EDISON

4SC

R&D update

Domatinostat programme to deliver Phase II data

Pharma & biotech

4SC has reported progress with both its clinical-stage assets – resminostat, a broad spectrum HDAC inhibitor, and domatinostat, a specific Class 1 HDAC inhibitor. In January 2019, the investigator-led Phase II EMERGE study was initiated, which is testing domatinostat in gastrointestinal cancer. 4SC has developed a broad development programme for this drug, which will include several strategic options to commercialize the asset including out-licensing based on data from multiple Phase II studies and internal pivotal development for Merkel cell carcinoma. In January 2019, the resminostat RESMAIN study received a second positive DSMB safety review and the top-line results are expected in H120. 4SC remains well funded with cash of €30.8m at end-Q318, which should fund operations into 2020. Our valuation is virtually unchanged at €328m or €10.7/share.

Year end	Revenue (€m)	PBT* (€m)	EPS* (€)	DPS (€)	P/E (x)	Yield (%)
12/16	2.1	(10.9)	(0.54)	0.0	N/A	N/A
12/17	4.2	(10.0)	(0.41)	0.0	N/A	N/A
12/18e	5.7	(16.6)	(0.54)	0.0	N/A	N/A
12/19e	3.1	(19.2)	(0.63)	0.0	N/A	N/A

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

Resminostat: Changing treatment paradigm in CTCL

In November 2018, the 100th patient was recruited into the pivotal RESMAIN study and top-line results are expected in H120. The RESMAIN study is evaluating resminostat in a novel indication – maintenance treatment of patients with advanced-stage cutaneous T-cell lymphoma (CTCL) who have achieved disease control with prior therapy. If the study results are positive, the company plans to submit applications for approval in Europe and potentially the US, while Yakult is expected to submit an application in Japan. If subsequently approved, resminostat would be the first HDAC inhibitor approved for CTCL in Europe, and the first and only therapy approved for maintenance in either Europe, Japan or the US.

Preclinical data add to domatinostat combo options

As part of the broad domatinostat development programme, a collaborator presented new preclinical data demonstrating the synergistic effect of domatinostat in combination with chemotherapy in pancreatic cancer cell lines. While pancreatic cancer is not a focus indication for 4SC, it nevertheless adds insight about the mode of action. In addition, we expect further preclinical combination studies with checkpoint inhibitors in H119 in other indications. The domatinostat Phase II EMERGE study in gastrointestinal cancer (investigator-led) has now been initiated, with the first study sites open for recruitment.

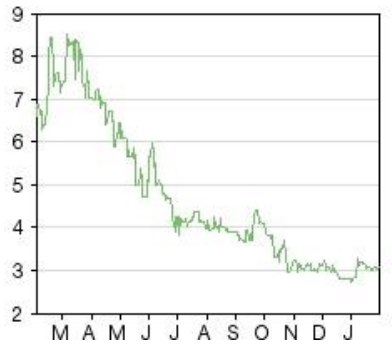
Valuation: €328m or €10.7/share

Our rNPV-based valuation is virtually unchanged at €328m or €10.7/share, due to rolling our model forward, which was offset by a lower net cash position. We keep all assumptions in our risk-adjusted NPV model unchanged. A key near-term catalyst is interim data from the SENSITIZE study (H119).

31 January 2019

Price	**€3.11**
Market cap	**€95m**
Net cash (€m) at end-Q318	30.8
Shares in issue	30.6m
Free float	35%
Code	VSC
Primary exchange	Frankfurt (Xetra)
Secondary exchange	N/A

Share price performance



%	1m	3m	12m
Abs	13.8	(2.8)	(53.6)
Rel (local)	7.5	(1.9)	(45.2)
52-week high/low		€8.5	€2.6

Business description

4SC is a Munich-based cancer biopharmaceutical company. Resminostat (HDAC inhibitor) is the lead candidate for cutaneous T-cell lymphoma (CTCL, pivotal study started in Q416). It has a second compound, domatinostat (Phase Ib/II started in Q317) and a preclinical asset, 4SC-208. 4SC also has several partners including Yakult Honsha for resminostat in Japan in various indications.

Next events

2018 full year results	20 March 2019
SENSITIZE top-line data published	H119
EMERGE early efficacy data published	H219
Top-line data from RESMAIN study	H120

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Edison profile page

Positioning resminostat for novel indication

Resminostat is an orally administered, broad spectrum histone deacetylase (HDAC) inhibitor, which could act as a monotherapy or in combination with other anti-cancer drugs. Resminostat inhibits HDAC classes I, IIb and IV. 4SC is currently running a pivotal trial (the RESMAIN study) with resminostat to evaluate it for a novel indication – maintenance treatment of patients with advanced-stage CTCL, who have achieved disease control with prior systemic therapy.

Typical symptoms of CTCL include painful and itchy skin lesions resulting in disfigurement and a severely impaired quality of life. Resminostat downregulates the expression of IL-31, which is upregulated in CTCL cells and strongly associated with pathological, chronic itching. In addition, studies have shown that resminostat upregulates STAT4 and downregulates STAT6 expression, which leads to T-cell differentiation to Th1-type helper T-cells and stabilization of the disease.

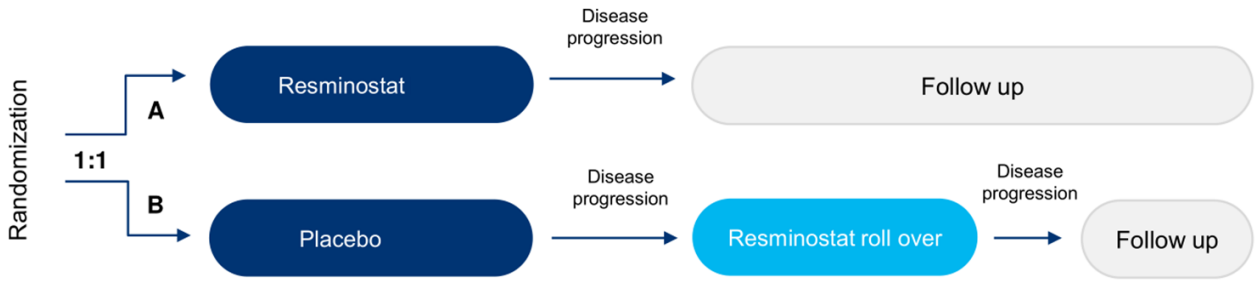
4SC's pivotal trial RESMAIN (Exhibit 1) is evaluating resminostat in a novel indication – maintenance treatment of patients with advanced-stage CTCL who have achieved disease control with prior therapy. The primary endpoint is progression-free survival (PFS). Late-stage CTCL is an incurable disease and patients typically receive many different lines of therapy over their lifetime, as none of the current therapeutic options achieves stable disease for long periods, with virtually all patients progressing after three to four months on average. Should resminostat show efficacy as a maintenance therapy – prolonging the period in which patients are stable and not progressing – it means that the target population for resminostat is virtually all late-stage patients who have received at least one line of therapy.

Overall 10-year survival rates vary from 98% if diagnosed at stage IA to 20% if diagnosed at clinical stage IVB. Theoretically, this means that patients could receive multiple cycles of therapy-resminostat-therapy-resminostat and so on. Because of resminostat's unique positioning as a maintenance therapy, the company believes this would clearly differentiate it from two other HDAC inhibitors approved in the US: vorinostat (Zolinza, Merck & Co) and romidepsin (Istodax, Celgene), which are indicated for patients with progressive disease in second or later lines and typically used only once as a single line of therapy. If approved, resminostat would be the first HDAC inhibitor approved for CTCL in Europe, and the first and only therapy approved for maintenance in either Europe, Japan or the US. The pivotal RESMAIN study and top-line results are expected in H120.

External validation of strategy from partner Yakult Honsha

In March 2018, 4SC's Japanese partner Yakult, which has in-licensed the rights to resminostat in Japan, announced that it had joined 4SC's pivotal RESMAIN study. By enrolling additional patients in Japan, Yakult will be able to submit resminostat for approval, assuming the data are positive. In our view, this indicates an external validation of 4SC's R&D strategy. Previously, Yakult conducted a Phase I study with resminostat in biliary tract cancer patients in Japan. Based on positive results, Yakult initiated its own Phase II study in biliary tract cancer (n=100) in combination with S-1 chemotherapy. S-1 is widely used in Japan and other Asian countries to treat patients following relapse after a first-line chemotherapy regimen. The final data readout is expected in mid-2020.

Exhibit 1: Design of the pivotal RESMAIN study



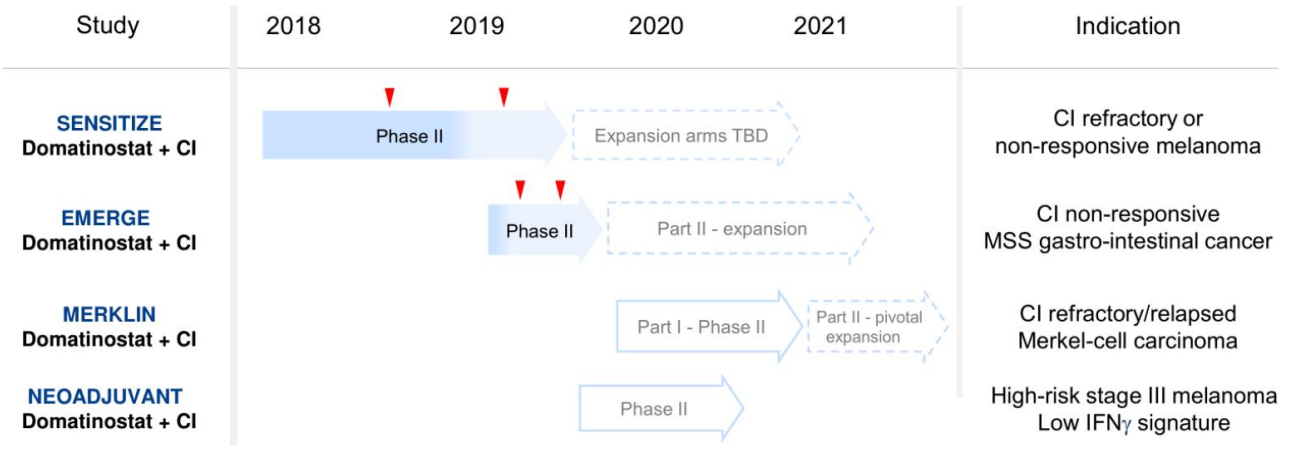
Source: 4SC

Domatinostat – broad R&D programme

Domatinostat is 4SC's second epigenetic drug, an orally administered small molecule Class I selective HDAC inhibitor. The drug was tested in a Phase I study with 24 heavily pre-treated patients with several types of advanced haematologic cancers and was shown to be well tolerated with signs of initial antitumor efficacy.

Checkpoint inhibitors have quickly become the mainstay treatment option in many solid tumours. However, there remain a majority of patients who neither respond to therapy nor experience durable responses. Preclinical data gathered by 4SC indicate that there is significant potential for domatinostat to be combined with anti-PD-L1 antibodies to expand the treatable patient population. With this in mind, 4SC has developed a broad programme for the drug (Exhibit 2).

Exhibit 2: Domatinostat development programme



Source: 4SC. Note: CI – checkpoint inhibitors

In late 2017, 4SC initiated the Phase Ib/II SENSITIZE study with domatinostat in combination with the anti-PD-1 checkpoint inhibitor pembrolizumab in advanced melanoma. In August 2018, the FDA approved 4SC's IND application, so the company now can expand the study into the US. Results are expected in H119. More recently, another investigator-led Phase II study, EMERGE, was initiated. It is testing domatinostat in combination with another checkpoint inhibitor, avelumab (anti-PD-L1 antibody), for treating microsatellite-stable gastrointestinal tumours, which tend to be resistant to checkpoint inhibition. Early efficacy data are expected in H219.

4SC believes that the broader mid-stage development program is a sensible strategy because the accumulated data will allow it to assess the safety profile and initial efficacy of domatinostat in combination with two main classes of checkpoint inhibitors (anti-PD-1 and anti-PD-L1). This would form the basis for potential partnering discussions in respective areas, while for pivotal development 4SC will aim for Merkel cell carcinoma (MCC), an orphan dermatological cancer. If the

data are sufficiently positive, domatinostat could be the first drug to market in a checkpoint inhibition refractory MCC population, which could prove a significant commercial opportunity.

Financials and valuation

In October 2018, 4SC announced that it had received a single-digit million euro milestone payment from its partner Link Health, which in-licensed the cancer therapeutic candidate 4SC-205 in 2016. We therefore add €1m as income to our 2018 estimate. 4SC's last reported cash was €30.8m (end-Q318). Average monthly cash burn for the first nine months of 2018 was €1.17m, which should bring the average monthly cash burn for FY18 to €1.3–1.5m, below previous guidance of €1.8–2.0m, and provide some flexibility for FY19. Current funds are sufficient to finance the company's activities into 2020, past several R&D catalysts (Exhibit 3).

Our rNPV-based valuation is unchanged at €328m or €10.7/share, due to rolling our model forward, which was offset by a lower net cash position. We keep all assumptions for the assets unchanged, as discussed in our previous reports. Main near-term catalysts are data readouts from the SENSITIZE and EMERGE studies expected over the course of this year.

Exhibit 3: Upcoming newsflow relating to clinical trials and other activities

	H119	H219	H120	H220
Resminostat clinical studies				
RESMAIN (Pivotal study, CTCL)			• **Top-line data expected**	• **Marketing authorisation filing in Europe**
Yakult study (Phase II, biliary tract cancer)			• **Final study results expected by partner Yakult**	
Domatinostat clinical studies				
SENSITIZE (Phase Ib/II, melanoma)	• Cohorts 1, 2 top-line data available • Cohort 3 enrolment expected to complete • **Cohort 3 data set published**			
EMERGE (Phase II, GI cancers)	• Safety data published	• **Early efficacy data published**		
Domatinostat in Merkel cell carcinoma	• MCC preclinical data to be published	• Initiation of MCC Phase II study (TBD)		
Additional domatinostat combination studies	• Update on R&D strategy • New preclinical triple combination data to be published	• Initiate the first triple combination therapy study in combination with a new partner		
Other activities				
Fund-raising			• Potential new fund-raise (current cash reach into early 2020)	

Source: 4SC, Edison Investment Research. Note: **Bold** indicates key catalysts (efficacy data, marketing authorisation).

Exhibit 4: Financial summary

€'000s	2016	2017	2018e	2019e
Year end 31 December	IFRS	IFRS	IFRS	IFRS
PROFIT & LOSS				
Revenue	2,060	4,197	5,724	3,133
Cost of sales	(76)	(574)	(574)	(574)
Gross profit	1,984	3,623	5,150	2,559
R&D expenditure	(10,601)	(11,475)	(19,555)	(19,461)
Administrative, distribution and other	(3,175)	(3,084)	(3,195)	(3,289)
Operating profit	(11,792)	(10,936)	(17,600)	(20,191)
Intangible amortisation	(892)	(892)	(892)	(892)
Exceptionals (impairment / restructuring costs)	0	0	0	0
Share-based payments	0	0	(20)	(20)
EBITDA	(10,900)	(9,819)	(16,463)	(19,054)
Operating Profit (before amort and except.)	(10,900)	(10,044)	(16,688)	(19,279)
Net interest	(14)	9	100	100
Other (profit/loss from associates)	711	0	0	0
Profit before tax (norm)	(10,914)	(10,035)	(16,588)	(19,179)
Profit before tax (FRS 3)	(11,095)	(10,927)	(17,500)	(20,091)
Tax	(71)	(33)	0	0
Profit after tax (norm)	(10,274)	(10,068)	(16,588)	(19,179)
Profit after tax (FRS 3)	(11,166)	(10,960)	(17,500)	(20,091)
Average Number of Shares Outstanding (m)	19.0	24.8	30.6	30.6
EPS - normalised (€)	(0.54)	(0.41)	(0.54)	(0.63)
EPS - FRS 3 (€)	(0.59)	(0.44)	(0.57)	(0.66)
Dividend per share (€)	0.0	0.0	0.0	0.0
BALANCE SHEET				
Fixed assets	7,096	6,365	5,452	4,539
Intangible assets	6,499	5,694	4,806	3,918
Tangible assets	497	570	545	520
Investments and other	100	101	101	101
Current assets	11,959	41,548	23,457	5,522
Stocks	0	0	0	0
Debtors	95	30	30	30
Cash	10,048	41,327	23,236	5,301
Other current assets	1,816	191	191	191
Current liabilities	(3,257)	(2,759)	(4,136)	(2,840)
Creditors	(834)	(1,175)	(1,175)	(1,175)
Short-term borrowings	0	0	0	0
Deferred revenue (short term)	(1,431)	(1,485)	(2,862)	(1,566)
Other current liabilities	(992)	(99)	(99)	(99)
Long-term liabilities	(525)	(461)	(511)	(486)
Long-term borrowings	0	0	0	0
Deferred revenue (long term)	(493)	(394)	(444)	(419)
Other long-term liabilities	(32)	(67)	(67)	(67)
Net assets	15,273	44,693	24,263	6,735
CASH FLOW				
Operating cash flow	(12,320)	(8,508)	(17,890)	(17,734)
Net interest	(531)	0	3	3
Tax	(71)	(33)	0	0
Capex	(404)	(168)	(200)	(200)
Expenditure on intangibles	(60)	(4)	(4)	(4)
Acquisitions/disposals	2,808	39	0	0
Financing	0	39,953	0	0
Other	650	0	0	0
Net cash flow	(9,928)	31,279	(18,091)	(17,935)
Opening net debt/(cash)	(19,514)	(10,048)	(41,327)	(23,236)
HP finance leases initiated	0	0	0	0
Other	462	0	0	0
Closing net debt/(cash)	(10,048)	(41,327)	(23,236)	(5,301)

Source: 4SC accounts, Edison Investment Research

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