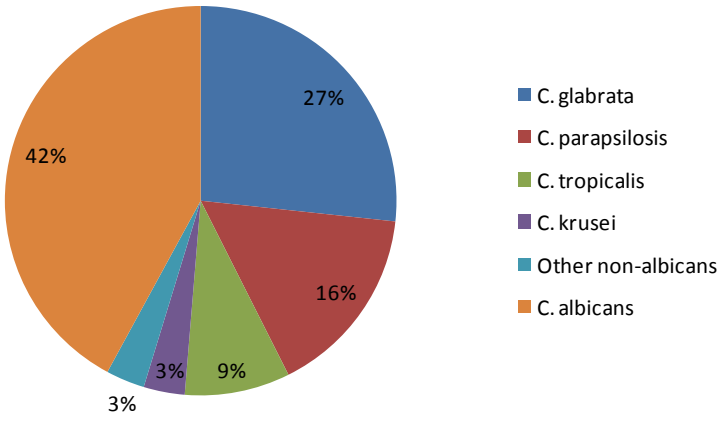
*Greater than 2 days from admission.

†Reported *P* values are 2-tailed.

Source: Moran C, Grussemeyer CA, Spalding J, et al. (2010).

According to ARTEMIS DISK global anti-fungal surveillance project (N=197,000), 90% of invasive candidiasis between 1997 and 2005 were caused by four species, *C albicans, Candida glabrata, C parapsilosis*, and *Candida tropicalis*. *C. albicans* (~50%) is commonly associated with nosocomial transmission among patients in burn units and geriatric short-stay units. *C. glabrata* (~20%) is the second most common cause of candidemia after *C. albicans* and can easily develop acquired resistance, especially in patients who have received prior fluconazole prophylaxis or treatment. It is frequently isolated from older patients, patients with cancer and prior exposure to fluconazole, and patients treated with Zosyn (piperacillin/tazobactam) or vancomycin. *C. tropicalis* (~10%) is commonly seen in patients with hematologic malignancies with mucositis and neutropenia. *C. parapsilosis* (~10%) can colonize skin, leading to nosocomial spread by hand carriage *C. krusei* is the fifth most common candida species, isolated and accounted for ~3% of invasive candidiasis. *C. krusei* is intrinsically resistant to fluconazole. It is often found in patients with hematologic malignancies and HSCT recipients with prior fluconazole and anti-fungal exposure. *C. krusei* is associated with the highest mortality of all candida species.

Exhibit 7: Distribution of Candida subtypes



Source: ARTEMIS DISK global anti-fungal surveillance project.

Aspergillus is another serious fungus that can affect the sinuses or lungs. Invasive aspergillosis occurs when this fungi invades the lungs and spreads from there to other organs, such as the brain or bones, via the blood. Aspergillus can be inhaled through soil or house dust. Invasive aspergillosis most commonly affects the lungs but can spread throughout the body. Invasive aspergillosis has emerged as an important cause of nosocomial and community acquired infection in immunocompromised patients, such as those receiving chemotherapy, transplants or with advanced infection. The overall mortality rate of invasive aspergillosis approaches 90% in the most immunocompromised patient populations despite treatment.

Cryptococcosis is another serious fungal infection that is caused by inhaling a fungus called Cryptococcus, which is found primarily in soil. This fungus can cause inflammation of the meninges and lungs.

Diagnosis is difficult so empiric therapy is common place

Timely diagnosis is important as delays can cause death. This generally means empiric therapy is common place.

Timely diagnosis of systemic or invasive fungal infections remains a challenge despite the introduction of new techniques. This matters because delayed initiation of anti-fungal therapy is associated with increased mortality. The first step in diagnosing invasive fungal infections are a blood test, culture, urinalysis, X-rays and even examination of cerebrospinal fluid. While treatment varies depending on the internal organ affected and the type of organism causing the infection often it is empirical as the rate of mortality goes up significantly even with a modest delay.

Four drug classes targeting systemic fungal infections

The types of drugs targeting systemic fungal infections can be broken up into four drug classes: polyenes, azoles/ triazoles, echinocandins, and flucytosine. No one drug class is perfect and each drug class has its own set of advantages and limitations. Most patients with invasive candidiasis were treated with fluconazole (48.3%) and the echinocandins (34.0%), while voriconazole (45.5%) was the main anti-fungal agent for invasive aspergillosis.

Guidelines are adapting to reflect new infection and resistance realities. The 2012 ESCMID guidelines for candidemia and invasive candidiasis changed to prioritize echinocandins as the first line of therapy while moving fluconazole to third-line. While the IDSA guidelines are not yet out, they are expected to follow ESCMID for candidemia and invasive candidiasis.

The azole class is available as an intravenous and an oral. However, resistance to azoles is going up. Echinocandins are only available in an intravenous form.

Azoles/Triazoles. Azoles achieve fungistatic activity by inhibiting cytochrome P450 dependent synthesis of ergosterol, a fungal cell membrane component. They are the most frequently used class of drugs for invasive fungal infections and are available in both intravenous and oral forms. Fluconazole, itraconazole, and voriconazole have similar activity against most candida species; however, azoles are not effective against *C. glabrata* and *C. krusei.* Triazoles also see widespread empiric use, i.e., they are used extensively for prevention and for unconfirmed cases of systemic fungal infection. The risks with azoles are drug-drug interactions and liver damage. CYP3A4 is an important liver enzyme that oxidizes foreign molecules, including toxins and drugs, and since azoles are both substrates and inhibitors of CYP3A4, their use can lead to higher concentrations of a number of drugs that would typically be metabolized by CYP3A4.

Fluconazole (oral and IV) has comparable efficacy to amphotericin B and its oral bioavailability is 90% of intravenous administration. Fluconazole is the treatment of choice in CNS and intraocular candidiasis. Voriconazole (oral and IV) is effective for both mucosal and invasive candidiasis and is typically used for step-down oral therapy for *C. krusei* and fluconazole-resistant, voriconazole-susceptible *C. glabrata.* Itraconazole (oral) is rarely used for invasive candidiasis due to lack of evidence. It is generally reserved for patients with mucosal candidiasis after fluconazole.

Recently, azole-resistant infections, especially with species such as Candida glabrata, are becoming more prevalent. Cross-resistance also exists in that once an azole has been tried and failed, another azole may not be effective.

Echinocandins are available only in the intravenous form. This means either patients must step down to an azole or stay in the hospital longer to receive infusions.

Echinocandins. Echinocandins are fungicidal and block fungal cell wall synthesis by inhibiting a glucan synthase enzyme. However, caspofungin, anidulafungin, and micafungin are available only in intravenous form. Since their mechanism of action is different from the azole class, echinocandins can work against azole resistant infections. Hence, use is increasing in invasive Candida infections. They also do not require dose adjustments nor have a lot of drug-drug interactions which make them easier to administer, especially in patients with renal insufficiency or who are on dialysis.

Typically, to discharge patients from the hospital as safely and quickly as possible the preferred practice is to transition eligible patients from an intravenous anti-fungal to an oral one. Without the availability of an oral echinocandin, physicians are forced to choose between switching to oral azoles as step down therapy and thereby risk re-emergence of an infection or keeping the patient on an IV therapy, which may require continued hospitalization.

Caspofungin, a novel echinocandin compound, has been approved for the treatment of esophageal and suspected invasive candidiasis and as salvage therapy for invasive aspergillosis.

The polyenes class are reserved as a drug of last resort or for rare fungi due to side effects.

Polyenes. Polyenes work by disrupting the fungal cell membrane by binding to ergosterol, the sterol component of the cell wall membrane. Once bound it forms transmembrane channels and alters cell permeability by facilitating monovalent ions (NA+, K+, H+, and Cl-) to leak out of the cell resulting in cell death. They are used to treat a wide variety of fungi, including rare and difficult-to-treat species. However, side effects include acute, potentially fatal kidney and heart injury, which typically makes them the drug of last resort, especially for treating invasive Candida and Aspergillus infections. Acute renal failure can occur in up to 50% of patients.

Flucytosine. Flucytosine has broad anti-fungal activity against most *Candida* species, except *C. krusei.* Flucytosine is taken up by fungal organisms via cytosine permease. Inside the cell,

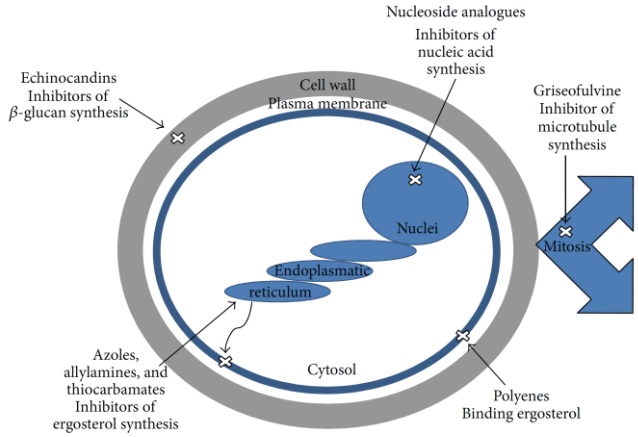
cytosine deaminase rapidly converts flucytosine to fluorouracil, which inhibits protein synthesis by being incorporated into fungal RNA or interferes with the biosynthesis of fungal DNA through the inhibition of thymidylate synthetase. The compound is available only as an oral formulation and typically used with amphotericin B. Dosing frequency is four times a day for patients with normal renal function due to its short half-life but adjustment is needed in patients with renal dysfunction.

Exhibit 8: Competitive profile of anti-fungal drug classes

Anti-Fungal Drug Class and Product	Dosing	Mechanism	Indication
Polyene			
Amphotericin B	IV (0.1 mg/mL) avg 19 days	Membrane leakage by binding to sterols in membrane	Patients with progressive, potentially life-threatening fungal infections
Abelcet (Amphotericin B)	IV (5 mg/kg) 14 days	Liposome enclosed Amphotericin B	Invasive fungal infections refractory/intolerant to amphotericin B
AmBisome (Amphotericin B)	IV (3-6mg/kg/day) 10-28 days	Liposome enclosed Amphotericin B	Cryptococcal meningitis in HIV infected patients Patients with Aspergillus, Candids and/or Cryptococcus species refractory to amphotericin B Patients where renal impairment precludes the use of amphotericin B
Amphotec (Amphotericin B)	IV (3-4mg/kg/day) 14 days	Liposome enclosed Amphotericin B	Invasive fungal infections refractory/intolerant to amphotericin B
Nucleoside analog			
Ancobon (Flucytosine)	IV (200mg/kg/day) varies PO (50-150mg/kg) q6h 2-10 weeks	Flucytosine is taken up by cytosine permiase and converted to flrouracil. Fluorouracil falsely incroporates into RNA or interferes with synthesis of fungal DNA through inhibition of thymidylate synthetase	Serious infections caused by susceptible strains of Candida/Cryptococcus Candida: Septicemia, endocarditis and urinary system infections effectively treated with flucytosine Cryptococcus: Meningitis and pulmonary infections have been treated effectively. Combination with Amphotericin B because of the emergence of resistance to Ancobon
Echinocandin			
Cancidas (Caspofungin)	IV (35-70 mg/day) 14 days	Caspofungin, an echinocandin, inhibits the synthesis of beta (1,3)-D-glucan, an essential component of the cell wall of susceptible Aspergillus species and Candida species.	Empirical therapy for presumed fungal infections in febrile, neutropenic patients Candida infections: intra-abdominal abscesses, peritonitis and pleural space infections Treatment of esophageal candidiasis Treatment of invasive aspergillosis in patients who are refractory/intolerant of other therapies
Eraxis (Anidulafungin)	IV (50-100mg/day) 7-14 days	Inhibition of 1,3-beta-D-glucan, an essential component of the fungal cell wall	Candidemia and Other Forms of Candida Infections (Intra-abdominal Abscess and Peritonitis) Esophageal Candidiasis
Mycamine (Micafungi)	IV (50-150mg/day) 15-19 days	Inhibition of 1,3-beta-D-glucan, an essential component of the fungal cell wall	Candidemia, Acute Disseminated Candidiasis, Candida Peritonitis and Abscesses Esophageal Candidiasi Prophylaxis of Candida Infections in Patients Undergoing Hematopoietic Stem Cell transplantation
Azole			
Diflucan (Flucanozole)	IV (100-400mg/day) 7-14 days PO (100-400mg/day) 7-14 days	Blocks the synthesis of ergosterol, a key component of the fungal cell membrane, through the inhibition of cytochrome P-450 dependent enzyme. Weakening the structure and function of the cell membrane	Vaginal candidiasis Oropharyngeal and esophageal candidiasis Cryptococcal meningitis Prophylaxis. Patients undergoing bone marrow transplantation and chemotherapy/radiation therapy
Noxafil (Posaconazole)	PO (200-800mg/day) 14 days	Blocks the synthesis of ergosterol, a key component of the fungal cell membrane, through the inhibition of cytochrome P-450 dependent enzyme. Weakening the structure and function of the cell membrane	Prophylaxis of Invasive Aspergillus and Candida Infections Treatment of Oropharyngeal Candidiasis Including Refractory to Itraconazole/Fluconazole
Vfend (Voriconazole)	IV (8-12mg/kg/day) 14-21 days PO (400mg) 14-21 days	Blocks the synthesis of ergosterol, a key component of the fungal cell membrane, through the inhibition of cytochrome P-450 dependent enzyme. Weakening the structure and function of the cell membrane	Invasive asperigillosis Candidemia and disseminated candidiasis in skin,abdomen, kidney, bladder wall, and wounds Esophageal candidiasis Serious infections caused by Scedosporium apiospermum and Fusarium spp. Fusarium solani infections intoleran/refractory to other threapy
Enfumafungin			
SCY-078	IV 5-7 days PO (500-750mg/day) up to 28 days	Interferes with the assembly of the fungal cell wall polymer β-(1,3)-D-glucan and prevents the growth of medically important fungal species	Invasive fungal infections caused by Candida and Aspergillus species Resistant fungal infections resistant to azole drugs such as fluconazole

Source: Prescribing information

Exhibit 9: Schematic of anti-fungal mechanisms of action



Source: Biomed Res Int. 2013;2013:204237. doi: 10.1155/2013/204237

Exhibit 10: Treatment guidelines for candidiasis

Candidiasis	Therapy	
Condition or treatment group	Primary	Alternative
Candidemia		
Nonneutropenic adults	Fluconazol or echinocandin	LFAmB or AmB-d or voriconazole
Neutropenic patients	Echinocandin or LRAmB	Fluconazole or voriconazole
Suspected candidiasis		
Nonneutropenic patients	Fluconazol or echinocandin	LFAmB or AmB-d
Neutropenic patients	LFAmB, caspofungin or voriconazole	Fluconazole or itraconzazole
Urinary tract infection		
Asymptomatic cystitis	Therapy not indicated	
Symptomatic cystitis	Fluconazole	AmB-d or flucytosine
Pyelonephritis	Fluconazole	Amb-d w/ or w/o 5-FC, or 5-FC alone
Urinary fungus balls	Surgical removal; fluconazole or AmB-d w/ or w/o 5-FC	-
Vulvovaginal candidiasis	Topical agents or fluconazole	-
Chronic disseminated candidiasis	Fluconazole or AmB-d then fluconazole	Echinocandin followed by fluconazole
Candida osteoarticular infection		
Osteomyelitis	Fluconazole or LFAmB, then fluconazole	Echinocandin or AmB-d then fluconazole
Septic arthritis	Fluconazole or LFAmB, then fluconazole	Echinocandin or AmB-d then fluconazole
CNS candidiasis	LFAmB w/ or w/o 5-FC, followed by fluconazole	Fluconazole
Candida endophthalmitis	AmB-d with 5-FC or fluconazole	LFAmB; voriconazole; or echinocandin
Candida infection of the cardiovascular system		
Endocarditis	LFAmB w/ or w/o 5-FC; or Amb-d w/ or w/o 5-FC; or echinocandin	Fluconazole
Pericarditis or myocarditis	LFAmB; fluconazole; echinocandin	Fluconazole
Suppurative thrombophlebitis	LFAmB; fluconazole; echinocandin	Fluconazole
Infected pacemaker, ICD, or VAD	LFAmB w/ or w/o 5-FC; or Amb-d w/ or w/o 5-FC; or echinocandin	Fluconazole
Neonatal candidiasis	Amb-d; fluconazole	LFAmB
Candida isolated from respiratory secretions	Therapy not recommended	
Nongenital mucocutaneous candidiasis		
Oropharyngeal	Clotrimazole toches; nystatin; fluconazole	Itraconazole; posaconazole; voriconazole; AmB; echinocandin; AmB-d
Esophageal	Fluconazole; echinocandin; AmB-d	Itraconazole; posaconazole; voriconazole; AmB; echinocandin; AmB-d

Source: Infectious Disease Society of America Clinical Practice Guidelines

Exhibit 11:Treatment guidelines for aspergillosis

Aspergillosis	Therapy	
Condition or treatment group	Primary	Alternative
Invasive pulmonary aspergillosis	Voriconazole	L-AMB; caspofungin; micafungin; posaconazole; itraconazole
Invasive sinus aspergillosis	Voriconazole	L-AMB; caspofungin; micafungin; posaconazole; itraconazole
Tracheobronchial aspergillosis	Voriconazole	L-AMB; caspofungin; micafungin; posaconazole; itraconazole
Chronic necrotizing pulmonary aspergillosis	Voriconazole	L-AMB; caspofungin; micafungin; posaconazole; itraconazole
Aspergillosis of the CNS	Voriconazole	L-AMB; caspofungin; micafungin; posaconazole; itraconazole
Aspergillus infections of the heart	AmB-d; voriconazole	L-AMB; caspofungin; micafungin; posaconazole; itraconazole
Aspergillus osteomyelitis and septic arthritis	AmB-d; voriconazole	L-AMB; caspofungin; micafungin; posaconazole; itraconazole
Aspergillus infections of the eye	Intracolular AMB idicated with partial virectomy	L-AMB; caspofungin; micafungin; posaconazole; itraconazole
Cutaneous aspergillosis	AmB-d; voriconazole	L-AMB; caspofungin; micafungin; posaconazole; itraconazole
Aspergillus peritonitis	AmB-d; voriconazole	L-AMB; caspofungin; micafungin; posaconazole; itraconazole
Empirical and preemptive antifungal therapy	L-AMB, caspofungin, itraconazole, voriconazole	-
Prophylaxis against invasive aspergillosis	Posaconazole	Itraconazole; micafungin
Aspergilloma	No therapy or sugical resection	Itraconazole; voriconazole
Chronic cavitary pulmonary aspergillosis	Itraconazole or voriconazole	L-AMB; caspofungin; micafungin; posaconazole; itraconazole
Allergic bronchopulmonary aspergillosis	Itraconazole	Voriconazole; posaconazole
Allergic aspergillus sinusitis	None or itraconazole	Few data on other agents

Source: Infectious Disease Society of America Clinical Practice Guidelines

Exhibit 12: Select summary of efficacy data for systemic anti-fungals

AmBisome	AmBisome	Amphotericin B
Pts receiving at least one dose of study drug	343	344
Overall Success	171 (49.9%)	169 (49.1%)
Fever resolution during neutropenic period	199 (58%)	200 (58.1%)
No treatment emergent fungal infection	300 (87.5%)	301 (87.7%)
Survival through 7 days post study drug	318 (92.7%)	308 (89.5%)
Study drug not prematurely discontinued due to toxicity or lack of efficacy	294 (85.7%)	280 (81.4%)
Safety		
Significanly lower incidence of grade 3 or 4 toxicity was observed in AmBisome compared with the amphotericin B group		

Cancidas	Cancidas	Ambisome	% Diff (CI)
Number of patients	556	539	
Overall Favorable Response	190 (33.9%)	181 (33.7%)	0.2 (-5.6, 6.0)
No documented breakthrough fungal infection	527 (94.8%)	515 (95.5%)	-0.8
Survival 7 days after end of treatment	515 (92.6%)	481 (89.2%)	3.4
No discontinuation due to tox or lack of efficacy	499 (89.7%)	461 (85.5%)	4.2
Resolution of fever during neutropenia	229 (41.2%)	223 (41.4%)	-0.2

V-fend	Voriconazole n/N (%)	Ampho B n/N (%)	Stratified Diff (95% CI) †
Efficacy as Primary Therapy			
Satisfactory Global Resp.	76/144 (53)	42/133 (32)	21.8% (10.5%, 33.0%) p<0.0001
Survival at Day 84	102/144 (71)	77/133 (58)	13.1% (2.1%, 24.2%)
Success by Species			
	Success n/N (%)		
Overall success	76/144 (53)	42/133 (32)	
Mycologically confirmed	37/84 (44)	16/67 (24)	
Aspergillus spp.			
A. fumigatus	28/63 (44)	12/47 (26)	
A. flavus	3/6	4/9	
A. terreus	2/3	0/3	
A. niger	1/4	0/9	
A. nidulans	1/1	0/0	
Safety			
treatment-related adverse events which most often led to discontinuation of voriconazole therapy were elevated liver function tests, rash, and visual disturbances			

Posaconazole Oral Suspension Clinical Success	Posaconazole	Fluconazole
Clinical Success at End of Therapy (Day 14)	155/169 (91.7%)	148/160 (92.5%)
Clinical Relapse (4 Weeks after End of Therapy)	45/155 (29.0%)	52/148 (35.1%)
Mycological Eradication (absence of CFU) at End of T	88/169 (52.1%)	80/160 (50.0%)
Mycological Relapse (4 Weeks after End of Treatmen	49/88 (55.6%)	51/80 (63.7%)
Safety- Serious and Otherwise Important Adverse Reactions		
Hypersensitivity		
Arrhythmias and QT Prolongation		
Hepatic Toxicity		

Source: Prescribing information

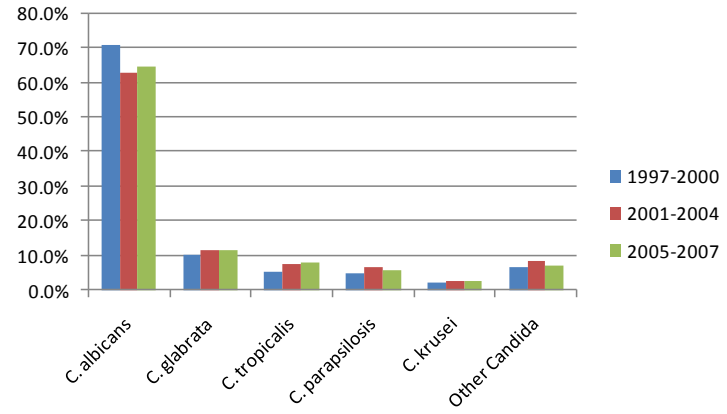
Resistance is becoming a serious issue for systemic fungal infections

Incidence of drug resistance in Candida and Aspergillus is likely to continue increasing

Broad use of the azole drug class, both as a treatment and as a prophylactic, has resulted in an increasing incidence of drug resistant Candida infections. Rates of reduced azole susceptibility are as high as 15-20% in certain hospitals. Resistance rates are shifting both because organisms can develop resistance if treated improperly and also because Candida species, such as Candida glabrata and krusei that are inherently resistant to azoles, are being selected for as the more susceptible species are eradicated.

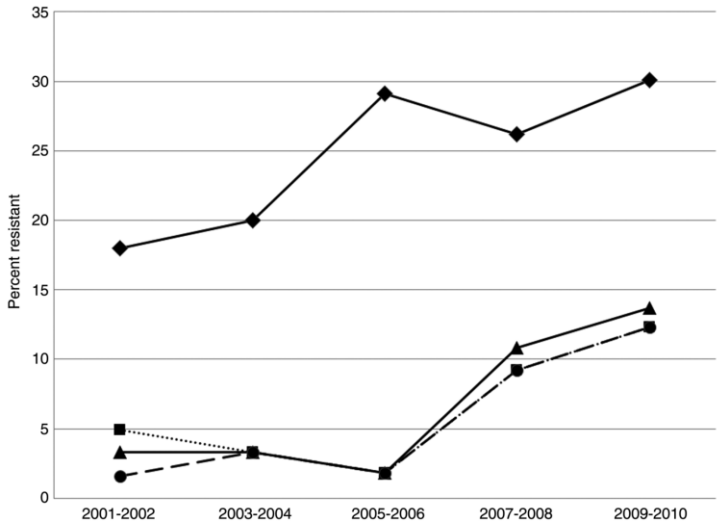
A decline in the efficacy of the azole class has led to the emergence of echinocandins being the first choice for most patients with invasive Candida infections. However, resistance to echinocandins though rare is increasing as well with more than 10% of Candida glabrata being echinocandin resistant.

Exhibit 13: Change in distribution of Candida over 10.5 years



Source: Journal of Clinical Microbiology, Apr. 2010, p. 1366-1377.

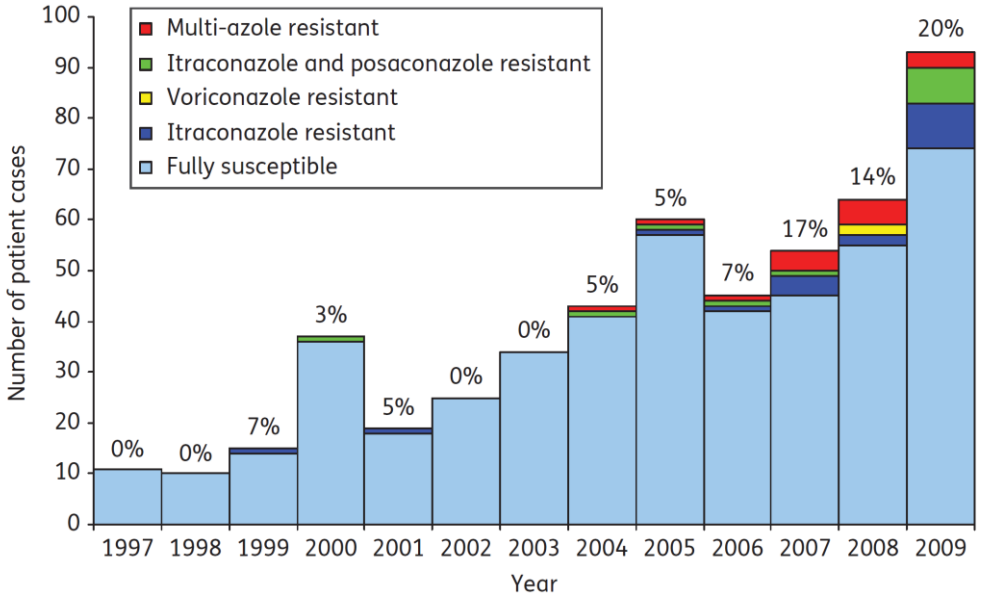
Exhibit 14: Change in resistance to fluconazole, caspofungin and other anti-fungals



Fluconazole (diamonds), anidulafungin (dashed line), caspofungin (triangles), and micafungin (long dashed line with circles)
Source: Clin Infect Dis. 2013 Jun;56(12):1724-32

Broad use of azoles is also generating resistance in Aspergillus. Roughly 50% of Aspergillus fumigatus, which accounts for the majority of Aspergillus fungal infections in the US, showed resistance to azoles.

Exhibit 15: Frequency of Azole resistance in A. Fumigatus



Source: J Antimicrob Chemother 2010; 65: 2116–2118

Exhibit 16: Antifungal mechanism of action, resistance and drug information

Antifungal class	Mode of Action	Mechanism of resistance	Drug	Brand Name	Patent
Azoles	Inhibitors of lanosterol 14-beta-demethylase	Efflux mediated multidrug transporter decrease of affinity in Erg1p by mutation upregulation of ERG11 alteration in ergosterol biosyn pathway	Miconazole Econazole Clotrimazole Ketoconazole Fluconazole Itraconazole Voriconazole Posaconazole	Oravig Spectazole Canesten or Lotrimin Nizoral Diflucan Sporanox Vfend Noxafil	2022 2004 2011 2019
Echinocandins	Inhibitors of (1,3)-beta-D-glucan synthase	alteratioin of affinity of echino. For beta(1,3)-glucan synthase	Caspofungin Micafungin Anidulafungin	Cancidas Mycamine Eraxis	2015 2016 2020
Polyenes	Binding ergosterol	Absense of ergosterol (loss of func. Of ERG3 or ERG6) Decrease of ergosterol conten in cells	Nystatin Amphotericin B	Nystatin AmBisome	 2016
5-fluorocytosine	inhibition of nucleic acids synthesis	Defect in cytosine permease Deficiency or lack of enzymes in metabolism of 5-FC Deregulation of the pyrimidin biosynthetic pathway	Flucytosine	Ancobon	

Source: Int J Microbiol. 2012;2012:713687 and Biomed Res Int. 2013;2013:204237

SCY-078: A unique mechanism of action

SCY-078 belongs to a new class of anti-fungals and can work against azole and echinocandin resistant invasive fungal infections

SCYX is developing SCY-078 as an oral and intravenous treatment for invasive fungal infections, especially candidiasis and aspergillosis. SCY-078 is a semi-synthetic derivative of the natural product triterpene glycoside enfumafungin, which potently inhibits the synthesis of the polymer β-(1,3)-D-glucan. β-(1,3)-D-glucan is an essential component of the cell wall of many pathogenic fungi, including Aspergillus and Candida. Inhibiting β-(1,3)-D-glucan synthesis is also a proven anti-fungal drug target and has been validated with the echinocandin class of anti-fungals.

Unlike echinocandins, however, SCY-078 is the first member of the enfumafungin class of anti-fungal agents to reach clinical trials. Enfumafungins are a structurally distinct class of glucan synthase inhibitor. It just so happens that they also inhibit fungal β-(1,3)-D-glucan synthesis but they appear to bind to a completely independent site. Since SCY-078 and echinocandins work via independent mechanisms, SCY-078 has activity against echinocandin resistant strains. Therefore, an increase in resistance to echinocandins is not expected to impact the potential efficacy of SCY-078 and in fact should be good for SCY-078.

As an oral and an i.v., SCY-078 overcomes the limitations of current anti-fungals by offering the efficacy and safety benefits of the echinocandin class and the convenience of the azole class

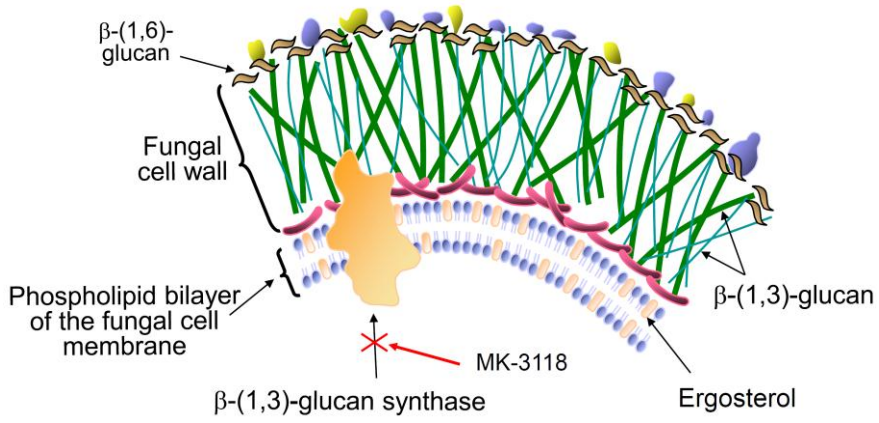
Similar to the echinocandin class SCY-078 is also expected to have a good safety profile, as the cell wall is not a target encountered in mammalian cells. Since SCY-078 has already been developed as an oral, with an intravenous form likely to enter the clinic in 2015, it could offer all the efficacy and safety advantages of the echinocandins while overcoming their limitations as echinocandins are only available as intravenous drugs.

Mechanism of action in greater detail

SCY-078 inhibits the synthesis of the fungal cell wall polymer β-(1,3)-glucan likely by inhibiting the enzyme UDP-glucose-β-(1,3)-D-glucan-β-(3)-D-glucosyltransferase (GS). The net effect is inhibition of fungal cell wall synthesis.

GS catalyzes the incorporation of monomeric glucose from UDP-glucose into the linear polymer. This catalytic machinery lies in the fungal cell membrane. The enzyme itself includes several proteins including Fks1p, an integral membrane protein, and Rho1p, which is a regulatory partner in the GS complex. SCY-078 and other enfumafungin analogs are noncompetitive inhibitors of GS activity.

Exhibit 17: SCY-078 and the fungal cell wall



Source: Company reports

SCY-078 was acquired from Merck so the pre-clinical and Phase I package is of high quality plus there is API

SCYX received all development and commercialization rights for SCY-078 (previously called MK-3118) from Merck in 2013. Importantly, this includes all pre-clinical data, clinical data from seven Phase I trials, which were conducted by Merck, and active pharmaceutical ingredient (API). In return, Merck receives milestones fro the start of Phase II and Phase III studies, NDA filing and marketing approvals in the US, EU and Japan, which total up to $19MM. Merck will also receive tiered, single-digit royalties on product sales for up to 10 years from product launch.

Cost of goods is expected to be similar to that of other small molecule drugs.

Manufacturing and supply of SCY-078. Since SCY-078 is a semi-synthetic natural product its production includes both fermentation and synthetic chemical steps. The first step involves fermentation to produce the natural product enfumafungin. Enfumafungin is then converted to SCY-078 in a series of chemical steps with an average yield of almost 90%. Cost of goods for SCY-078 is expected to be similar to that of other small molecule drugs.

The API, which was received from ex-partner Merck, is sufficient for the manufacture and development of an intravenous formulation for clinical studies and toxicology studies. The tablets currently on hand are sufficient to complete Phase II studies.

Oral already has QIDP; intravenous form likely to get it as well

Just like antibiotics, anti-fungals benefit from the GAIN Act. SCY-078 already has QIDP designation for the oral form and the i.v. form will likely get it too. This could mean FDA engagement and a potentially efficient path through the clinical and regulatory process.

The GAIN Act, which has been a catalyst for reinvigorating the antibiotics arena, also applies to anti-fungal drug development. The Act is designed to encourage the development of new antibiotics and new anti-fungal drugs for the treatment of life threatening infections. Benefits for having a qualified product include extended exclusivity periods, fast track designation, and a priority review. The oral form of SCY-078 was designated a qualified infectious disease product (QIDP) by the FDA on Jan. 2014 and we believe the intravenous form is likely to qualify for the same designation.

We believe SCY-078 is well protected so the main benefit here would be greater FDA engagement and as rapid a path to the market as quality development permits, and a priority review. Recently, Cubist Pharmaceuticals' (CBST) Sivextro (tedizolid), Durata Therapeutics' (DRTX) Dalvance (dalbavancin) and The Medicine Company's (MDCO) oritavancin all appear to be benefiting from the QIDP designation with a quick path through the approval process.

To qualify drug candidates must be an anti-fungal for the treatment of serious or life-threatening infections, including:

- Infections caused by an anti-fungal resistant pathogen, including novel or emerging infectious pathogens; or
- Qualifying pathogens listed by the FDA in accordance with the GAIN Act.

Other benefits of the GAIN Act include a five-year extension to the five-year exclusivity period typically awarded for being a new chemical entity and a review clock that is eight months from the date of submission until the FDA decision is announced (PDUFA date).

Seven Phase Is completed for SCY-078; Phase I for intravenous and Phase II for oral in 2015

Phase I studies show the oral form of SCY-078 is ready to enter Phase II trials.

SCY-078 has been evaluated in seven Phase I safety and pharmacokinetic studies in over 100 healthy human volunteers. Four of these seven studies evaluated a single oral dose while three evaluated multiple oral doses. In all seven studies, SCY-078 was shown to be safe and well tolerated. Furthermore, SCY-078 reached sustained blood concentrations at levels that were considered clinical relevant and therapeutically effective. Based on this data, at least the oral form is ready to enter Phase II studies and we believe chances of the intravenous being safe and effective are high as well.

Phase I studies consistently showed a favorable safety profile

Systemic fungal infections are a serious disease and on balance SCY-078's safety and tolerability profile appears to indicate a wide therapeutic window.

The Phase I studies evaluated oral doses of up to 1,800 mg in a single day and doses up to 800 mg per day for 28 consecutive days. Despite multiple days of exposure the safety profile of SCY-078 is fairly clean.

The majority of adverse events seen have been generally transient and primarily mild-to-moderate. The most frequently reported adverse events were gastrointestinal. In multiple dose studies, these included diarrhea, abdominal pain or discomfort, and vomiting. These gastrointestinal side effects were not considered serious in nature and only one subject discontinued dosing with SCY-078 due to gastrointestinal adverse events.

Another patient experienced significant liver function test (LFT) increases after the first dose and discontinued. The investigator thought this was study drug related. However, markers of liver injury, such as alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were already increasing in this patient prior to the administration of SCY-078. In fact, pre-treatment levels of ALT had increased above the upper limit of normal. After discontinuation, ALT and AST levels decreased over a 48-hour period and LFTs returned to the normal range without any medical intervention.

SCY-078 reached blood levels that were considered to be therapeutically effective

Oral administration shows SCY-078 blood levels can reach therapeutically effective exposures.

Oral administration showed sustained blood concentrations in the range required for clinical efficacy. These ranges were determined from preclinical PK/ PD studies. In human subjects who received SCY-078 as a loading oral dose of 600 mg three times per day (1800 mg/ day) followed by a maintenance daily dose of 500 mg, the circulating levels of SCY-078 exceeded those that cured the infection in the mouse models of invasive Candida infections. These results provide initial comfort that SCY-078 can be given to patients with invasive Candida infections at doses that are predicted to be effective and therefore could lead to the infection being cured.

Exhibit 18: Summary of Phase I studies for SCY-078

Design/Objective	Clinical endpoints	Subject Population	Results
Single-Dose Studies			
Phase 1, randomized, double-blind, placebocontrolled, single ascending-dose, safety, tolerability, and PK study	Safety and tolerability by physical examination, vital signs, ECGs and laboratory safety valuations (hematology, chemistry, urinalysis), gastrin levels; PK data in fasted state and after high fat meal	16 healthy males (18-45 years)	Safety: SCY-078 up to 1600mg was generally safe and well tolerated; no serious adverse events (SAEs) reported. 1) Dose proportionality was observed for doses up to 1600 mg 2) Dosing SCY-078 drug-filled capsules with a high fat meal increased drug exposure levels by ~20% compared to levels observed in fasted subjects, which was within intersubject variability
Phase 1, double-blind randomized, single dose study to evaluate the safety, tolerability, and PK in elderly subjects	Safety and tolerability by physical examination, vital signs, ECGs and laboratory safety evaluations (hematology, chemistry, urinalysis);	17 healthy males and females (65- 85 years)	Safety: SCY-078 generally well tolerated. One non-drug -related SAE of metastatic carcinoid tumor was reported. The most common adverse events (AEs) were gastrointestinal disorders and nervous system disorders.
Phase 1, Open label biocomparison study of two formulations of SCY-078 and a pantoprazole interaction study with SCY-078 in healthy subjects	Safety, tolerability and PK of fit-forpurpose (FFP) drug filled capsules compared to FFP compressed tablets; impact of multiple doses of a proton pump inhibitor on single doses of SCY-078; impact of high fat meal on FFP compressed tablets	16 healthy males (18-45 years)	Safety: SCY-078 generally well tolerated. One SAE of elevated liver enzymes that led to discontinuation was reported. The most common AEs were gastrointestinal disorders.
Multiple-Dose Studies			
Phase 1, randomized, double-blind, plcebo controlled, multiple ascending-dose safety, tolerability and PK study	Safety and tolerability by physical examination, vital signs, ECGs and laboratory safety evaluations (hematology, chemistry, urinalysis), gastrin levels and gastric histology; Plasma PK data and concentrations of intact drug in urine after multiple doses of SCY-078	32 healthy males (18-45 years)	Safety: SCY-078 was generally safe and well tolerated. Most common AEs were headache, lack of energy, dizziness, and gastrointestinal disorders.
Phase 1, randomized, partially-blind, placebo controlled study of multiple doses of ketoconazole on single dose PK of SCY-078	Safety and tolerability of SCY-078 Single dose PK profile of SCY-078 after multiple doses of ketoconazole	12 healthy males (18-45 years)	Safety: SCY-078 was generally well tolerated when dosed alone or with ketoconazole. The most common AEs were headache and increased ALT/AST.
Phase 1, randomized, double-blind, placebo controlled multiple dose study to assess the safety, tolerability, and PK of a loading dose of SCY-078	Safety and tolerability of SCY-078; PK profile of SCY-078 after a loading dose on day 1	8 healthy males (18-45 years)	Safety: SCY-078 was generally well tolerated. No SAEs or discontinuations. The most common AE was diarrhea; 1 subject had elevated bilirubin.
Phase 1, open-label, fixedsequence, multiple-dose study investigating the effect of diltiazem on the PK and safety of SCY-078 in healthy subjects	Safety and tolerability of SCY-078; PK profile of SCY-078 after multiple doses of diltiazem	16 males (20-45 years)	Safety: SCY-078 generally well tolerated. The most common AE was headache. No SAEs; 1 discontinuation due to first degree heart block following administration of diltiazem only 1) Drug exposures as measured by AUC were ~2.5 fold higher 2) C was increased 2 fold

Source: SCYX S-1 Filing, Company reports

Pharmacokinetic data looks good as well; supports once-daily dosing with the oral

SCY-078 seems simple to dose orally.

SCY-078 has a half-life of ~20 hours, which supports once daily dosing. Coupled with a loading dose on day 1 therapeutically effective concentrations are achieved on the first day of treatment. Drug exposure also increased proportionally and in a predictable manner with doses up to the maximum dose tested. No major differences in the pharmacokinetics or safety of SCY-078 in healthy elderly vs. younger subjects were observed. This is an important consideration since many patients experiencing invasive fungal infections are elderly.

Drug-drug interaction studies were also largely positive. They showed that with SCY-078 can be used in combination with moderate inhibitors of CYP3A, the most common enzyme for metabolizing drugs and toxins in the human body, with dose adjustments. SCY-078 does not appear to strongly inhibit drug metabolizing enzymes especially when compared to the azole class meaning there are fewer drug-drug interactions.

SCYX will be using compressed tablets in the planned Phase II study, which is different than the capsules used in the Phase I studies. A biocomparison study was conducted between the drug filled capsules and compressed tablets and showed that the latter had concentrations that were ~20% higher. The compressed tablets are also likely to reduce the daily dosing from several capsules to 2 to 3 tablets per day.

Pre-clinical data shows SCY-078 efficacy against resistant organisms; a Phase II/III would test this in 2016

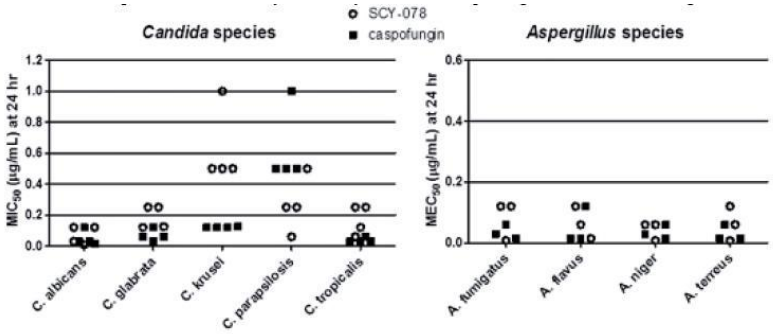
In vitro data shows potent activity, including against drug resistant strains

SCY-078 kills Candida and Aspergillus. Activity in wild-type organisms is similar to that of caspofungins.

SCY-078 was tested against a variety of Candida and Aspergillus strains and demonstrated potent activity against approximately 650 laboratory and clinically important isolates of both. Importantly, these included strains that are resistant to azoles and echinocandins, the two most commonly used drug classes for the treatment of invasive fungal infections.

In vitro activity against wild-type organisms. SCY-078 showed potent activity in vitro against over 500 strains from eleven Candida species and over 150 strains from four Aspergillus species. Wild type organisms are those that have no known drug resistance. The potency of SCY-078 against these Candida and Aspergillus strains is comparable to caspofungin, the leading echinocandin.

Exhibit 19: In vitro activity against "wild type" Candida strains



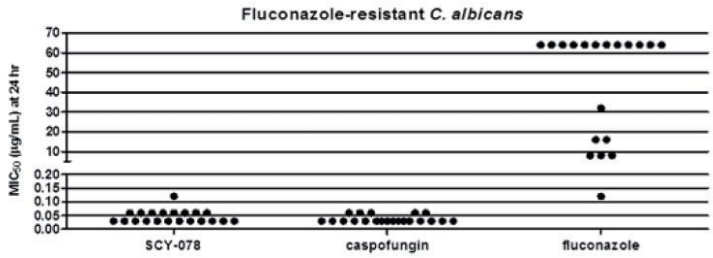
Source: Company reports

Activity against azole and echinocandin resistant strains demonstrated

SCY-078 is effective against azole and echinocandin resistant strains of Candida.

In vitro activity against resistant strains. Given the widespread use of anti-fungal drugs such as the azoles, resistant strains of Candida and Aspergillus are increasingly prevalent. These are strains against which the azole class no longer works. SCY-078 showed activity against all azole-resistant Candida strains tested. Of note the level of activity was comparable to that observed against wild-type strains. Furthermore, the in vitro activity of SCY-078 against Candida albicans strains resistant to fluconazole, a leading azole, was comparable to that of caspofungin, the leading echinocandin.

Exhibit 20: In vitro activity against "azole resistant" Candida strains

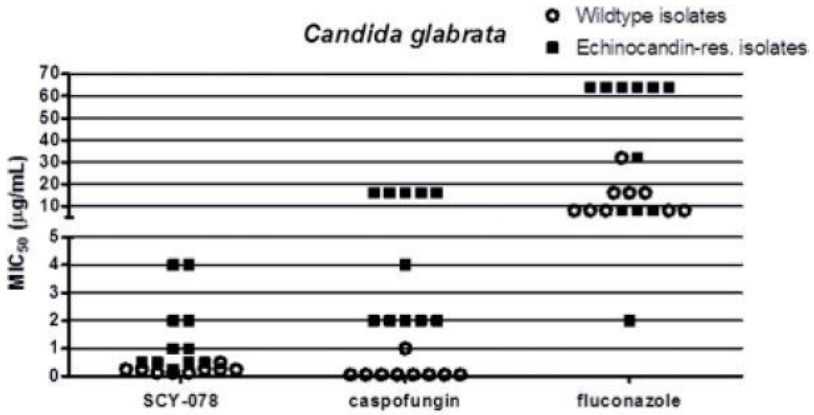


Source: Company reports

SCY-078 could be a therapeutic option for multi-drug resistant Candida strains

In vitro activity against drug resistant echinocandins. The fact that SCY-078 has activity against the majority of echinocandin resistant strains tested suggests that SCY-078 belongs to a new class of anti-fungals that acts on a target distinct from the echinocandins. Echinocandin resistance is also increasing, especially among azole-resistant species such as Candida glabrata. In vitro testing showed SCY-078 retained activity against the majority of echinocandin-resistant Candida glabrata strains as well as against other echinocandin resistant Candida species.

Exhibit 21: In vitro activity against "echinocandin resistant" Candida strains



Source: Company reports

Exhibit 22: In vitro activity on Candida spp. clinical isolates with comparators

Candida Spp	Fluconazole	Caspofungin	SCY-078
C. albincans	0.06- ≥ 128	0.015 - 8	0.06 - 2
C. glabrata	2 - ≥ 128	0.03 - 16	0.5 - 2
C. krusei	16 - ≥ 128	0.012 - 8	0.5 - 2

Source: J Antimicrob Chemother 2013; 68: 858–863 and company reports

SCY-078 shows activity in proven animal models; provides confidence in potential activity in humans

Animal models that have been good at predicting the effectiveness of currently approved drugs also show SCY-078 is active in models of invasive and systemic fungal infections.

SCY-078 has been tested in animal models of invasive fungal infections, which were also used to test several currently approved anti-fungal agents. In these animal models, SCY-078 was highly active against both Candida and Aspergillus species. The same animal models were used to determine the drug concentration required in blood to achieve SCY-078's full anti-fungal effect.

Similar mouse models of Candida and Aspergillus infections have been predictive of clinical efficacy for all approved glucan synthesis inhibitors. In studies with Candida albicans infected mice, SCY-078 treated animals had no measurable Candida following doses, which resulted in drug levels in the blood similar to those that have been safely achieved in humans. Comparable results were observed in mice infected with other Candida species, including Candida glabrata. The in vivo activity of SCY-078 was also evaluated against Aspergillus fumigatus. Typically immune deficient mice infected with Aspergillus develop aggressive infections and die. However, treatment with SCY-078 resulted in dose-dependent increases in survival rates up to 90%. These data show that SCY-078 could have activity against both Candida and Aspergillus strains.

Safety also clean in animal models. SCYX tested doses of SCY-078 that were several fold the level that is targeted for human treatment. At such high levels, the company observed an impact on the stomach lining and on the liver. Reproductive toxicity studies and markers of cardiovascular, respiratory or central nervous system function were also clean.

Next pre-clinical steps for SCY-078

Next steps for SCY-078 could include longer-term toxicity studies. SCY-078 could also be tested in other models of drug resistant Candida and Aspergillus. However, no further work is required for the Phase II study.

Phase II and Phase I studies due in 2015; Potentially pivotal trials starting 2016

SCYX expects to enroll the first patient in the Phase II intravenous-to-oral step down study for oral SCY-078 by year end 2014. The Phase I i.v. SCY-078 study should begin in early 2015. Results from both could be available in 2015 allowing the start of a potentially pivotal Phase II/III study in 2016 targeting patients with drug resistant systemic fungal infections. These in turn could read out by YE:17/early 2018. SCYX could initiate a standard Phase III study in 2016 as well.

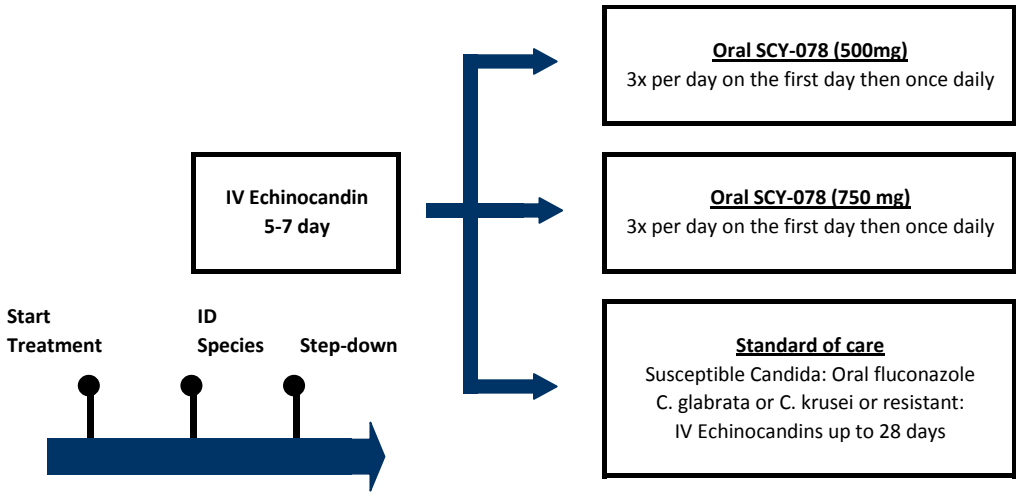
Phase II trial design for oral SCY-078

SCYX plans to evaluate SCY-078 in a Phase II oral step down study. Patients could receive intravenous caspofungin, the leading echinocandin, for five to seven days and then step down to oral SCY-078 or an azole. The primary objective is the achievability of the pharmacokinetic target, which in turn is based on non-clinical PK/PD studies. SCYX will evaluate two doses, 500 mg and 750 mg of oral SCY-078, and select which dose achieves therapeutically balanced exposures. There are no oral echinocandins available making SCY-078 potentially the most suitable alternative for patients who are eligible for oral therapy. Phase II data should be available in 2015.

Phase I trial design for intravenous SCY-078

The purpose of the i.v. SCY-078 study is to assess the pharmacokinetic profile. The goal is to match the exposure for the i.v. to the oral version of SCY-078 and ensure that there are no tolerability issues. Phase I data should be available in 2015.

Exhibit 23: Potential Phase II i.v.-to-oral SCY-078 study design



Source: Company reports

Potential pivotal Phase II/III trial design for oral and intravenous SCY-078

SCYX could begin a Phase II/III i.v. to oral step down study with SCY-078 in 2016. While the design remains to be finalized, the study population will likely include patients with invasive fungal infections who are failing treatment with azoles and echinocandins. Typical clinical criteria for non-responsiveness include fever, signs and symptoms of ongoing infection, and unstable blood pressure, among others. Organisms of interest could include C. glabrata and C. krusei. This could be the first true efficacy and safety data for SCY-078 in a high-unmet need patient population.

Results from this potentially pivotal Phase II/III study could be available by year end 2017 or first half 2018. However, final timelines are likely subject to how many patients need to be enrolled and what percentage of patients are deemed relapsed or refractory, which could vary by geography and institution. Historically, the rate of failure for invasive candidiasis has been 25-30%.

Potential Phase III trial designs for oral and intravenous SCY-078

While the Phase II/III study is ongoing, SCYX could initiate a standard Phase III study for SCY-078, which seeks to establish SCY-078 as the drug of choice for invasive candidiasis, including for resistant pathogens. There are several designs possible and details are likely to be finalized and revealed in 2015 or 2016.

Standard Phase III study. Standard Phase III trial designs include a non-inferiority endpoint. The trial could compare intravenous and oral SCY-078 to an echinocandin and/or azole-containing regimen in first-line patients with invasive candidiasis.

Salvage treatment for resistant patients Phase III study SCYX could also evaluate SCY-078 in invasive aspergillosis or as salvage therapy in patient refractory to or intolerant of currently approved treatments.

Prophylaxis in vulnerable patient populations Phase III study. Other companies have evaluated their compounds in the prophylaxis setting. We believe SCYX could consider such a trial design as well to maximize the value of the SCY-078 franchise.

Potential development and filing strategy for i.v. and oral SCY-078

Given the QIDP designation, SCYX is likely to develop SCY-078 for invasive fungal infections that are refractory to azoles or echinocandins. This could demonstrate differentiation vs. drugs already on the market and accelerate the path to the market. Simultaneously, or with a modest lag, SCYX could conduct a Phase III first-line study where SCY-078 would be compared to the standard of care or an echinocandin followed by an oral azole. Finally, SCYX could also develop SCY-078 as a prophylactic for empirical treatment, for invasive Aspergillus, and/or for pediatric patients.

Exhibit 24: Invasive fungal infection phase III trial designs

Trial Type	Title	Intervention	N	Endpoints Primary	Date Start	End
Prophylaxis	Caspofungin Acetate or Fluconazole in Preventing Invasive Fungal Infections in Patients With Acute Myeloid Leukemia Who Are Undergoing	Caspofungin vs. Fluconazole	550	Time to development of proven or probable invasive fungal infections (IFI)	Apr-11	Mar-15
Prophylaxis	Caspofungin Acetate, Fluconazole, or Voriconazole in Preventing Fungal Infections in Patients Following Donor Stem Cell Transplant	Caspofungin vs. Voriconazole	590	Development of proven or probable IFI	Mar-13	Sep-18
Treatment	An Evaluation Of The Effectiveness And Safety Of Anidulafungin Compared To Caspofungin For The Treatment Of Deep Tissue Infection Due To Candida	Anidulafungin vs. Caspofungin*	41	Percentage of Participants With Global Response at End of Treatment (Day 14 To Day 42)	Apr-09	Jun-12
Treatment	An Evaluation Of The Effectiveness And Safety Of Anidulafungin Compared To Caspofungin For The Treatment Of Serious Fungal Infection Due To Candida In Patients With A Dysfunctional Immune	Anidulafungin vs. Caspofungin*	21	Global Response at End of Intravenous Treatment (EOIVT)	Aug-09	Oct-11
Treatment	Isavuconazole (BAL8557) in the Treatment of Candidemia and Other Invasive Candida Infections	Isavuconazole vs. Caspofungin vs. Voriconazole	526	Overall response at end of intravenous (IV) therapy (up to day 56)	Dec-06	Mar-15
Treatment	Study of Micafungin in Patients With Invasive Candidiasis or Candidemia	Micafungin vs. Caspofungin	611	Overall treatment success	Sep-04	Apr-06
Prophylaxis	Liver Transplant European Study Into the Prevention of Fungal Infection	Micafungin vs. Fluconazole vs. Liposomal amphotericin B vs.	350	Clinical success at the End of Prophylaxis	Dec-09	May-12
Treatment	Comparison of Fluconazole Versus Voriconazole to Treat Fungal Infections in Individuals Receiving Blood and Marrow Transplants	Fluconazole vs. Voriconazole	600	Fungal-free survival (180 days post-transplant)	Nov-03	Sep-06

Source: Cliniicaltrials.gov

Phase I and Phase II results could be a major inflection point for SCYX shares

Though SCY-078 presents an attractive new mechanism of action for a disease where resistance is increasing, activity is based on in vitro and animal model data. As such, the ability to demonstrate efficacy via the intravenous-to-oral Phase II study evaluating oral SCY-078 and the ability to develop an intravenous form of SCY-078 with Phase I data makes them important potential inflection point for SCYX shares in our view. The Phase II study could show that oral SCY-078 is effective in patients with systemic fungal infections and can successfully and safely manage patients who step down from an intravenous drug to an oral one. The Phase I study is important because the ideal anti-fungal would be available both as an intravenous, to treat patients in the hospital, and in the oral form so patients can be shifted to a more convenient regimen and possibly discharged sooner than they would be on an intravenous drug. Success in these two trials would also increase the likelihood of demonstrating SCY-078's value proposition in the planned Phase II/III and Phase III studies that could being in 2016.

Pipeline is not the focus though it too holds opportunities for upside

Non-core pipeline and R&D business could be a source of non-dilutive capital for SCY-078 development.

In addition to SCY-078, which is SCYX's lead program, the company possesses: 1) a platform of enfumafungin derivatives, 2) a cyclophilin inhibitor program to treat viral diseases, 3) including SCY-635 for the potential treatment of HCV and HBV infections, 4) SCY-641 as a potential treatment for dry eye disease, as well as 5) SCY-7158 for sleeping sickness. SCYX also generates revenues from its animal health R&D business. The company could pursue the opportunistic development of one or more of these programs but is more likely to partner them out for non-dilutive capital to fund the development of SCY-078. Altogether, SCYX's pipeline reflects on its early stage but robust discovery capabilities that could lead to more candidates being taken into the clinic in the future.

Enfumafungin platform could result in a pipeline of drugs against systemic fungal infections both wild-type and resistant.

Enfumafungin derivative platform. SCYX will use its platform of enfumafungin derivatives to expand its anti-fungal portfolio. These could target both commonly known strains of fungi such as Candida and Aspergillus as well as organisms that are rarer in occurrence but have higher rates of morbidity and mortality associated with them. We expect the initial focus to remain on SCY-078 but as the program advances we believe SCYX could use its anti-fungal focus to expand the number of therapeutic drug candidates against systemic fungal infections.

Cyclophilin inhibitor platform. SCYX has developed a proprietary platform for cyclophilin inhibitors, which are derived from cyclosporine A to target a variety of diseases. Cyclophilins are a family of enzymes found in all mammalian cells, which play a key role in a number of important cellular functions. SCYX has a library of more than 1,000 cyclophilin inhibitor compounds to test against a wide array of human and animal disorders. SCYX could in the future select and develop other compounds from this proprietary platform as the company's financial resources grow or partner some out opportunistically in return for future economics.

SCY-635 for HCV infection. SCY-635 is a novel, orally available cyclophilin inhibitor that has demonstrated clinical activity against Hepatitis C Virus (HCV) as a single agent and when dosed in combination with pegylated interferon and ribavirin. SCYX has also explored the mechanism in other viruses, such as HBV infection. Since the treatment landscape for HCV infection has changed with recently approved drugs and since HBV infections is now an active development focus for a number of biopharma companies, it is likely that SCYX could partner out these programs, which are non-core to its current R&D efforts.

SCY-641 for dry eye disease. SCY-641 is a novel cyclophilin inhibitor with activity similar to cyclosporine, the active ingredient in Restasis and Optimmune. Restasis is approved for the treatment of dry eye in humans and Optimmune is used as an eye lubricant for dogs. SCYX's SCY-641 could have markedly improved water solubility versus Restasis, which could potentially improve tolerability, dosing and effectiveness. As a rough benchmark, sales of Restasis totaled $792MM in 2012 and $940MM in 2013 demonstrating that this is a very attractive market for new drugs. We believe SCYX is likely to explore a partnership for human development in dry eye. The development of dry eye for dogs is partnered with Dechra.

SCY-7158 for sleeping sickness. In partnership with the Bill & Melinda Gates foundation SCYX discovered SCY-7158 as a potential treatment for sleeping sickness. The product candidate is currently in Phase I studies.

Contract research and development services. SCYX spun out from Aventis (SNY) in 2000 and began as a chemistry focused and animal health services company that provided contract research services to third parties. The company posses more than 30 unique, broad-spectrum screens, and proprietary protocols and algorithms, deemed to be trade secrets. For instance, SCYX's partnership with Merial, the animal health division of SNY, resulted in the discovery of two new drug candidates to treat parasitic infections.

Competitor overview: Pipeline for anti-fungals appears sparse

We have conducted an overview of systemic anti-fungal drugs and relative to the antibiotics, oncology, and other disease areas, the landscape for new and innovative agents appears sparse. The most advanced drugs in development are isavuconazole, an azole, VT-1161 and MGCD290.

- **Isavuconazole**, currently in Phase III studies, is a once-daily intravenous and oral broad-spectrum antifungal for the potential treatment of severe invasive and life-threatening fungal infections. In vitro, it has demonstrated broad coverage of Candida and Aspergillus species, and against mucormycosis. The drug is being co-developed by Astellas and Basilea.
- **MGCD290** (MethylGene) is a first in class orally available small molecule inhibitor of the fungal enzyme Hos2 Histone Deacetylase. In vitro activity showed synergy with fluconazole, posaconazole, and voriconazole, in a variety of fungal species, including in azole resistant Candida and Aspergillus. However, data from a Phase II did not show a statistically significant benefit for MGCD290 plus fluconazole over fluconazole alone.
- **VT-1161** (Viatmet) is an orally available small molecule metalloenzyme inhibitor of demethylase (CYP51), which is involved in fungal cell wall sterol synthesis. The ability of VT-1161 to selectively target fungal CYP51 over human cytochrome P450 enzymes is unique in comparison to other approved antifungal therapies that block CYP51. VT-1161 has shown strong activity in multiple preclinical animal models and is currently conducting two proofs of concept Phase 2 clinical trials.
- **NDV-3a** (NovaDigm) is novel as it is the first vaccine to provide preclinical "cross-kingdom" protection against both fungal and bacterial pathogens. NDV-3a contains an N-terminal portion of the Candida albicans aggulutinin-like sequence 3 protein (Als3p) and may provide an immune system the ability to combat and protect a fungal infection. Pre-clinical studies demonstrated that Als3p vaccine antigen was able to protect mice from oropharyngeal, vaginal, and intravenous exposure to C. albicans and other Candida species. Results from a Phase I trial showed safety and NovaDigm is conducting a Phase I/II study in recurrent vulvovaginal candidiasis.

Commercial competitors would include generics, as well as branded drugs including V-fend (voriconazole), Cancidas (caspofungin), and AmBisome (amphotericin B), as well as Eraxis (anidulafungin), Noxafil (posaconazole), and Mycamine (micafungin). Oral generics of voriconazole, fluconazole, and itraconazole are also available.

Adnan Butt (415) 633-8588; adnan.butt@rbccm.com

Exhibit 25: Anti-fungal drugs in development for systemic candidiasis and aspergillosis infections

Interventions	Indication	Sponsor/Collaborators	Ticker	Phase	Patients	Start Date	Completion Date	Primary Comp Date	NCT Number
Phase III									
Interferon-gamma	Candidemia	Biomerieux	BIM	Phase 3	20	Jan-14		Jan-14	NCT01270490
Isavuconazole	Inv. Candidiasis	Basilia, Astellas Pharma	BSLN, 4503-JP	Phase 3	526	Dec-14	Jul-14	Mar-14	NCT00413218
Anidulafungin	Candidemia	Pfizer	PFE	Phase 3	60	Feb-14	Jun-14	Jun-14	NCT00761267
Micafungin	Candidiasis	Astellas Pharma	4503-JP	Phase 3	225	Jun-14	Dec-14	Dec-14	NCT00815516
Posaconazole	Inv. Aspergillosis	Merck Sharp	MRK	Phase 3	600	Sep-13	Oct-17	May-17	NCT01782131
Phase II									
MGCD290	Vulvovaginal Candidiasis	MethylGene Inc.		Phase 2	220	Dec-11	Apr-13	Apr-13	NCT01497223
VT-1161	Candidiasis, Vulvovaginal	Viamet Pharma		Phase 2	48	Aug-13	Aug-14	Aug-14	NCT01891331
NDV-3a	Vulvovaginal Candidiasis	NovaDign Therap.		Phase 1/2	189	Jul-13	Jul-15	Dec-14	NCT01926028
Caspofungin	Inv. Candidiasis	Merck Sharp	MRK	Phase 2	90	Jan-14	Mar-16	Mar-16	NCT01945281
Phase I									
F901318	Inv. Aspergillosis	F2G Ltd.; Simbec		Phase 1	40	Jul-14	Dec-14	Nov-14	NCT02142153

Source: Clinicaltrials.gov

Exhibit 26: Profiles of anti-fungal drugs on the market

Drug family	Drug	Adm route	Oral Bioavail (%)	Cmax (ug/ml)	AUC (mg*h/L)	Protein binding	Half life (h)	Elimination
Azoles	Fluconazole	Oral / IV	>90	0.7	400	10-12	27-31	Urine
	Itraconazole	Oral / IV	>55	1.1	29.2	99.8	21-64	Hepatic
	Voriconazole	Oral / IV	>90	4.6	20.3	60	6	Renal
	Posaconazole	Oral / IV	>98	7.8	17	99	15-35	Feces
Echinocandins	Caspofungin	IV	<5	9.5-12.1	93.5-100.5	96	10.6	Urine
	Micafungin	IV	<5	7.1-10.9	59.9-111.3	99.8	41960	Feces
	Anidulafungin	IV	<5	3.4-7.5	44.4-104.5	84	18.1-25.6	Feces
Polyenes	Amphotericin B	IV	<5	1.5-2.1	13-17	>95	6.8-50	Feces
Nucleoside analog.	Flucytosine	Oral / IV	76-89	80	62	4	3-6	Renal

Source: Clinicaltrials.gov

Value proposition: Differentiated mechanism, convenience, safety and efficacy all provide advantages for SCY-078

Aside from possessing 1) a new mechanism of action, SCY-078 could also differentiate itself on the basis of 2) activity against resistant organisms, 3) seamless transition from the i.v. to the oral form, especially compared to the echinocandin class, 4) potentially earlier discharge from the hospital, 5) savings for the healthcare system, and 6) better safety, especially compared to the azole and polyene classes of drugs.

New mechanism of action. SCY-078 belongs to a new class of anti-fungal drugs that are enfumafungin derivatives. While SCY-078 hits a validated target similar to that of the echinocandins, in vitro data has demonstrated activity against organisms that are resistant to the echinocandin class underscoring SCY-078's unique mechanism of action.

Activity against resistant organisms. In vitro studies show SCY-078 is active against samples that are resistant to the azole and echinocandin drug classes. This is important as resistance against the azole class is already increasing. Even the echinocandins will see increasing resistance, as their use increases necessitating the development and use of a new anti-fungal like SCY-078.

Availability of an i.v. and oral form. While the azoles are available as i.v. and orals, resistance against them is increasing. The echinocandin class is seeing more usage because of the development of resistance; however, they are available as intravenous drugs only. SCY-078 would be available both in i.v. and oral form, which means patients can stay on the same drug class and be transitioned seamlessly from one to the other without the need to switch drug classes or to worry about resistant organisms.

Earlier discharge from the hospital. Since the echinocandins are only available as i.v. drugs, patients may need to stay hospitalized until their infection clears up completely. Physicians could discharge them on an oral azole drug, however, that increases the risk of the infection coming back. Since SCY-078 could be available both as an i.v. and as an oral, physicians could discharge patients on SCY-078 sooner.

Healthcare system savings. Earlier discharge from the hospital means savings for the system as a whole. This is a possibility both for patients who receive intravenous SCY-078 followed by oral SCY-078 and those who may be on an i.v. echinocandin yet be discharged on oral SCY-078 as no oral echinocandins are available.

Better safety profile. The azole class is known for potential drug-drug interactions and other side effects. The polyene class is recognized as being much more toxic, especially when it comes to renal toxicity. The side effect profile of SCY-078 has been fairly clean to date and that presents an advantage over the azole and polyene classes of anti-fungals and possibly even the echinocandin class.

Limitations associated with drugs currently used to treat systemic anti-fungal infections

Azoles. The biggest risk to the azole class is an increase in resistance, which has already led to higher echinocandin use. Once resistance develops against one azole drug given cross resistance on other drugs in the azole class will not be effective against the resistant organism. Azole drugs are also associated with a higher rate of side effects and a less favorable tolerability profile given the drug-drug interactions and potential for hepatic toxicity.

Echinocandins. The biggest limitation here is the lack of availability of an oral form. This necessitates either a patient staying in the hospital longer than is absolutely necessary or being discharged on an oral azole when switching between drug classes, especially to one where there is risk of resistance, is not optimal therapy. Both hypersensitivity reactions and liver function tests abnormalities are potential side effects. Resistance to the echinocandin class is also emerging.

Polyenes. This drug class is available as i.v. only and known for its toxicity and for this reason is often used as a drug of last resort. The main side effect is renal toxicity.

Long patent life and wholly owned asset

SCY-078 protected until 2030 and potentially 2035. SCYX owns all rights except Russia and certain smaller regions which are partnered out.

SCYX essentially owns all rights to SCY-078 giving it nearly full flexibility in either bringing SCY-078 to the market itself in the US, partnering SCY-078 regionally in the US, EU and/or Asia (as it has for Russia and certain other countries), or having the company acquired outright should development progress and the company succeed in clinical studies. We currently assume SCYX will find a partner outside the US and receive royalties on product sales.

SCY-078's patent protected life extends into 2030 in the US with the composition of matter patent. However, this term could be extended by another five years based on the Hatch-Waxman Act. Given the QIDP designation SCY-078 also benefits from an additional five years of protection in addition to the five years granted for new chemical entities. This essentially covers SCY-078 in multiple ways. As further evidence of its scientific prowess, SCYX has 14 issued US patents and 154 issued non-US patents. Several more patents are being pursued.

Partnerships underscore the science at Scynexis

SCYX has several partnerships in place, which are focused on its human and animal healthcare focused R&D. SCY-078 was re-acquired from MRK and is now partnered regionally with R-Pharm. Other partners include Aventis (Sanofi) and other animal health focused companies.

SCY-078 based obligations and partnerships

Merck (remaining terms for SCY-078). SCYX received all development and commercialization rights for SCY-078 (formerly MK-3118) back from Merck (MRK) in May 2013. We do not believe the decision reflects on the potential for SCY-078 but more likely reflects MRK's recent pipeline prioritization and resource allocation choices. SCYX received preclinical data, data from seven Phase I studies, drug product and substance, active pharmaceutical ingredient, and patents, among other things. The API is sufficient to help the development and manufacturing of an intravenous form of SCY-078. In return, MRK will receive milestone payments for Phase II and Phase III trial initiations, NDA filings, and marketing approvals in the US, EU and Japan. However, the total milestone obligation is fairly modest at $19MM. MRK will also receive tiered royalties on worldwide sales of SCY-078, which are in the single digits. Royalties will be paid for 10 years from launch on a country-by-country basis.

R-Pharm (regional partner for SCY-078). SCYX entered into a partnership with R-Pharm in August 2013 to develop and commercialize SCY-078 in Russia, Turkey, and certain other countries in Eastern Europe, Central Asia and Africa. SCYX retains the right to commercialize SCY-078 in North and South America, Europe and Asia. In return SCYX received an upfront payment of $1.5MM, is eligible to receive another $18MM in development and sales based milestones, and royalties in the teens. Royalties will be paid for up to 12 years from registration on a country-by-country basis.

Other partnerships for human and non-human products

- **Aventis**. SCYX entered an agreement with Aventis (SNY) for know-how, compounds and patents concerning cyclosporine derivatives exclusively for HIV/AIDS and non-exclusively for other diseases. SCYX is obliged to maintain reasonable efforts to develop and commercialize a product. However, the agreement ends when the US patent expires on December 23, 2017.
- **C-Chem**. SCYX received certain patents and know-how for cyclosporine derivatives from C-Chem. The agreement expires roughly with the US patent on SCY-641 on June 10, 2019.
- **Dechra**. SCYX partnered SCY-641 for the treatment of canine keratoconjunctivitis sicca (dry eye) with Dechra.
- **Elanco Animal Health**. SCYX performs research services for Elanco, which in turn will use the R&D from SCYX to develop pesticides for animals, animal products, animal feed, human food, or the food chain.
- **Merial**. SCYX provides contract and R&D services to Merial for animal health.

Large market opportunity: Attractive potential as first and second line drug

Global sales of systemic anti-fungal drugs totaled ~$3.6B worldwide according to SCYX. Roughly 400,000 patients are confirmed as cases of invasive Candida infections and another 200,000 patients as invasive Aspergillus infections. The unmet need remains high as the mortality rate for Candida ranges between 27-42% and for Aspergillus infections it is over 50%. SCYX estimates that confirmed cases of Candida blood infections account for only 25% to 33% of Candida treatments, which means the number of patients receiving treatment with systemic anti-fungals could be over one million worldwide. Treatment has to be empiric as diagnosis can be difficult, takes time and because delay increases mortality. Most patients receive intravenous treatment in hospitals and then are switched over or stepped down to oral formulations once their condition improves and/or for discharge from the hospital. The numbers of patient with systemic anti-fungal infections, especially those who are resistant to currently available drugs, is increasing and is expected to continue to increase given the rising numbers of patient who are immune compromised, prophylactic and empiric use of anti-fungals, and the selection pressures expected with broader usage of echinocandins or as generics become available.

We estimate SCY-078 could launch in 2019 in the US and project US and ROW market shares between 35-40% in our base case scenario. Assuming a price similar to branded antibiotics, peak sales in the US could be $300-400M and $1B+ for the rest of the world. We forecast first year sales of ~$24M in 2019 and a modest ramp to ~$116M in 2023, which could prove conservative. Outside the US, we forecast sales of ~$55M in 2020 which increase to $430M in 2024. This trend is in line with sales of currently available anti-fungal drugs whose sales totals remain as if not more significant outside than in the US. We expect SCYX to receive royalties of ~$9M in 2020 and $65M in 2024, which assumes a royalty rate of 15%. A higher royalty rate could be an upside driver for SCYX.

We see six paths to the market for SCY-078 in patients with systemic anti-fungal infections, from resistant organisms to first-line and prophylaxis

SCY-078 could address all the limitations of the existing drug classes. We see potential use in resistant patients and then on to newly diagnosed patients given the novel mechanism of action.

SCY-078 has the potential to address all the short comings of the currently available anti-fungal drugs, including resistance against the azole class, lack of an oral being available for the echinocandin class, and severe side effects associated with the polyene class. We see eventual use as a first-line treatment but more rapid uptake in the market initially where resistance is suspected. SCY-078 addresses all the weaknesses of the currently available drugs and drug classes and could be used in most or all of the following settings:

- **Drug resistant azole strains**. Resistant strains cause high rates of morbidity and mortality and lead to extended hospital stays. SCY-078 has shown efficacy vs. Candida species inherently resistant to azoles, such as Candida glabrata and Candida krusei, and against azole resistant strains of other species such as Candida albicans.
- **Drug resistant echinocandin strains**. SCY-078 has also been shown to be effective against the majority of echinocandin-resistant Candida strains tested in vitro.
- **Alternative to azoles and echinocandins as part of step-down therapy**. Physicians are reluctant to prescribe azoles in hospitals where azole resistance is prevalent. They prescribe echinocandins, which are i.v. only, and step down to an azole to permit earlier discharge from the hospital could risk relapse for an azole resistant infection, especially if the original organism was not identified and susceptibility not determined. Instead of keeping the patient on i.v. echinocandins, they could be discharged on SCY-078, which would be available as an oral.
- **Treatment of invasive Candida infections**. SCY-078 could overtake echinocandins as the drug of choice for these infections because it will be available as both an i.v. and oral form.

- **Treatment of invasive Aspergillus infections**. SCY-078 could also offer advantages over voriconazole, the current first line azole which has numerous drug-drug interactions and adverse events associated with it.
- **Prevention of Candida and Aspergillus infections**. Since SCY-078 has demonstrated in vitro activity against drug resistant strains of Candia and Aspergillus, using it as a prophylactic could be advantageous.

Exhibit 27: Sales of select anti-fungal drugs

($ in MM)						
Vfend	2008	2009	2010	2011	2012	2013
US	230	250	260	86	89	61
Inter.	513	548	565	661	665	714
EU	N/A	N/A	296	304	281	305
ROW	N/A	N/A	130	153	162	154
EM	N/A	N/A	139	204	222	255
Cancidas	2008	2009	2010	2011	2012	2013
US	100	73	61	44	32	31
Inter.	496	543	550	595	587	630
Total	2008	2009	2010	2011	2012	2013
US	$330	$323	$321	$130	$121	$92
Inter.	$1009	$1091	$1115	$1256	$1252	$1344
Total	**$1,339**	**$1,414**	**$1,436**	**$1,386**	**$1,373**	**$1,436**

Source: Company reports

Scynexis could commercialize the drugs itself in the US

SCYX expects physicians treating invasive fungal infections will be concentrated at major medical centers, focused on critical care, infectious diseases, and treating immune-compromised or immune-suppressed patients. This is a group of physicians that could be targeted by a small biotech. SCYX is likely to partner SCY-078 outside the US. It is already partnered with R-Pharm in Russia and certain other countries. The message for SCY-078 is likely to be a new mechanism of action, efficacy against resistant organisms, clean safety, and a convenient intravenous to oral switch on the same drug.

Exhibit 28: SCY-078 US and EU revenue build

		2019	2020	2021	2022	2023	2024	2025	2026	2027	2028	2029	2030	2031	2032
US Patients	150,000	168,924	172,303	175,749	179,264	182,849	186,506	190,236	194,041	197,922	201,880	205,918	210,036	214,237	218,522
% Growth	2.0%	2.0%	2.0%	2.0%	2.0%	2.0%	2.0%	2.0%	2.0%	2.0%	2.0%	2.0%	2.0%	2.0%	2.0%
% Penetration / Growth	3.0%	3.0%	5.5%	8.0%	10.5%	13.0%	15.5%	18.0%	20.5%	23.0%	25.5%	28.0%	30.5%	33.0%	35.5%
Patietnts on SCY-078		5,068	9,477	14,060	18,823	23,770	28,908	34,243	39,778	45,522	51,479	57,657	64,061	70,698	77,575
US $ per course / % Growth	$5,500	$24.6	$46.1	$68.4	$91.5	$115.6	$140.6	$166.5	$193.4	$221.3	$250.3	$280.3	$311.5	$343.7	$377.2
Gross-to-net	15.0%														
US Sales ($MM)		24.6	46.1	68.4	91.5	115.6	140.6	166.5	193.4	221.3	250.3	280.3	311.5	343.7	377.2
		2019	**2020**	**2021**	**2022**	**2023**	**2024**	**2025**	**2026**	**2027**	**2028**	**2029**	**2030**	**2031**	**2032**
ROW Patients	450,000	506,773	516,909	527,247	537,792	548,547	559,518	570,709	582,123	593,765	605,641	617,754	630,109	642,711	655,565
% Growth	2.0%														
% Penetration / Growth	2.0%	0.00%	2.00%	5.00%	8.00%	11.00%	14.00%	17.00%	20.00%	23.00%	26.00%	29.00%	32.00%	35.00%	38.00%
Patietnts on SCY-078		0	10,338	26,362	43,023	60,340	78,333	97,020	116,425	136,566	157,467	179,149	201,635	224,949	249,115
ROW $ per course / % Growth	$5,500	0.0	56.9	145.0	236.6	331.9	430.8	533.6	640.3	751.1	866.1	985.3	1,109.0	1,237.2	1,370.1
Gross-to-net	0.0%														
ROW Royalty ($ MM)	15.0%	0.0	8.5	21.7	35.5	49.8	64.6	80.0	96.1	112.7	129.9	147.8	166.3	185.6	205.5

Source: RBC Capital Markets estimates

Financial projections and model assumptions

Current revenue for SCYX primarily comes from contract research and developmental services for animal health but additional revenue is expected with SCY-078 that is in clinical development at this time. We expect SCY-078 to get approved and be on the market in 2019 in the US and 2020 in the EU. Since SCYX has worldwide rights, excluding certain regions such as Russia, it could opt to partner outside the US. A partnership could involve a profit split or co-promote structure or more likely straight royalties on product sales. We assume SCYX will receive royalties of 15% on SCY-078 sales outside the US.

Revenues. We forecast SCY-078 revenues of $24.6MM in 2019, $91.5MM in 2022, the third full year of products on the market, and $166.5MM in 2025. Our estimates could prove conservative especially if SCY-078 succeeds in showing the overall best safety and efficacy profile of any drug currently available for invasive fungal infections, especially against resistant disease. Upside could also come from SCY-078 outside the US and if rates of resistance continue to rise.

Royalty revenues. We forecast EU approval and launch to lag roughly one-year behind US timelines. We forecast a royalty rate of 15%, and royalties of $8.5MM in 2020, $49.8MM in 2023, and $96.1MM in 2026.

COGS and gross margin. SCY-078 is a small molecules so we assume a cost of goods sold of ~10% and a gross margin of ~90%, which remains steady over time.

R&D expenses could go down once pivotal trials are completed. We expect R&D expenses to increase from $10.0MM in 2014 to $35.0MM in 2018 and then decline thereafter.

SG&A expenses likely to ramp up starting in 2019. Currently, we model SCYX could market SCY-078 in the US by itself. Since we forecast SCY-078 approval in 2019, we begin ramping up SG&A in 2018, one year ahead of launch, followed by bigger increases in 2019 and 2020. We estimate SG&A is ~20% of product sales starting 2022 and going forward.

Income tax rate. We forecast a tax rate of 34%.

Net income. SCYX could be profitable in 2021 depending upon how quickly product sales ramp and whether or not it chooses to continue to invest in the pipeline beyond SCY-078. We forecast an EPS of $0.81 in 2021, which increases to $1.73 in 2022, the third full year of products on the market, and $2.61 in 2023.

Shares outstanding. SCYX has approximately ~8.5MM shares outstanding after the recently closed initial public offering. This total excludes stock options, warrants, restricted stock units, and any other employee stock purchase plans.

Cash and equivalents of ~$58MM from the IPO. SCYX completed its US initial public offering (IPO) on May 2, 2014 to raise approximately $62MM. We currently assume further financings. However, depending upon whether the business development activities SCYX undertakes, including whether SCYX partners SCY-078 outside the US or not and the terms of that partnership could determine how much, if any, capital SCYX needs before achieving sustained profitability.

Valuation: Base, upside and downside case

Our base, upside and downside case are based on a sum-of-the-parts discounted cash flow (DCF) analysis for SCYX's SCY-078. We also use a P/E multiple based approach.

- **Sum-of-the-parts DCF (primary valuation approach)**. We arrive at our $17 per share price target using a sum-of-the parts discounted cash flow analysis for SCYX shares. The primary components of our valuation include SCYX's SCY-078 product sales in the US and royalty revenues from sales in the rest of the world (ROW). Our base, upside and downside scenarios use a discount rate of 15% to reflect potential clinical risk and assign a 60% probability of success to SCY-078. This probability of success is based on what we think the chances are of SCY-078 being successfully developed. Each set of clinical data is likely to lead to us adjusting this probability to reflect a positive development.
- **P/E based valuation**. However, valuation using a P/E multiple based methodology supports $20 per share.

While we believe clinical risk is low, as an anti-fungal product candidate's efficacy is typically demonstrated in the test tube, both regulatory and commercial risk could be high as the FDA needs to sign off on the pivotal trial plan for SCY-078 and because commercial viability requires a value proposition that includes safety, efficacy, convenience and activity against drug resistant organisms.

Potential levers for upside. Upside would come from positive Phase I data for SCY-078 and phase II results from the oral SCY-078 step down study. A partnership with a pharmaceutical or biotechnology company for the development of SCY-078 could also lead us to include milestones for clinical, regulatory and commercial success as well as to lower the discount rate as SCYX could benefit from the capabilities of a potentially larger partner with greater resources. An additional 5-years of patent protection could also serve as upside.

Base case: $17 per share

We value SCYX at $17 per share, which includes US and ROW sales of SCY-078. We assign a probability of success of 60% and a value of ~$10 per share to the US and $7 per share to the ROW opportunity. We assume a US launch in 2019 and an ROW launch in 2020. Currently, we assume that SCYX will sell SCY-078 in the US and a partner will commercialize these compounds outside the US. We forecast peak SCY-078 sales of $300-400MM in the US and $1.0-1.4B in the ROW. We currently assign no additional value to the earlier stage pipeline. Finally, we assume product sales extend into 2030 and include a terminal value based on a terminal growth rate of -50% and a discount rate of 15%.

Upside case: $34 per share

Our upside scenario includes ~$18 per share in value for the US opportunity and ~$16 per share in value for the ROW opportunity. We forecast peak SCY-078 sales of $600-700MM in the US and $1.7B-$2B in the ROW. We assign SCY-078 a 60% probability of success, a discount rate of 15%, and use a terminal growth rate of -50%.

Downside case: $5 per share

Our downside scenario assumes that SCY-078 may not be successful clinically or commercially either because efficacy against resistant organisms was not borne out or it was not long lasting or an unexpected adverse event was seen. Under such a scenario shares would trade at roughly cash per share which is currently ~$5.

Exhibit 29: Scynexis sum of the parts scenario analysis and valuation summary

($ in MM; except per share) Sum of the Parts	Discount Rate	Prob.	Sales (5-years post launch) US	Sales (5-years post launch) ROW	Value per Share US	Value per Share ROW Royalty	Value per Share ROW 100%	Total
Base Case	15.0%	60.0%	$141	$534	$6	$11	$38	$17
Upside Case	15.0%	60.0%	$197	$769	$16	$18	$71	$34
Downside Case	N/A	N/A	N/A	N/A	N/A	N/A	N/A	$5 *
		P/ E	Periods	EPS				
P/E Based	15.0%	15	9	$2.61				$11

*Downside scenario reflects cash per share
Source: RBC Capital Markets

Scynexis P/E multiple based valuation

We use a P/E multiple of 15x our 2024 fully taxed GAAP EPS estimate of $2.61 and a discount rate of 15% for nine years to arrive at our price target of $11/share. This P/E multiple could be conservative given that the median P/E for a group of large and profitable biotechnology companies is 22x and 26x, respectively.

Exhibit 30: SCYX P/E multiple based valuation analysis

		PE Multiple						
	$11.11	12.0	13.0	14.0	15.0	16.0	17.0	18.0
	9.0%	$14.39	$15.59	$16.79	$17.99	$19.19	$20.39	$21.59
	11.0%	$12.22	$13.24	$14.26	$15.28	$16.30	$17.31	$18.33
Discount	13.0%	$10.41	$11.27	$12.14	$13.01	$13.88	$14.74	$15.61
Rate	15.0%	$8.89	$9.63	$10.37	$11.11	$11.85	$12.59	$13.33
	17.0%	$7.61	$8.24	$8.88	$9.51	$10.15	$10.78	$11.41
	19.0%	$6.53	$7.08	$7.62	$8.17	$8.71	$9.26	$9.80
	21.0%	$5.62	$6.09	$6.56	$7.03	$7.50	$7.97	$8.43

Source: RBC Capital Markets

Price target impediments

Our price target is dependent solely on the clinical, regulatory, and commercial success of SCY-078. A Phase II study for oral SCY-078 and a Phase I for intravenous SCY-078 is expected by 2015 and data expected in 2015. Failure to demonstrate efficacy or safety in these studies would be a significant setback as would failure to advance to the next stage of clinical trials. Furthermore, any setbacks in regulatory approvals in the US or EU, delay in launch, failure to secure a partnership outside the US for SCY-078, increased competition or other limitations to the market potential of SCY-078 could negatively impact our valuation.

Seasoned management team is a veteran of the anti-infective and anti-fungal space

Management team, board/ advisor experience is an advantage.

Yves J. Ribeill, Ph.D., President, Chief Executive Officer and member board of directors. Dr. Ribeill has been CEO and a board member since November 1999. **Prior experience (select)**: Discovery chemistry group leader for antiviral research and director of chemistry for the anti-infective group at Aventis Pharma S.A. and its predecessor. **Education**. Ph.D. in Chemistry from the University of Montpellier in France.

Carole Sable, MD, Chief Medical Officer. Dr. Sable has been the CMO since January 2014. **Prior experience (select)**: Vice President, Merck (2010- 2013); CMO, Novexel SA (2007-2010); various positions, Merck (1995-2007), including Executive Director in 2006; Assistant Professor of Medicine and Infectious Diseases, University of Virginia. **Education**: Jefferson Medical College and a residency in internal medicine and fellowship in infectious disease at the University of Virginia.

Charles F. Osborne, Jr., Chief Financial Officer. Mr. Osborne has been CFO since November 2003. **Prior experience (select)**: CFO, Nobex (1999-2003); VP, Finance, Murex Technologies (1992-1998), including sale of the company to Abbott Laboratories. **Education**: B.S., Accounting, University of North Carolina at Chapel Hill.

Denis Schmatz, Ph.D., Advisor. Over 35 years of drug discovery and development experience in pharmaceutical research. He was Vice President of Infectious Disease Research and Animal Health at Merck for more than a decade. Significant contributions include the discovery of; new biochemical pathways and drug targets, novel natural products with antimicrobial activity, and several approved drugs including Cancidas, an antifungal agent for treating serious life threatening hospital infections.

Scynexis - Income Statement

FYE December 31

Adnan Butt (415) 633-8588
Adnan.Butt@rbccm.com

(in MM; except per share)	2012A	2013A	1Q:14E	2Q:14E	3Q:14E	4Q:14E	2014E	1Q:15E	2Q:15E	3Q:15E	4Q:15E	2015E	2016E	2017E	2018E	2019E	2020E	2021E	2022E	2023E
Revenue:																				
SCY-078																24.6	46.1	68.4	91.5	115.6
Other Revenue	9.4	9.6	4.3	4.3	4.3	4.3	17.0	4.3	4.3	4.3	4.3	17.1	17.2	17.3	17.4	17.5	17.6	17.7	17.8	17.9
Total Revenue	16.8	16.9	4.3	4.3	4.3	4.3	17.0	4.3	4.3	4.3	4.3	17.1	17.2	17.3	17.4	42.1	72.2	107.8	144.8	183.3
Operating expenses:																				
Cost of Other Revenue	14.4	16.3	4.1	4.1	4.1	4.1	16.4	4.1	4.1	4.1	4.1	16.5	16.6	16.7	16.8	16.9	17.0	17.1	17.2	17.3
R&D	8.9	4.4	2.0	2.3	2.8	3.0	10.0	3.3	3.5	3.8	4.5	15.0	20.0	30.0	35.0	25.0	22.5	25.0	27.5	30.0
SG&A	4.7	4.4	1.3	1.3	1.3	1.3	5.0	1.5	1.5	1.5	1.5	8.0	8.5	9.0	10.0	22.5	28.8	30.0	28.3	28.1
Gain on sale of asset	(3.4)	(1.0)																		
Total Expenses	24.6	24.1	7.4	7.6	8.1	8.4	31.4	8.9	9.1	9.4	10.1	37.5	45.1	55.7	61.8	66.9	72.9	78.9	82.2	87.0
Operating Income (Expense)	(7.8)	(7.2)	(3.1)	(3.4)	(3.9)	(4.1)	(14.4)	(4.6)	(4.9)	(5.1)	(5.9)	(20.4)	(27.9)	(38.4)	(44.4)	(24.7)	(0.7)	28.9	62.7	96.3
Other:																				
Amortization of deferred financing cost and debt discount	(2.9)	(3.5)																		
Interest expense for beneficial conversion feature		(10.8)																		
Interest expense-related party	(0.7)	(0.9)	(0.2)	(0.2)	(0.2)	(0.2)	(0.9)													
Interest expense	(0.2)	(0.2)	(0.0)	(0.0)	(0.0)	(0.0)	(0.2)													
Derivative fair value adjustment	0.2	(7.9)																		
Other income	0.0		0.1	0.1	0.1	0.1	0.2	0.1	0.1	0.1	0.1	0.2	0.1	0.1	0.1	0.1	0.2	0.4	0.6	0.8
Income before Tax	(11.5)	(30.5)	(3.3)	(3.6)	(4.1)	(4.3)	(15.3)	(4.6)	(4.9)	(5.1)	(5.9)	(20.4)	(27.9)	(38.4)	(44.4)	(24.7)	(0.7)	28.9	62.7	96.3
Taxes																		9.8	21.3	32.7
Net income (loss)	(11.5)	(30.5)	(3.3)	(3.6)	(4.1)	(4.3)	(15.3)	(4.6)	(4.9)	(5.1)	(5.9)	(20.4)	(27.9)	(38.4)	(44.4)	(24.7)	(0.7)	19.1	41.4	63.5
EPS, Basic (GAAP)	($1.73)	($6.84)	($0.48)	($0.37)	($0.42)	($0.44)	($1.69)	($0.47)	($0.49)	($0.51)	($0.58)	($2.05)	($1.83)	($2.47)	($2.80)	($1.17)	($0.03)	$0.87	$1.84	$2.78
EPS, Diluted (GAAP)	($1.41)	($5.61)	($0.40)	($0.32)	($0.36)	($0.38)	($1.45)	($0.40)	($0.42)	($0.44)	($0.51)	($1.78)	($1.67)	($2.26)	($2.56)	($1.09)	($0.03)	$0.81	$1.73	$2.61
Shares outstanding, Basic	6.6	6.8	6.9	9.7	9.8	9.8	9.0	9.9	9.9	10.0	10.0	9.9	15.2	15.5	15.8	21.1	21.6	22.0	22.4	22.9
Shares outstanding, Diluted	8.1	8.3	8.4	11.2	11.3	11.3	10.5	11.4	11.4	11.5	11.5	11.4	16.7	17.0	17.3	22.6	23.1	23.5	23.9	24.4
Operating Ratios	2012A	2013A	1Q:14E	2Q:14E	3Q:14E	4Q:14E	2014E	1Q:15E	2Q:15E	3Q:15E	4Q:15E	2015E	2016E	2017E	2018E	2019E	2020E	2021E	2022E	2023E
COGS																10.0%	10.0%	10.0%	10.0%	10.0%
Gross Margin	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	90.0%	90.0%	90.0%	90.0%	90.0%
R&D	53.0%	25.9%	47.1%	52.9%	64.7%	70.6%	58.8%	76.0%	81.9%	87.7%	105.3%	87.7%	116.3%	173.4%	201.1%	59.3%	31.2%	23.2%	19.0%	16.4%
SG&A	28.2%	26.0%	29.4%	29.4%	29.4%	29.4%	29.4%	35.1%	35.1%	35.1%	35.1%	46.8%	49.4%	52.0%	57.5%	53.4%	39.8%	27.8%	19.5%	15.3%
Operating Margin	-46.2%	-42.7%	-72.9%	-78.8%	-90.6%	-96.5%	-84.7%	-107.6%	-113.5%	-119.3%	-136.8%	-119.3%	-162.2%	-222.0%	-255.2%	-58.7%	-0.9%	26.8%	43.3%	52.5%
Taxes	34.0%	34.0%	34.0%	34.0%	34.0%	34.0%	34.0%	34.0%	34.0%	34.0%	34.0%	34.0%	34.0%	34.0%	34.0%	34.0%	34.0%	34.0%	34.0%	34.0%
Net Margin	-68.2%	-180.7%	-78.1%	-84.0%	-95.8%	-101.7%	-89.9%	-107.6%	-113.5%	-119.3%	-136.8%	-119.3%	-162.2%	-222.0%	-255.2%	-58.7%	-0.9%	17.7%	28.6%	34.7%
Source: Company reports and RBC Capital Markets estimates.																				
Balance Sheet - Select Items	2012A	2013A	1Q:14E	2Q:14E	3Q:14E	4Q:14E	2014E	1Q:15E	2Q:15E	3Q:15E	4Q:15E	2015E	2016E	2017E	2018E	2019E	2020E	2021E	2022E	2023E
Cash and cash equivalents	2.4	1.4	0.5	55.7	52.7	49.5	49.5	46.0	42.3	38.3	33.5	33.5	89.5	54.5	14.1	85.8	87.4	108.8	152.4	218.2
Total current assets	5.2	3.0	1.0	56.2	53.2	50.0	50.0	46.5	42.8	38.8	34.0	34.0	90.0	55.5	15.1	88.3	91.6	115.0	160.8	228.8
Total assets	12.1	12.4	2.5	59.0	57.4	55.5	55.5	53.4	51.0	48.3	45.0	45.0	106.3	77.2	42.2	120.8	129.4	158.3	209.5	282.8
Current Liabilities																				
Total current liabilities	14.2	18.5	8.4	8.7	9.0	9.3	9.3	9.6	9.9	10.2	10.5	10.5	11.7	13.4	14.6	17.2	20.7	24.2	27.8	31.5
Total liabilities	17.2	14.9	14.9	14.9	14.9	14.9	14.9	14.9	14.9	14.9	14.9	14.9	14.9	14.9	14.9	14.9	14.9	14.9	14.9	14.9
Accumulated deficit	(82.8)	(113.3)	(113.1)	(114.6)	(116.5)	(118.6)	(118.6)	(121.1)	(123.8)	(126.7)	(130.4)	(130.4)	(150.2)	(180.9)	(217.2)	(235.2)	(229.5)	(203.9)	(156.1)	(86.1)
Total stockholders' equity	(19.3)	(21.0)	(20.8)	35.4	33.5	31.4	31.4	28.9	26.2	23.3	19.6	19.6	159.6	128.9	92.6	262.6	268.3	293.9	341.7	411.7
Total liabilities and stockholders Equity	12.1	12.4	2.5	59.0	57.4	55.5	55.5	53.4	51.0	48.3	45.0	45.0	186.2	157.1	122.1	294.7	303.8	332.9	384.4	458.0
Cash Flow Statement - Select Items	2012A	2013A	1Q:14E	2Q:14E	3Q:14E	4Q:14E	2014E	1Q:15E	2Q:15E	3Q:15E	4Q:15E	2015E	2016E	2017E	2018E	2019E	2020E	2021E	2022E	2023E
Net Income (loss)	(11.5)	(30.5)	(3.3)	(3.6)	(4.1)	(4.3)	(15.3)	(4.6)	(4.9)	(5.1)	(5.9)	(20.4)	(27.9)	(38.4)	(44.4)	(24.7)	(0.7)	19.1	41.4	63.5
Gain on sale of asset, net of transaction expenses	(3.4)	(1.0)	(1.0)	(1.0)	(1.0)	(1.0)	(4.0)	(1.0)	(1.0)	(1.0)	(1.0)	(4.0)	(4.0)	(4.0)	(4.0)	(4.0)	(4.0)	(4.0)	(4.0)	(4.0)
Stock-based compensation expense	0.4	0.2	0.4	0.4	0.4	0.4	1.4	0.4	0.4	0.4	0.4	1.4	1.4	1.4	1.4	1.4	1.4	1.4	1.4	1.4
Net cash provided (used) by operating activities	(10.6)	(4.3)	(0.6)	(2.1)	(2.6)	(2.9)	(8.1)	(3.1)	(3.4)	(3.6)	(4.4)	(14.5)	(22.5)	(33.5)	(39.0)	(20.8)	3.0	22.9	45.1	67.2
Purchases of property and equipment	(0.4)	(0.4)	(0.4)	(0.4)	(0.4)	(0.4)	(1.4)	(0.4)	(0.4)	(0.4)	(0.4)	(1.4)	(1.4)	(1.4)	(1.4)	(1.4)	(1.4)	(1.4)	(1.4)	(1.4)
Net cash used in investing activities	3.1	0.6	(0.4)	(0.4)	(0.4)	(0.4)	(1.4)	(0.4)	(0.4)	(0.4)	(0.4)	(1.4)	(1.4)	(1.4)	(1.4)	(1.4)	(1.4)	(1.4)	(1.4)	(1.4)
Proceeds from sale of preferred stock		2.5																		
Net cash provided by (used in) financing activities	6.0	2.8		57.7			57.7						79.9			94.0				
Decrease in cash and cash equivalents	(1.6)	(1.0)	(0.9)	55.2	(3.0)	(3.2)	48.1	(3.5)	(3.7)	(4.0)	(4.7)	(16.0)	55.9	(35.0)	(40.5)	71.8	1.5	21.4	43.6	65.7
Cash and cash equivalents at the beginning of the year	4.0	2.4	1.4	0.5	55.7	52.7	1.4	49.5	46.0	42.3	38.3	49.5	33.5	89.5	54.5	14.1	85.8	87.4	108.8	152.4
Cash and cash equivalents at the end of the year	2.4	1.4	0.5	55.7	52.7	49.5	49.5	46.0	42.3	38.3	33.5	33.5	89.5	54.5	14.1	85.8	87.4	108.8	152.4	218.2

Source: Company reports and RBC Capital Markets estimates.

Required disclosures

Conflicts disclosures

The analyst(s) responsible for preparing this research report received compensation that is based upon various factors, including total revenues of the member companies of RBC Capital Markets and its affiliates, a portion of which are or have been generated by investment banking activities of the member companies of RBC Capital Markets and its affiliates.

Please note that current conflicts disclosures may differ from those as of the publication date on, and as set forth in, this report. To access current conflicts disclosures, clients should refer to https://www.rbccm.com/GLDisclosure/PublicWeb/DisclosureLookup.aspx?entityId=1 or send a request to RBC CM Research Publishing, P.O. Box 50, 200 Bay Street, Royal Bank Plaza, 29th Floor, South Tower, Toronto, Ontario M5J 2W7.

A member company of RBC Capital Markets or one of its affiliates managed or co-managed a public offering of securities for SCYNEXIS Inc. in the past 12 months.

A member company of RBC Capital Markets or one of its affiliates received compensation for investment banking services from SCYNEXIS Inc. in the past 12 months.

A member company of RBC Capital Markets or one of its affiliates expects to receive or intends to seek compensation for investment banking services from SCYNEXIS Inc. in the next three months.

RBC Capital Markets, LLC makes a market in the securities of SCYNEXIS Inc..

RBC Capital Markets is currently providing SCYNEXIS Inc. with investment banking services.

RBC Capital Markets has provided SCYNEXIS Inc. with investment banking services in the past 12 months.

Explanation of RBC Capital Markets Equity rating system

An analyst's 'sector' is the universe of companies for which the analyst provides research coverage. Accordingly, the rating assigned to a particular stock represents solely the analyst's view of how that stock will perform over the next 12 months relative to the analyst's sector average. Although RBC Capital Markets' ratings of Top Pick (TP)/Outperform (O), Sector Perform (SP), and Underperform (U) most closely correspond to Buy, Hold/Neutral and Sell, respectively, the meanings are not the same because our ratings are determined on a relative basis.

Ratings

Top Pick (TP): Represents analyst's best idea in the sector; expected to provide significant absolute total return over 12 months with a favorable risk-reward ratio.

Outperform (O): Expected to materially outperform sector average over 12 months.

Sector Perform (SP): Returns expected to be in line with sector average over 12 months.

Underperform (U): Returns expected to be materially below sector average over 12 months.

Risk Rating

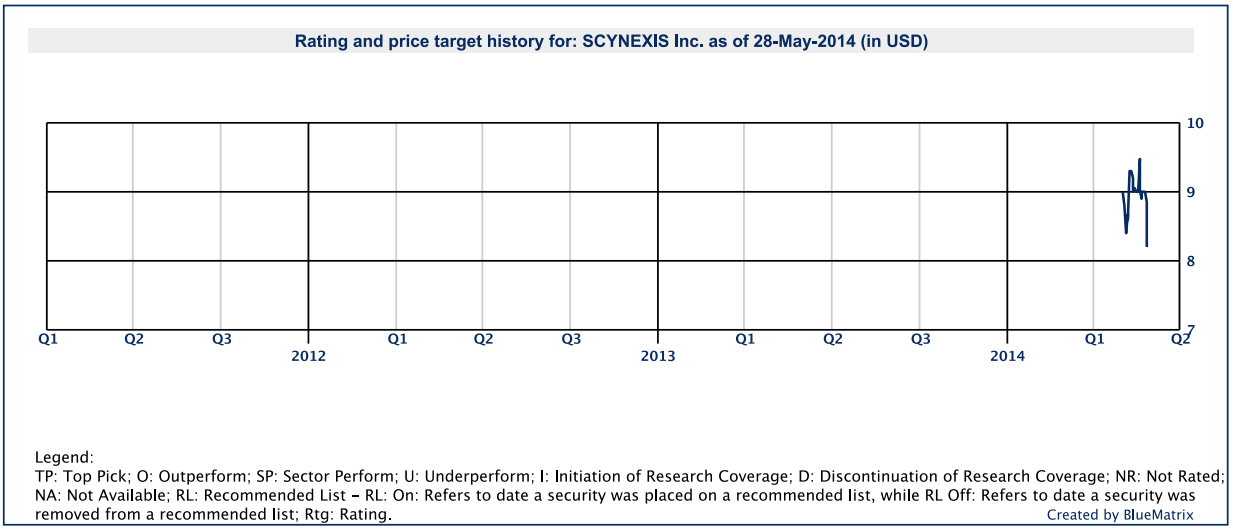
As of March 31, 2013, RBC Capital Markets suspends its Average and Above Average risk ratings. The **Speculative** risk rating reflects a security's lower level of financial or operating predictability, illiquid share trading volumes, high balance sheet leverage, or limited operating history that result in a higher expectation of financial and/or stock price volatility.

Distribution of ratings

For the purpose of ratings distributions, regulatory rules require member firms to assign ratings to one of three rating categories - Buy, Hold/Neutral, or Sell - regardless of a firm's own rating categories. Although RBC Capital Markets' ratings of Top Pick(TP)/ Outperform (O), Sector Perform (SP), and Underperform (U) most closely correspond to Buy, Hold/Neutral and Sell, respectively, the meanings are not the same because our ratings are determined on a relative basis (as described below).

Distribution of ratings
RBC Capital Markets, Equity Research
As of 31-Mar-2014

			Investment Banking Serv./Past 12 Mos.	
Rating	Count	Percent	Count	Percent
BUY [Top Pick & Outperform]	822	52.49	303	36.86
HOLD [Sector Perform]	654	41.76	170	25.99
SELL [Underperform]	90	5.75	11	12.22



References to a Recommended List in the recommendation history chart may include one or more recommended lists or model portfolios maintained by RBC Wealth Management or one of its affiliates. RBC Wealth Management recommended lists include a former list called the Prime Opportunity List (RL 3), the Guided Portfolio: Prime Income (RL 6), the Guided Portfolio: Large Cap (RL 7), the Guided Portfolio: Dividend Growth (RL 8), the Guided Portfolio: Midcap 111 (RL 9), the Guided Portfolio: ADR (RL 10), and the Guided Portfolio: Global Equity (U.S.) (RL 11). RBC Capital Markets recommended lists include the Strategy Focus List and the Fundamental Equity Weightings (FEW) portfolios. The abbreviation 'RL On' means the date a security was placed on a Recommended List. The abbreviation 'RL Off' means the date a security was removed from a Recommended List.

Equity valuation and risks

For valuation methods used to determine, and risks that may impede achievement of, price targets for covered companies, please see the most recent company-specific research report at https://www.rbcinsight.com or send a request to RBC Capital Markets Research Publishing, P.O. Box 50, 200 Bay Street, Royal Bank Plaza, 29th Floor, South Tower, Toronto, Ontario M5J 2W7.

Conflicts policy

RBC Capital Markets Policy for Managing Conflicts of Interest in Relation to Investment Research is available from us on request. To access our current policy, clients should refer to

https://www.rbccm.com/global/file-414164.pdf
or send a request to RBC Capital Markets Research Publishing, P.O. Box 50, 200 Bay Street, Royal Bank Plaza, 29th Floor, South Tower, Toronto, Ontario M5J 2W7. We reserve the right to amend or supplement this policy at any time.

Dissemination of research and short-term trade ideas

RBC Capital Markets endeavours to make all reasonable efforts to provide research simultaneously to all eligible clients, having regard to local time zones in overseas jurisdictions. Subject to any applicable regulatory considerations, "eligible clients" may include RBC Capital Markets institutional clients globally, the retail divisions of RBC Dominion Securities Inc. and RBC Capital Markets LLC, and affiliates. RBC Capital Markets' equity research is posted to our proprietary websites to ensure eligible clients receive coverage initiations and changes in rating, targets and opinions in a timely manner. Additional distribution may be done by the sales personnel via email, fax or regular mail. Clients may also receive our research via third party vendors. Please contact your investment advisor or institutional salesperson for more information regarding RBC Capital Markets research. RBC Capital Markets also provides eligible clients with access to SPARC on its proprietary INSIGHT website. SPARC contains market color and commentary, and may also contain Short-Term Trade Ideas regarding the securities of subject companies discussed in this or other research reports. SPARC may be accessed via the following hyperlink: https://www.rbcinsight.com. A Short-Term Trade Idea reflects the research analyst's directional view regarding the price of the security of a subject company in the coming days or weeks, based on market and trading events. A Short-Term Trade Idea may differ from the price targets and/or recommendations in our published research reports reflecting the research analyst's views of the longer-term (one year) prospects of the subject company, as a result of the differing time horizons, methodologies and/or other factors. Thus, it is possible that the security of a subject company that is considered a long-term 'Sector Perform' or even an 'Underperform' might be a short-term buying opportunity as a result of temporary selling pressure in the market; conversely, the security of a subject company that is rated a long-term 'Outperform' could be considered susceptible to a short-term downward price correction. Short-Term Trade Ideas are not ratings, nor are they part of any ratings system, and RBC Capital Markets generally does not intend, nor undertakes any obligation, to maintain or update Short-Term Trade Ideas. Short-Term Trade Ideas discussed in SPARC may not be suitable for all investors and have not been tailored to individual investor circumstances and objectives, and investors should make their own independent decisions regarding any Short-Term Trade Ideas discussed therein.

Analyst certification

All of the views expressed in this report accurately reflect the personal views of the responsible analyst(s) about any and all of the subject securities or issuers. No part of the compensation of the responsible analyst(s) named herein is, or will be, directly or indirectly, related to the specific recommendations or views expressed by the responsible analyst(s) in this report.

Disclaimer

any of its affiliates, nor any other person, accepts any liability whatsoever for any direct or consequential loss arising from any use of this report or the information contained herein. No matter contained in this document may be reproduced or copied by any means without the prior consent of RBC Capital Markets.

Additional information is available on request.

To U.S. Residents:
This publication has been approved by RBC Capital Markets, LLC (member FINRA, NYSE, SIPC), which is a U.S. registered broker-dealer and which accepts responsibility for this report and its dissemination in the United States. Any U.S. recipient of this report that is not a registered broker-dealer or a bank acting in a broker or dealer capacity and that wishes further information regarding, or to effect any transaction in, any of the securities discussed in this report, should contact and place orders with RBC Capital Markets, LLC.

To Canadian Residents:
This publication has been approved by RBC Dominion Securities Inc.(member IIROC). Any Canadian recipient of this report that is not a Designated Institution in Ontario, an Accredited Investor in British Columbia or Alberta or a Sophisticated Purchaser in Quebec (or similar permitted purchaser in any other province) and that wishes further information regarding, or to effect any transaction in, any of the securities discussed in this report should contact and place orders with RBC Dominion Securities Inc., which, without in any way limiting the foregoing, accepts responsibility for this report and its dissemination in Canada.

To U.K. Residents:
This publication has been approved by RBC Europe Limited ('RBCEL') which is authorized by the Prudential Regulation Authority and regulated by the Financial Conduct Authority ('FCA') and the Prudential Regulation Authority, in connection with its distribution in the United Kingdom. This material is not for general distribution in the United Kingdom to retail clients, as defined under the rules of the FCA. However, targeted distribution may be made to selected retail clients of RBC and its affiliates. RBCEL accepts responsibility for this report and its dissemination in the United Kingdom.

To Persons Receiving This Advice in Australia:
This material has been distributed in Australia by Royal Bank of Canada - Sydney Branch (ABN 86 076 940 880, AFSL No. 246521). This material has been prepared for general circulation and does not take into account the objectives, financial situation or needs of any recipient. Accordingly, any recipient should, before acting on this material, consider the appropriateness of this material having regard to their objectives, financial situation and needs. If this material relates to the acquisition or possible acquisition of a particular financial product, a recipient in Australia should obtain any relevant disclosure document prepared in respect of that product and consider that document before making any decision about whether to acquire the product. This research report is not for retail investors as defined in section 761G of the Corporations Act.

To Hong Kong Residents:
This publication is distributed in Hong Kong by RBC Investment Services (Asia) Limited, RBC Investment Management (Asia) Limited and RBC Capital Markets (Hong Kong) Limited, licensed corporations under the Securities and Futures Ordinance or, by the Royal Bank of Canada, Hong Kong Branch, a registered institution under the Securities and Futures Ordinance. This material has been prepared for general circulation and does not take into account the objectives, financial situation, or needs of any recipient. Hong Kong persons wishing to obtain further information on any of the securities mentioned in this publication should contact RBC Investment Services (Asia) Limited, RBC Investment Management (Asia) Limited, RBC Capital Markets (Hong Kong) Limited or Royal Bank of Canada, Hong Kong Branch at 17/Floor, Cheung Kong Center, 2 Queen's Road Central, Hong Kong (telephone number is 2848-1388).

To Singapore Residents:
This publication is distributed in Singapore by the Royal Bank of Canada, Singapore Branch and Royal Bank of Canada (Asia) Limited, registered entities granted offshore bank and merchant bank status by the Monetary Authority of Singapore, respectively. This material has been prepared for general circulation and does not take into account the objectives, financial situation, or needs of any recipient. You are advised to seek independent advice from a financial adviser before purchasing any product. If you do not obtain independent advice, you should consider whether the product is suitable for you. Past performance is not indicative of future performance. If you have any questions related to this publication, please contact the Royal Bank of Canada, Singapore Branch or Royal Bank of Canada (Asia) Limited.

To Japanese Residents:
Unless otherwise exempted by Japanese law, this publication is distributed in Japan by or through RBC Capital Markets (Japan) Ltd., a registered type one financial instruments firm and/or Royal Bank of Canada, Tokyo Branch, a licensed foreign bank.