EDISON

Sunesis Pharmaceuticals

Clinical outlook

First signs of efficacy coming up

Pharma & biotech

Sunesis is currently in the dose-escalation portion of the Phase Ib/II study of its BTK inhibitor vecabrutinib, and the first signs of clinical efficacy are expected in the upcoming doses. The drug is being tested in a range of B-cell malignancies where BTK inhibitors have historically shown some activity. The company will provide its next clinical update at the European Hematology Association (EHA) Congress in June 2019. In this note we review the clinical data to date and provide our clinical outlook.

Year end	Revenue ($m)	PBT* ($m)	EPS* ($)	DPS ($)	P/E (x)	Yield (%)
12/17	0.7	(35.5)	(1.45)	0.00	N/A	N/A
12/18	0.2	(26.6)	(0.75)	0.00	N/A	N/A
12/19e	0.0	(28.7)	(0.42)	0.00	N/A	N/A
12/20e	0.0	(33.3)	(0.46)	0.00	N/A	N/A

Note: *PBT and EPS are normalised, excluding amortisation of acquired intangibles, exceptional items and share-based payments.

Potential activity in Imbruvica-resistant patients

Vecabrutinib is an inhibitor of Bruton's tyrosine kinase (BTK), which is the same mechanism of action as Imbruvica (ibrutinib, AbbVie/Janssen, $4.4bn in 2018 sales), which is approved for the treatment of chronic lymphocytic leukemia (CLL) and other B-cell malignancies. However, vecabrutinib is a non-covalent inhibitor of the enzyme, which provides the potential for activity in Imbruvica-resistant patients, notably those with mutations in cysteine-481. In the upcoming cohorts we hope to see some engagement of the BTK enzyme in patients known to carry this mutation.

What are the first signs of efficacy?

Historically, BTK inhibitors have shown clinical efficacy when they achieve occupancy over approximately 80%, which should be achieved at doses between 100mg and 300mg twice a day. It is unlikely, though, given the short duration of time on drug that patients will be evaluable for partial or complete response. The first histological signs of BTK drug activity are nodal responses and paradoxically an increase in lymphocytosis correlated with symptom improvement.

Hoping for broad activity

The main target market for BTK inhibitors including vecabrutinib is CLL, which affected an estimated 20,940 new patients in the US in 2018. However, the ongoing clinical trial is enrolling patients from a range of B-cell cancers, and it would be encouraging to see activity across these diseases. Additionally, the trial has enrolled some patients previously treated with the competing CLL drug Venclexta (venetoclax, AbbVie/Roche) and we hope to see some activity in these patients.

Valuation: $241m or $2.92/diluted share

Our valuation remains relatively unchanged at $241m (from $243m) albeit slightly lower per share ($2.92 diluted from $2.97). We expect to update our valuation with increasing data released from the ongoing vecabrutinib study. We forecast that the company will need an additional $115m in capital to reach profitability in 2023.

22 March 2019

Price	**US$0.96**
Market cap	**US$65m**
Net cash ($m) YE18 + offering	24.7
Basic shares in issue	67.6m
Free float	86.11%
Code	SNSS
Primary exchange	NASDAQ
Secondary exchange	N/A

Share price performance

%	1m	3m	12m
Abs	81.2	300.0	(71.3)
Rel (local)	76.1	238.6	(72.8)
52-week high/low	US$3.20		US$0.24

Business description

Sunesis Pharmaceuticals is a pharmaceutical company focused on oncology. Its lead asset is vecabrutinib, a Bruton's tyrosine kinase inhibitor for chronic lymphocytic leukemia for Imbruvica-refractory patients. The program is entering a dose-escalation Phase Ib/II. It has also developed TAK-580 with partner Takeda, and the preclinical PDK1 inhibitor SNS-510.

Next events

Vecabrutinib clinical update at EHA	June 2019

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Edison profile page

Investment summary

Company description: Targeting refractory CLL

Sunesis is a pharmaceutical company developing drugs for the treatment of cancer. Its lead program is vecabrutinib, an inhibitor of Bruton's tyrosine kinase (BTK) that is being developed for refractory chronic lymphocytic leukemia. The drug's mechanism of action (as a non-covalent BTK inhibitor) enables potential activity in patients who have progressed on the standard of care Imbruvica (ibrutinib, AbbVie/Janssen). Approximately 25% or more of those treated with Imbruvica develop resistance and this number is expected to increase with more patients on the drug for an extended amount of time. The company is in the dosing phase of its ongoing Phase Ib/II study, and is expected to provide a clinical update on the program at the EHA Congress in June 2019.

Valuation: Unchanged at $241m or $3.57/basic, $2.70/diluted

Our valuation remains relatively unchanged at $241m (from $243m) albeit lower on a per share basis ($2.70 per diluted share including new convertible preferred stock, warrants and options, from $2.97). This valuation is based on a risk-adjusted NPV analysis of the company's development programs. We value the lead vecabrutinib program at $187m, based on peak sales of $666m at a 20% probability of success. We expect the company to be able to launch vecabrutinib in 2023 if it remains on schedule, which in our assumptions includes advancing to the Phase II portion of the trial in 2019. We expect to update the valuation with more information regarding the efficacy of vecabrutinib, which we expect as the drug progresses through the higher dosing cohorts: efficacy is expected in the range of 100mg to 300mg, and the 100mg arm is fully enrolled.

Financials: $115m in additional capital needed

We estimate that Sunesis will require $115m in additional capital before profitability in 2023 ($40m in 2020, $40m in 2021, $35m in 2022). These costs are driven largely by R&D and the vecabrutinib development program. The company spent $14.6m in 2018 on R&D and we expect these values to increase in 2019 with the advancement of the clinical program to the Phase II portion of the study. The company recently completed an offering in January 2019 of $20m for 23m shares of common stock and 17,000 shares (equivalent to 17m common shares), which should provide a cash runway through the end of 2019.

Sensitivities: De-risked mechanism of action

All clinical-stage development companies face a series of similar risks associated with clinical drug development. There is unavoidable uncertainty regarding the outcomes of clinical trials. However, we have a higher degree of confidence in the vecabrutinib program than in other Phase I assets because the drug's target BTK has already been the basis of two successful drug approvals. Sunesis has also demonstrated attractive biochemistry and pharmacokinetics suggesting that it can engage the target *in vivo*. This being said, there are no guarantees and multiple factors outside of the company's control. For instance, there are multiple other BTK inhibitors and other drugs for CLL in development competing for patients in the clinical trials, and eventually on the market. Moreover, the eventual size of the market has a degree of uncertainty, because the true rate of the various BTK resistance mutations is a matter of ongoing study. If the company encountered significant hurdles in the development of vecabrutinib, its options are limited, because it is the primary value driver in the company. Finally, the company faces financing risk as it may face significant dilution raising the additional capital needed to complete development of vecabrutinib.

A focused oncology company

Sunesis's primary focus is on the clinical development of vecabrutinib for the treatment of B-cell malignancies. Vecabrutinib is an inhibitor of Bruton's tyrosine kinase (BTK), a target that has already been validated for the treatment of chronic lymphocytic leukemia (CLL) and other B-cell cancers through the success of the approved BTK inhibitor Imbruvica (ibrutinib, AbbVie/Janssen). Vecabrutinib, however, is a non-covalent inhibitor and therefore has potential activity in patients who are resistant to Imbruvica and other covalent BTK inhibitors. The drug is currently in the dose-escalation portion of a Phase Ib/II clinical study. Sunesis has two additional early stage programs. SNS-510 is a preclinical phosphoinositide dependent protein kinase 1 (PDK1) inhibitor being investigated for solid and hematological tumors. PDK1 is a novel target that could have improved efficacy in tumors with PI3K and PTEN mutations, which are exceptionally common (30–50% of certain cancers). Lastly, Sunesis has out-licensed the pan-Raf inhibitor TAK-580 to Takeda, which is being investigated for the treatment of pediatric glioma. Pan-Raf inhibitors are a new class of drug that avoids the paradoxical enhancement of tumor growth in some patients who take B-Raf inhibitors.

Exhibit 1: Sunesis pipeline

Product	Indication	Class	Phase	Catalyst	Timing	Commercial advantage
Vecabrutinib	CLL and other B-cell cancers	BTK inhibitor	Phase Ib/II	Clinical update	Q219	Non-covalent inhibitor effective in Imbruvica-resistant tumors
SNS-510	Pan cancer	PDK1 inhibitor	Preclinical	IND filing	2020	Potential efficacy similar to PI3K inhibitors, resistant to PI3K or PTEN mutations
TAK-580	Pediatric glioma	Pan-Raf inhibitor	Phase I/II	Phase I data	2019–20	Avoids "paradoxical activation" present in B-Raf inhibitors, effective in Ras mutants

Source: Sunesis Pharmaceuticals

Developing a better BTK

Vecabrutinib is currently being investigated for a series of B-cell malignancies that are being enrolled for the Phase Ib/II study. These include CLL, mantle cell lymphoma (MCL) and Waldenström's macroglobulinemia (WM), diffuse large B-cell lymphoma (DLBCL), follicular lymphoma (FL), and others. However, given the potential of the drug in Imbruvica-resistant CLL patients, this remains the primary target market. CLL is a hematologic malignancy indicated by the proliferation of mature B-cell lymphocytes and the clinical course of CLL can vary from indolence with a relatively normal life expectancy to a rapidly progressive disease leading to an early death. There were an estimated 20,940 new patients in the US in 2018 (4.7 per 100,000 on an age-adjusted basis).[1] The treatment of B-cell malignancies has been an area of substantial investment and it has been transformed over the past decade by the development of new, targeted drugs for these diseases. One of the greatest successes in this field was the development of Imbruvica by Pharmacyclics (acquired by AbbVie in May 2015, partnered with Janssen). The drug was approved in 2013 with accelerated approval following a three-year Phase III trial and it retails for approximately $150,000. Imbruvica substantially improved the standard of care for relapsed and refractory CLL by more than doubling the survival rate for these patients (HR=0.43 vs ofatumumab at 18 months). Imbruvica is also approved in MCL and WM. In 2018, worldwide sales were approximately $4.4bn.

Vecabrutinib is a non-covalent inhibitor of BTK, which means that it does not form a permanent chemical bond with the target protein. This is in contrast to the majority of other BTK inhibitors in development as well as the two currently approved inhibitors Imbruvica and Calquence (acalabrutinib, AstraZeneca) (Exhibit 2).

[1] National Cancer Institute.

Exhibit 2: BTK inhibitors (selection)

Drug	Company	Status	Lead indication	Binding mode
Imbruvica	AbbVie	Approved	CLL, MCL, WM	Covalent
Calquence	AstraZeneca	Approved	MCL	Covalent
Zanubrutinib	BeiGene	Filed	WM	Covalent
ONO/GS-4059	Ono/Gilead	Phase II	CLL, Sjogren's	Covalent
Vecabrutinib	Sunesis	Phase Ib/II	CLL, MCL, WM, DLBCL, FL	Non-covalent
LOXO-305	Eli Lilly	Phase I/II	B cell lymphoma	Non-covalent
ARQ-531	ArQule	Phase I	CLL, DLBCL, MCL, WM	Non-covalent
TG-1701	TG Therapeutics	Phase I	B-cell malignancies	Covalent
PRN2246	Principia	Preclinical	CNS	Covalent
CG'806	Aptose	Preclinical	AML, B-cell cancers	Non-covalent

Source: BioCentury, ClinicalTrials.gov, Edison Investment Research

These covalent inhibitors derive their activity by forming a covalent bond to cysteine 481 (C481) in the BTK protein. However, if patients develop a mutation of this amino acid, they will become resistant to treatment.[2] Vecabrutinib, in contrast, retains its activity in C481 mutants, and therefore has the potential to work in resistant patients (Exhibit 3). Moreover, it prevents the generation of activated BTK (auto-phosphorylated BTK, pBTK) in the presence of the mutant, whereas this effect is lost by Imbruvica.

Exhibit 3: Comparison of Imbruvica and vecabrutinib inhibition of wild type and mutant BTK

	Kinase inhibition			Inhibition of activated BTK formation		
IC50 (nM)	BTK	Mutant BTK	Fold change	BTK	Mutant BTK	Fold change
Imbruvica	0.58	25.2	43.4	0.016	25.5	>1,000
Vecabrutinib	2.9	4.5	1.6	0.57	0.8	1.4

Source: Sunesis Pharmaceuticals

Given the only recent approval of Imbruvica, there is limited experience with resistant patients, and the mechanisms of resistance are an area of ongoing research. However, by all accounts C481 mutations (in particular the serine mutation C481S) appear to be the predominant mechanism of resistance. Estimates of the rate of C481 mutations in resistant individuals are typically derived from small anecdotal studies at this point, but are found in the range of 60% to 80%.[3,4]

Outside of BTK inhibitors, we expect vecabrutinib to face some competition from Venclexta (venetoclax, AbbVie/Roche), a B-cell lymphoma 2 (Bcl-2) inhibitor that was approved in 2016 for the treatment of refractory CLL (and in 2018 for AML). The drug had sales of $344m in 2018. Venclexta does not necessarily preclude treatment with vecabrutinib, but is an additional factor in the treatment algorithm. However, AbbVie has also recently reported Phase II results showing the effective use of Venclexta in combination with Imbruvica in the first-line setting. We view this as a positive for vecabrutinib, because it suggests both the potential to combine Venclexta with other BTK inhibitors (such as vecabrutinib) in the second line, and the potential to move Venclexta to the front line, where it would compete less with vecabrutinib. Examining activity in patients exposed to Venclexta is a key objective on the ongoing Phase Ib/II clinical study.

Phase Ia results

Sunesis presented the results of a Phase Ia healthy volunteer study of vecabrutinib via a poster at the Second International Conference on New Concepts in B-Cell Malignancies in September 2016. The clinical trial examined the pharmacokinetic and pharmacodynamic profile and adverse events

[2] JA Woyach, RR Furman (2014) Resistance mechanisms for the Bruton's tyrosine kinase inhibitor ibrutinib. *NEJM*. 370;24, 2286-94.

[3] Bonifiglio S, et al. (2018) Half of Chronic Lymphocytic Leukemia Patients Relapsing Under Ibrutinib Carry BTK and PLCG2 Mutations: a European Research Initiative on Cll (Eric) Real-World Study. "EHA 2018 Annual Meeting," 218883.

[4] Kami J. Maddocks, MD1; Amy S. Ruppert (2015) Etiology of Ibrutinib Therapy Discontinuation and Outcomes in Patients With Chronic Lymphocytic Leukemia. *JAMA Oncol*. 1(1): 80-87.

in volunteers following a single dose of the drug at four different dosing levels (from 50mg to 300mg) or with placebo. Six volunteers received drug for each active arm (n=24 total for vecabrutinib) and eight received placebo. Although these results are from a small set of healthy volunteers, we consider them very important for evaluating the viability of this drug, because while the targeted mechanism of action has already been validated through prior approvals of other drugs, this study provides vital hints of other key vecabrutinib attributes (the pharmacokinetic, pharmacodynamic and safety profile of the molecule).

The primary endpoint of the trial was safety, and in general the adverse event (AE) profile was similar between patients who received drug and those who received placebo (Exhibit 4). 33% of patients who received active drug (at all tested doses) had an AE, compared to 38% in the placebo arm. The adverse events observed in the trial were all mild (grade 1) except for a single patient on the 300mg arm who reported grade 2 fatigue and headache. Also, an important AE to note is that a single patient reported supraventricular tachycardia (racing heart) on the 300mg arm. Although the event was asymptomatic and resolved in 20 seconds, adverse events related to heart rhythm have been associated with BTK inhibitors in the past and 6–9% of patients receiving Imbruvica experience atrial fibrillation, typically after prolonged exposure. Importantly, the trial also monitored patients via laboratory blood testing and via electrocardiogram, and no other abnormalities were found.

Exhibit 4: Adverse event profile from Phase Ia

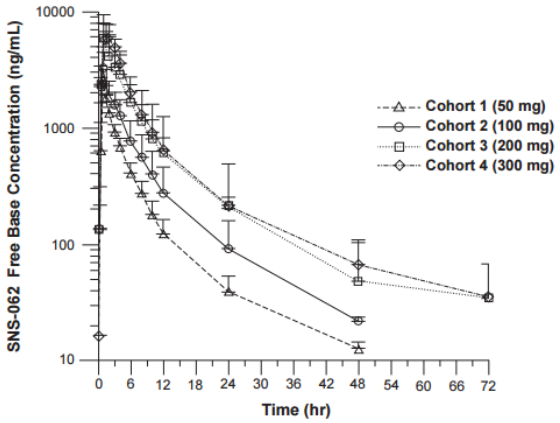
	Vecabrutinib										Placebo (n=8)	
	50mg (n=6)		100mg (n=6)		200mg (n=6)		300mg (n=6)		All active (n=24)			
Headache	4	67%	0	0%	0	0%	1	17%	5	21%	2	25%
Supraventricular tachycardia	0	0%	0	0%	0	0%	1	17%	1	4%	0	0%
Constipation	0	0%	1	17%	0	0%	0	0%	1	4%	0	0%
Nausea	0	0%	0	0%	1	17%	0	0%	1	4%	2	25%
Diarrhea	0	0%	0	0%	0	0%	0	0%	0	0%	1	13%
Fatigue	0	0%	0	0%	0	0%	1	17%	1	4%	0	0%
Bronchitis	0	0%	0	0%	0	0%	1	17%	1	4%	0	0%
Orthostatic hypotension	0	0%	0	0%	0	0%	1	17%	1	4%	0	0%
Total patients with AE	4	67%	1	17%	1	17%	2	33%	8	33%	3	38%

Source: Sunesis Pharmaceuticals

Sunesis also reported initial pharmacokinetic and pharmacodynamic data from the active arms of the trial, which included both blood concentrations (Exhibit 5) and the degree of BTK inhibition (Exhibit 6) following dosing. Patients were followed for up to 72 hours and the results showed that the molecule had a long half-life in humans (eight to 17 hours depending on dose), and that at the plasma levels observed in this study, BTK inhibition of 85% or more was seen for approximately 12 hours for all the doses studied. 85% inhibition of BTK has previously been identified as sufficient for clinical activity during studies of AstraZeneca's Calquence.[5] This profile presents the possibility of a twice-a-day dosing regimen, which the company has proposed using when moving forward with clinical trials.

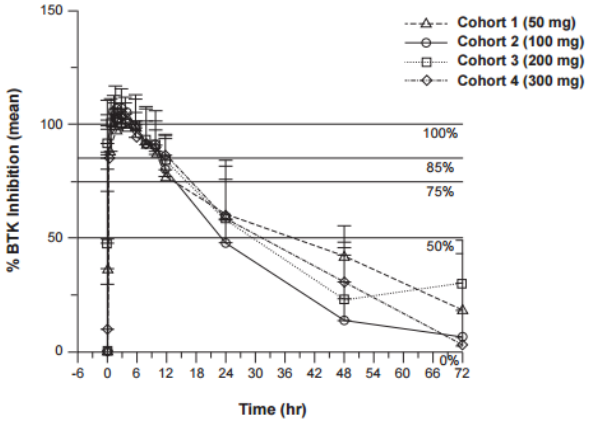
[5] Byrd JC, et al. (2016) Acalabrutinib (ACP-196) in Relapsed Chronic Lymphocytic Leukemia. *N Engl J Med.* 374, 323-32

Exhibit 5: Plasma concentrations of vecabrutinib



Source: Sunesis Pharmaceuticals

Exhibit 6: BTK inhibition by vecabrutinib



Source: Sunesis Pharmaceuticals

The ongoing Phase Ib/II study

Sunesis is currently in the dose-escalation portion of an ongoing Phase Ib/II study of vecabrutinib. The Phase Ib dosing portion of the study follows a standard 3+3 protocol with three patients per ascending dose (potentially expanding to six patients following observations of dose-limiting events). There are seven planned dosing cohorts (25mg, 50mg, 100mg, 200mg, 300mg, 400mg and 500mg twice daily), although the company has stated that it expects to see the first signs of efficacy in the 100mg to 300mg cohorts. Each cohort receives one four-week treatment cycle. Once the effective dose is reached, the study is planned to expand into a Phase II study at that dose with an estimated trial size of 124 patients. The program is taking place at some of the leading cancer institutes in the US, including the Dana-Farber Cancer Institute, MD Anderson Cancer Center and Memorial Sloan Kettering Cancer Center, among others (eight in total).

The company provided an update of the study at the 2018 American Society of Hematology annual meeting in December 2018. At the time of the presentation, the company was on the second (50mg bid) dosing cohort. The company provided a detailed breakdown of the AE profile from the 10 patients with data available (Exhibit 7). Hematologic AEs were common but are not unusual for this class of drug or this patient population. Four grade three events that were potentially related to drug were observed, three hematologic and the third being an ALT elevation. Of note in this profile is that the rate of GI events is low. This is in contrast to Imbruvica, which has high rates of GI effects (51% diarrhea, 31% nausea, 25% constipation, etc). Calquence also has high rates of reported GI effects, albeit at lower levels than Imbruvica. This indicates that the AE profile of vecabrutinib may be significantly different than these drugs, although higher doses will need to be evaluated before drawing any definitive conclusions.

Exhibit 7: Vecabrutinib dose-escalation safety

Adverse Event	All Grades >15% N(%)[a]	Grade ≥ 3 N	Related, Grade ≥ 3 N
Anaemia	7 (70)	6	1
Neutropenia	5 (50)	5	1
Night sweats	5 (50)		
AST increased	4 (40)	1	
Thrombocytopenia	4 (40)	4	
Hypoalbuminaemia	3 (30)		
Hypocalcaemia	3 (30)	1	
Pyrexia	3 (30)		
Abdominal distension	2 (20)		
ALT increased	2 (20)	1	1[b]
Back pain	2 (20)		
Alk phos increased	2 (20)	1	
Cellulitis	2 (20)	1	
Chills	2 (20)		
Constipation	2 (20)		
Cough	2 (20)		
Diarrhea	2 (20)		
Dyspepsia	2 (20)		
Dyspnoea	2 (20)		
Fatigue	2 (20)	1	
Haematuria	2 (20)		
Headache	2 (20)		
Hyperglycaemia	2 (20)	1	
Hyperkalaemia	2 (20)		
Hypermagnesemia	2 (20)		
Hyponatremia	2 (20)	1	
Leukopenia	2 (20)	2	
Lymphopenia	2 (20)	2	

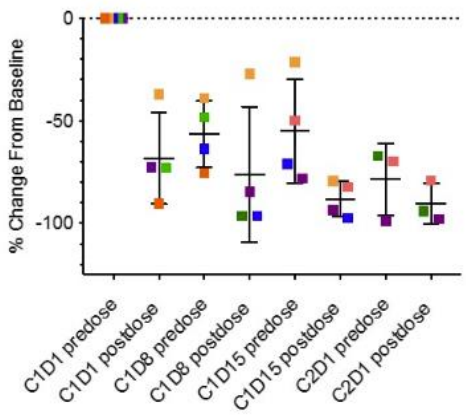
Additional Grade ≥3, N=1: Blood bilirubin increased, Hyperuricaemia, Hypophosphataemia, Intestinal perforation, Leukocytosis (related), Neutrophil count decreased, Pneumonia, Platelet count decreased.

[a]Preliminary safety data available for 10 of 13 treated subjects
[b]One patient in Cohort 2 experienced a DLT of an inadequate number of Cycle 1 doses administered due to a related grade 3 ALT increase

Source: Sunesis Pharmaceuticals

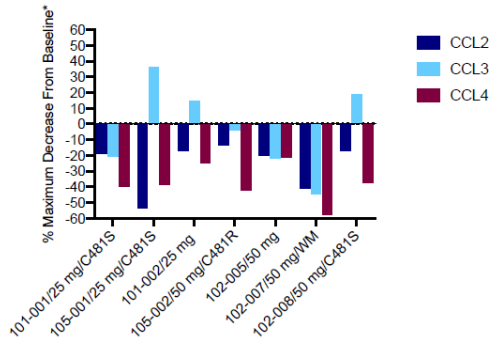
Sunesis also provided additional PK and pharmacodynamic data to support the proposition of vecabrutinib. The PKs in the trial appear similar to previous *in vivo* measurements. The company also provided a breakdown of the impact of vecabrutinib on the concentrations of pBTK (Exhibit 8). pBTK is the active form of the enzyme and the efficacy of BTK inhibitors is driven by reductions in its concentration. These data also include patients with a C481 mutation. Moreover, the company provided evidence that the drug was having an impact on B-cell function, as indicated by a reduction in cytokines measured in a selection of patients (Exhibit 9). One would expect to see reductions in cytokine release in the presence of a BTK inhibitor, because the enzyme is a key effector of cytokine release pathways. These data provide evidence that the drug is working as intended, and is having a physiological impact.

Exhibit 8: Inhibition of pBTK production



Source: Sunesis Pharmaceuticals

Exhibit 9: Reduction in cytokines



Source: Sunesis Pharmaceuticals

Based on these data we expect the upcoming cohorts to provide data on the efficacy of the drug. The company noted that early indications of drug effect were seen but it did not report any measures of efficacy in this data. Of the 13 patients enrolled at the time of the ASH update, the majority (nine) had CLL. Patients with mantle cell lymphoma and Waldenström's macroglobulinemia have also been enrolled in the trial, and although earlier in the year the company expanded

enrolment to include other B-cell malignancies none were recruited at the time. The company reiterated on the 2018 earnings conference call in March 2019 that the majority of patients in the study have CLL.

Upcoming data expectations

The most recent progress report on the study was presented in early January 2019, when Sunesis announced that it had progressed to the 100mg dosing cohort. The slots for this cohort were filled in early January, so it is expected to progress quickly. The company continued to over-enrol the dosing arm to a total of six patients, which should hopefully limit unforeseen delays. The company will be presenting an update on the study at the EHA conference in June 2019.

The company previously guided that based on pharmacokinetic data, it expects to see the first signs of clinical efficacy in the range of 100mg to 300mg. Patients on the trial are evaluated after four weeks for the safety endpoints, but they may remain on treatment until they progress or withdraw from the study. However, given the short period of treatment that patients will have had at the time of the update, we consider it unlikely that these earliest signs of efficacy will be evaluable as remissions (although it is possible), but some hematologic signs of efficacy may be present. BTK inhibitors historically induce strong nodal responses, which correlate with improvement in disease symptoms.[6] Paradoxically, the cells mobilized from the lymph nodes can cause a dramatic increase in blood lymphocytes, which is canonically a sign of progressive disease. However, in these patients symptoms improve over this period and eventually lymphocytosis resolves in the majority of cases.

At the very least, data from the upcoming dosing cohorts should show high occupancy rates for the BTK enzyme. Rates above 80% are historically associated with clinical responses. Importantly, to support the premise that vecabrutinib can maintain activity in C481 mutant cancers, we hope for any direct evidence of BTK binding in patients harbouring this mutation. We expect biomarkers of BTK inhibition (such as reduction in cytokines and FC receptor activity) to correlate with higher doses. Ideally these data should correlate with some early signs of symptom improvement, and any indication of nodal response or lymphocyte mobilization will be indicative of direct drug activity.

Early stage programs

Sunesis has two additional programs: SNS-510, a phosphoinositide dependent protein kinase 1 (PDK1) inhibitor for hematological and solid tumors; and TAK-580, a pan-Raf inhibitor program being investigated for pediatric glioma.

SNS-510

The receptor tyrosine kinase (RTK) signaling pathway has been central to the development of targeted cancer therapies for the past two decades. RTKs are a class of protein that respond to signals from growth factors and other signaling molecules, but mutations in this pathway can lead to a constitutive growth signal that is characteristic of cancer. Drugs have been developed targeting the receptor itself (for instance Herceptin targeting HER2), as well as the downstream effectors of RTKs in the so-called PI3K/AKT pathway, for instance PI3K (Gilead's Zydelig) and mTOR (Pfizer's Torisel). The RTK pathway is central to the pathology of a wide array of different cancer types, as evidenced by the indications this class of drug has been approved for in both solid tumor and hematologic malignancies. One of the multiple downstream pathways from RTK is the PI3K/AKT

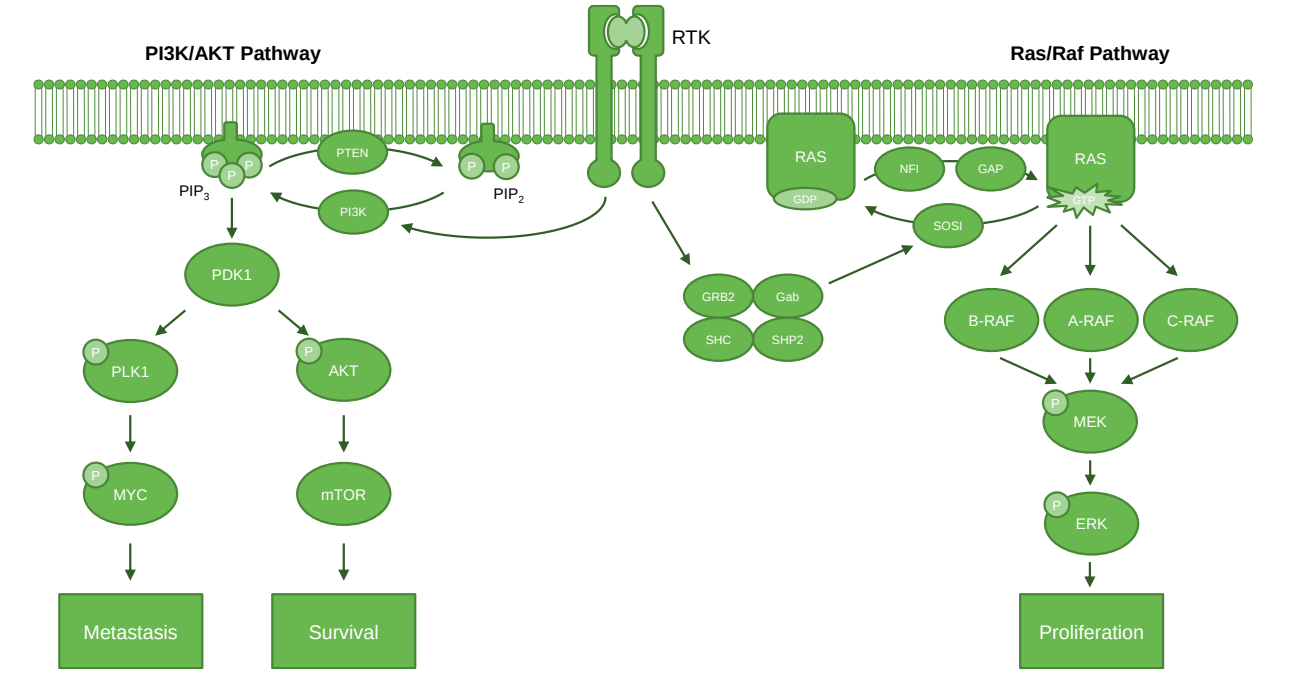
[6] Advani RH, et al. (2013) Bruton tyrosine kinase inhibitor ibrutinib (PCI-32765) has significant activity in patients with relapsed/refractory B-cell malignancies. *J Clin Oncol* 31, 88-94.

pathway, which has been a topic of considerable development interest due to its role in promoting cancer cell survival and metastasis.

Sunesis has developed SNS-510 as an inhibitor of PDK1, a previously unstudied target in the PI3K/AKT pathway. PDK1 is an effector of PI3K, and therefore it is reasonable to expect a potential efficacy profile comparable to PI3K inhibitors like Zydelig (idelalisib, Gilead). Zydelig was approved for the treatment of B-cell malignancies such as CLL and non-Hodgkin lymphoma. Because the RTK pathway is implicated in such a broad array of cancers, SNS-510 could potentially have many applications. However, the drug would be uniquely effective in malignancies where PI3K or PTEN is frequently mutated such as breast cancer (27% PI3K mutation frequency), or endometrial cancer (38% PTEN mutation frequency). In these cases, a PDK inhibitor could potentially limit the effect of these mutations as it is the immediate downstream effector of these proteins. A potential risk to this program is opportunistic infections among patients, considering that inhibition of this pathway by Zydelig is associated with this risk. In early 2016, a series of deaths in clinical trials involving Zydelig prompted Gilead to terminate further clinical development. Sales of the drug have been declining (from a peak of $168m in 2016), but in spite of this it had sales of $133m in 2018.

There are no other PDK1 inhibitors in development to our knowledge. Sunesis has completed SNS-510 non-GLP toxicology studies, and is currently engaged in IND enabling studies. The drug was initially developed in a collaboration with Biogen Idec, whose rights were acquired by Takeda. Sunesis will owe royalties and $9.2m in development milestones to Takeda for these rights. It is protected by composition of matter patent 8,778,977. Research to support an IND filing is ongoing, but the timeline has been delayed until after 2019 to prioritize vecabrutinib development.

Exhibit 10:PI3K/AKT and Ras/Raf pathways



Source: Edison Investment Research

TAK-580

There has been substantial success recently developing and getting approval for inhibitors of the oncogene B-Raf. There are currently three B-Raf targeted medications approved in the US (Nexavar, Bayer; Zelboraf, Roche; Tafinlar, Novartis) and at least four others in development. B-Raf is a very common oncogene that is mutated in 20% of cancers. When mutated it activates a pathway that triggers uncontrolled growth of cells.

However, a major limiting factor in the efficacy of B-Raf inhibitors is that they can have a detrimental effect when the upstream signaling protein Ras is mutated. Cancers with a Ras mutation have a very similar phenotype to B-Raf mutations and activate the same pathway, but the signal is transduced through all three Raf isoforms (A-Raf, B-Raf, and C-Raf aka Raf1). The presence of a B-Raf inhibitor paradoxically enhances tumor aggression by encouraging the association of B-Raf with other isoforms. Because Ras mutations are exceptionally common in certain cancers (eg 34% of colon cancer, 57% of pancreatic cancer), the potential application for B-Raf inhibitors is limited to only certain cancer indications where paradoxical activation is not an issue.

TAK-580 was developed as a pan-Raf inhibitor by Sunesis and inhibits all Raf isoforms, therefore preventing the activation of the pathway even in the presence of Ras mutations. The drug was developed in collaboration with Biogen Idec and is out-licensed to Takeda. Following a study in which it was investigated for a range of tumors in multiple combinations, it was decided to focus development on the treatment of low-grade glioma in children, which is currently being investigated in a Phase I/II study. Glioma is a rare cancer, and rarer in children with a rate of 4.84 per 100,000 in the US per year.[7] There are few treatment options for the disease, with surgery in the front line, followed by radiation and chemotherapy. Sunesis is entitled to up to $57.5m in development milestones from the collaboration, of which some undisclosed portion would be triggered upon the initiation of a registration trial. Eli Lilly is currently the only other major pharmaceutical company with a pan-Raf in clinical trials (Phase I). TAK-580 is protected by composition of matter patent 8,802,657.

Sensitivities

Sunesis faces a series of risks that are typical to similar, clinical-stage drug development companies. Clinical trials carry a range of risks both inherent to the program itself as well as outside of the company's control. We believe that vecabrutinib is partially de-risked because it is employing a vetted mechanism of action. Moreover, it has shown attractive pharmacokinetics and biochemistry to indicate that it can bind BTK *in vivo* similarly to the approved BTK inhibitors, albeit the number of patients this has been examined in is small. However, this cannot eliminate all the risk in the clinical studies. For instance, vecabrutinib must compete with a number of other treatments in development for patients to enrol, which may result in delays. Moreover, the treatment of hematologic malignancies is quickly evolving, and the company cannot ensure that it will be able to fill its current niche in the future. Despite increasing evidence that C481 mutations are the primary mechanism of Imbruvica resistance, the size of this market is still largely theoretical. Additionally, the survival for these patients is typically measured in months, presenting issues initiating them on a new therapy. Finally, vecabrutinib is not the only drug developed in this class, and Sunesis may face future direct competition. Vecabrutinib represents the vast majority of the value in the company, and although the TAK-580 and SNS-510 programs are principled in design, they do not provide a significant hedge against potential issues with the lead program. Sunesis also faces financing risk, as we predict that it will need an additional $115m in additional capital to reach profitability in 2023. Raising this capital may result in significant dilution.

Valuation

Our valuation remains relatively unchanged at $241m (from $243m), albeit slightly lower on a per share basis ($2.92 per diluted share including new convertible preferred stock, warrants and options; from $2.97 previously). We have updated our model by rolling forward our NPVs, which

[7] Oncolink, University of Pennsylvania

was offset by lower Q418 net cash ($25.1m). We have delayed the development and commercialization timeline of SNS-510 based on company guidance that it does not expect to file an IND in 2019. This has lowered the value of this program to $23m from $25m, previously. We expect to update our valuation with more information regarding the efficacy of vecabrutinib. We currently estimate peak sales of $666m for vecabrutinib, which represents 50% penetration into the US and European market of BTK inhibitor refractory patients with a C481S mutation. We currently assume pricing on par with Imbruvica (adjusted for some future price growth), with a gross/net sales of 80%, and an expected time on drug of 18 months. Our probability of success (20%) reflects partial de-risking of the program given the proven mechanism of action. Our current timeline for the program assumes that Sunesis will be able to find the effective dose of the drug in 2019, which is expected in the range of 100mg to 300mg.

Although a lead indication has not been announced for SNS-510, and the potential indications for this drug are wide (both solid and hematologic tumors), we currently use breast cancer as our target market. We include only metastatic patients with PI3K mutations, which corresponds to approximately 7% of patients. Our launch pricing is based on Zydelig. We model TAK-580 with an orphan oncology pricing of $500,000 per course, and high penetration (50%) given the lack of available options.

Exhibit 11: Valuation of Sunesis

Development Program	Clinical stage	Expected commercialization	Prob. of success	Launch year	Launch Pricing ($)	Peak sales ($m)	Patent/exclusivity protection	Royalty/ margin	rNPV ($m)
TAK-580	Phase I/II	Licensed to Takeda	10%	2025	500,000	603	2032	15%	$19
Vecabrutinib	Phase Ib/II	Proprietary	20%	2023	152,000	666	2034	56%	$191
SNS-510	IND ready	Proprietary	10%	2025	137,000	344	2031	51%	$23
Unallocated costs (discovery programs, administrative costs, etc.)									($17)
Total									$217
Net cash and equivalents (YE18 + offering) ($m)									$24.7
Total firm value ($m)									**$241.3**
Total basic shares (m)									67.6
Value per basic share ($)									**$3.57**
Convertible Pref stock (m)*									16.2
Warrants and Options (m)									4.4
Total diluted shares (m)									88.2
Value per diluted share ($)**									**$2.92**

Source: Edison Investment Research, Sunesis Pharmaceuticals reports. Note: *Accounts for conversion of preferred shares into 7.1m of common stock since the end of the 2018. **Includes $17m cash on exercise of warrants and options.

Financials

Historically the company's primary expenses have been associated with R&D. Sunesis had losses of $26.6m in 2018, of which $14.6m were associated with the R&D program. We expect these R&D costs to accelerate in 2019 if the company expands the ongoing vecabrutinib study to the Phase II portion of the trial (estimated at $16.4m). We have revised these estimates down from previous reports due to continued cost control at the company (vs $17.5m in 2019 R&D spending previously).

The company recently completed an offering in January 2019 of $20m for 23m shares of common stock and 17,000 shares (equivalent to 17m common shares), at an offering price of $0.50 per common share or equivalent. This should provide a cash runway throughout 2019 and into 2020. The company ended 2018 with $13.7m in cash (and $7.3m in debt). We have adjusted our financing schedule as a result and expect the company to need $115m in additional capital to reach profitability in 2023 ($40m in 2020, $40m in 2021 and $35m in 2022).

Exhibit 12: Financial summary

$000s	2017	2018	2019e	2020e
Year end 31 December	US GAAP	US GAAP	US GAAP	US GAAP
PROFIT & LOSS				
Revenue	669	237	0	0
Cost of Sales	0	0	0	0
Gross Profit	669	237	0	0
Research and development	(21,540)	(14,615)	(16,427)	(17,230)
Selling, general & administrative	(13,548)	(11,332)	(11,672)	(12,022)
EBITDA	(34,428)	(25,719)	(28,107)	(29,261)
Operating Profit (before GW and except.)	(34,419)	(25,710)	(28,098)	(29,252)
Intangible Amortisation	0	0	0	0
Exceptionals/Other	0	0	0	0
Operating Profit	(34,419)	(25,710)	(28,098)	(29,252)
Net Interest	(1,039)	(905)	(632)	(4,048)
Other (change in fair value of warrants)	0	0	0	0
Profit Before Tax (norm)	(35,458)	(26,615)	(28,730)	(33,300)
Profit Before Tax (IFRS)	(35,458)	(26,615)	(28,730)	(33,300)
Tax	0	0	0	0
Deferred tax	0	0	0	0
Profit After Tax (norm)	(35,458)	(26,615)	(28,730)	(33,300)
Profit After Tax (IFRS)	(35,458)	(26,615)	(28,730)	(33,300)
Average Number of Shares Outstanding (m)	24.5	35.6	68.9	72.0
EPS - normalised ($)	(1.45)	(0.75)	(0.42)	(0.46)
EPS - IFRS ($)	(1.45)	(0.75)	(0.42)	(0.46)
Dividend per share ($)	0.0	0.0	0.0	0.0
BALANCE SHEET				
Fixed Assets	1,401	124	2	(7)
Intangible Assets	0	0	0	0
Tangible Assets	20	11	2	(7)
Other	1,381	113	0	0
Current Assets	32,933	15,200	8,866	18,688
Stocks	0	0	0	0
Debtors	0	0	0	0
Cash	31,750	13,696	7,362	17,184
Other	1,183	1,504	1,504	1,504
Current Liabilities	(8,901)	(8,789)	(1,435)	(1,494)
Creditors	(1,697)	(1,393)	(1,435)	(1,494)
Short term borrowings	(7,204)	(7,396)	0	0
Long Term Liabilities	(112)	(8)	(7,404)	(47,404)
Long term borrowings	0	0	(7,396)	(47,396)
Other long term liabilities	(112)	(8)	(8)	(8)
Net Assets	25,321	6,527	29	(30,216)
CASH FLOW				
Operating Cash Flow	(36,142)	(24,404)	(24,734)	(30,178)
Net Interest	0	0	0	0
Tax	0	0	0	0
Capex	(26)	0	0	0
Acquisitions/disposals	0	0	0	0
Financing	32,930	6,343	18,400	0
Dividends	0	0	0	0
Other	0	0	0	0
Net Cash Flow	(3,238)	(18,061)	(6,334)	(30,178)
Opening net debt/(cash)	(28,153)	(24,546)	(6,300)	34
HP finance leases initiated	0	0	0	0
Exchange rate movements	0	0	0	0
Other	(369)	(185)	0	0
Closing net debt/(cash)	(24,546)	(6,300)	34	30,212

Source: Edison Investment Research, Sunesis Pharmaceuticals accounts

Contact details	Revenue by geography
Sunesis Pharmaceuticals, Inc. 395 Oyster Point Boulevard, Suite 400 South San Francisco, CA 94080 (650) 266-3500 www.sunesis.com	N/A

Management team

Interim CEO: Dayton Misfeldt	CFO: William P Quinn
Dayton Misfeldt has served as a member of Sunesis's board of directors since April 2009 and was appointed interim chief executive officer in January 2018. Mr Misfeldt is a managing director at Bay City Capital LLC and focuses on biopharmaceutical investment opportunities. Prior to joining Bay City Capital in May 2000, Mr Misfeldt was a vice president at Roth Capital Partners where he worked as a sell-side analyst covering the biopharmaceutical industry. Mr Misfeldt has also worked as a project manager at Life Science Economics. Mr Misfeldt received a BA in economics from the University of California, San Diego.	Willie Quinn joined Sunesis in 2017 as chief financial officer and senior vice president, finance and corporate development. From 2011 to 2017, he served as president and CEO of Bullet Bio, a company he co-founded to develop cancer immunotherapies based on Stanford technology. Prior to that, Willie was one of the first employees at Jazz Pharmaceuticals, where he worked for more than eight years. As head of corporate development his role included strategy development and execution, helping Jazz transform from a raw start-up to a public, profitable specialty pharma company. Before Jazz, Willie was CFO and COO at Novation Biosciences, a biotech software company acquired by Agilent Technologies.
CSO: Judy Fox	**Chairman: James W Young, PhD**
Judy Fox, PhD, rejoined Sunesis in 2017 as chief scientific officer. She previously served as vice president, product & preclinical development. She has over 25 years of experience both as a scientist and program leader from companies including Genentech, Chiron and emerging immuno-oncology companies. Her career has focused on the translation of basic mechanistic understanding of promising drugs into coherent, evidence-based clinical development. Previously, she was senior director in translational sciences at Chiron Corporation and she established the Pharmacological Sciences Department at Genencor International. Dr Fox's industry career began at Genentech, Inc. where she contributed to the development of products such as Herceptin, Xolair, Raptiva and Avastin.	Since April 2009, James W Young, PhD, has been non-executive chairman of the board of directors. From 2000 until April 2009 Dr Young served as executive chairman. Dr Young was the chief executive officer of Sunesis from May 2000 until November 2003. In April 2006, Dr Young joined 5AM Ventures, a venture capital firm, as a venture partner. Prior to joining Sunesis, Dr Young served as vice president for research; senior vice president, research and development; and group vice president at ALZA Corporation from 1995 to 2000. From 1992 to 1995, Dr Young served as senior vice president for Business Development and as president of the Pharmaceuticals Division of Affymax, NV. From 1987 to 1992, he served as Senior vice president for business development and as senior vice president and general manager of the pharmaceuticals division at Sepracor Inc.

Principal shareholders	(%)
Aisling Capital	11.25
JFL Capital Management	7.30
MPM Oncology Impact Management	4.93
Bvf Inc	3.39
Eventide Asset Management	3.35

Companies named in this report

AbbVie (ABBV), AstraZeneca (AZN), Bayer (BAYN), Janssen (JNJ), Novartis (NVS), Roche (RHHBY), Takeda (4502.T)

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