EDISON

4SC

Menarini partnership

Menarini deal highlights resminostat options

Pharma & biotech

Menarini will develop 4SC's resminostat in Asia Pacific in a deal worth up to €95m. With Yakult already a key partner in Japan (Phase II ongoing), resminostat can now be developed in a region that accounts for 75% of all liver cancer cases (HCC) globally. Although 4SC is committed to advancing resminostat for HCC, the deal could allow other development pathways to be pursued, subject to partner/finance being secured. We note recent developments in the HDAC field (eg Syndax-Merck deal for an HDAC/PD-1 combination) as proof of continuing interest from pharma companies.

Year end	Revenue (€m)	PBT* (€m)	EPS* (€)	DPS (€)	P/E (x)	Yield (%)
12/13	4.9	(8.0)	(0.80)	0.0	N/A	N/A
12/14	7.1	(8.8)	(0.88)	0.0	N/A	N/A
12/15e	8.5	(9.7)	(0.95)	0.0	N/A	N/A
12/16e	6.8	(13.7)	(1.34)	0.0	N/A	N/A

Note: *PBT and EPS are normalised, excluding intangible amortisation, exceptional items.

Multiple resminostat options on the table…

To date, 4SC's focus has been on securing the finance and/or partner required to initiate a Phase II study of resminostat for the first-line treatment of liver cancer (hepatocellular carcinoma, HCC) in the EU/US. However, with Yakult and Menarini now advancing resminostat in the key HCC markets in Asia Pacific, 4SC may seek alternative/faster pathways. This could include niche haematological indications, validated by the approvals of other HDAC inhibitors, or potentially in combination with cancer immunotherapies, given the recent Syndax/Merck deal and 4SC's own presentation of preclinical data that indicate a potential efficacy benefit from combining resminostat with anti-PD-1s and other cancer immunotherapies.

…while 4SC-202 and 4SC-205 remain in the mix

4SC reported encouraging Phase I data from its earlier-stage cancer candidates last year, and the company continues to assess partnering/financing options for further development. 4SC-202, another epigenetic compound (targets cancer stem cell pathways HH/WNT, via specific inhibition of HDAC1,2,3/LSD1), is perhaps the most advanced in terms of supporting data in haematological tumours, although 4SC-205 is an interesting candidate in the kinesin Eg5 inhibitor class, as the only oral agent. Final study reports for both candidates are expected in 2015.

Valuation: Raised to €115m, or €11.32/share

Our valuation for 4SC has increased to €115m (vs €102m), or €11.32/share after the 1-for-5 share consolidation. This results from adding China to resminostat's potential in HCC (€250m peak sales at 20% probability) following the Menarini deal, and raising the probability in NSCLC to 40% to match HCC. Securing fresh finance and/or a partner for resminostat, for further development in HCC or haematological indications, is key to the investment case. In addition, licensing and/or financing the further development of 4SC-202 and/or 4SC-205 would also be significant. 4SC's existing cash and equity/debt facilities are sufficient to beyond Q116; the recently completed share consolidation should increase the funding options available.

28 April 2015

Price	**€6.62**
Market cap	**€68m**
Net debt (€m) at 31 December 2014	3.25
Shares in issue	10.2m
Free float	36%
Code	VSC
Primary exchange	Frankfurt
Secondary exchange	N/A

Share price performance

%	1m	3m	12m
Abs	68.4	36.8	3.4
Rel (local)	70.9	20.3	(16.4)
52-week high/low		€7.5	€3.4

Business description

4SC is a Munich-based drug discovery and development company focused on small-molecule compounds for cancer. Resminostat (HDAC inhibitor) is the lead candidate in Phase II for liver cancer (partnered with Yakult Honsha in Japan), with two further agents in Phase I.

Next events

Potential Phase II financing and/or partnership for resminostat	2015
Q115 results	7 May 2015
Final study report from TOPAS Phase I with 4SC-202	Mid-2015
Potential start of resminostat Phase II study in first-line liver cancer	H215

Analysts

Christian Glennie	+44 (0)20 3077 5727
Dr Philippa Gardner	+44 (0)20 3681 2521
Dr Mick Cooper	+44 (0)20 3077 5734

healthcare@edisongroup.com

Edison profile page

Menarini to develop resminostat in APAC

4SC has licensed resminostat to the Singapore-based division of Menarini (Menarini Asia-Pacific Holdings) for development and commercialisation of the cancer drug in the Asia Pacific region (APAC), excluding Japan. This includes key countries such as China, South Korea and Australia. 4SC will receive upfront and milestone payments up to €95m, on achieving specified development, regulatory and commercialisation milestones. We estimate the upfront fee at €1m and assume approximately 50% of the total milestones relate to clinical and regulatory progress. 4SC will also be eligible for double-digit royalties (we estimate 15%) on sales of resminostat by Menarini.

The agreement covers all oncological indications, and in particular liver cancer (hepatocellular carcinoma, or HCC), given the high prevalence and incidence of this cancer in this region, mainly owing to high endemic rates of chronic hepatitis B virus (HBV) infection. According to Globocan there will be approximately 845,000 new cases of liver cancer globally in 2015. Of these, roughly 75% will occur in the Asia Pacific region. China alone will account for 50% (~435,000) of these cases.

Menarini is a private Italian specialty pharmaceutical group, with €3.4bn in revenues in FY14, derived from a large portfolio of marketed drugs in multiple therapeutic areas (eg cardiovascular, respiratory, anti-infectives, gastro-intestinal), sold across the globe. Its Asia Pacific operations were significantly enhanced through the acquisition of Invida (Singapore) in 2011. Menarini does not currently commercialise any cancer drugs, but oncology is a key focus in its R&D activities, with a number of novel cancer drugs (in-licensed or internally developed) in its pipeline.

Renewed interest in HDACs

Recent developments in the HDAC (histone deacetylase) inhibitor field provide further validation of this class of drug. This includes the FDA approval (in February) of the fourth HDAC inhibitor onto the market, with the granting of a licence for Novartis' Farydak (panobinostat) for use in combination with bortezomib and dexamethasone to treat patients with multiple myeloma who have received at least two prior regimens. Novartis has also filed Farydak for approval in the EU, where no HDAC inhibitors have yet been approved.

Other FDA-approved HDAC inhibitors include Celgene's Istodax (romidepsin) for cutaneous T-cell lymphoma (CTCL) and peripheral T-cell lymphoma (PTCL), and Spectrum's Beleodaq (belinostat) for PTCL. The clinical and regulatory success with these compounds points to 4SC's renewed intention to assess the potential development of resminostat for niche haematological indications.

Other HDAC inhibitors in development include: entinostat (Syndax Pharmaceuticals) in Phase III for breast cancer; mocetinostat (Mirati Theapeutics) in Phase II studies for diffuse large B-cell lymphoma (DLBCL) and bladder cancer (or urothelial carcinoma); and ricolinostat/ACY-1215 (Acetylon Pharmaceuticals) in Phase I and II trials in relapsed/refractory lymphoma and multiple myeloma, respectively.

Offsetting some of these positive HDAC developments was news that pracinostat (MEI Pharma), in combination with azacitidine, failed to improve complete remission in a Phase II study in myelodysplastic syndrome (MDS). MEI is assessing further development options for pracinostat in MDS and AML (open-label Phase II ongoing).

Potential cancer immunotherapy combination option

Of further particular relevance to development options for resminostat was the recently announced Syndax/Merck & Co collaboration to investigate the combination of Syndax's entinostat with

Merck's anti-PD-1 Keytruda (pembrolizumab). A Phase Ib/II study is expected to start in H215, to evaluate the combination in patients with either advanced non-small cell lung cancer (NSCLC) or melanoma. This deal follows 4SC's recent presentation of preclinical data, which indicate a potential efficacy benefit from combining resminostat with anti-PD-1s and other immunotherapies.

Entinostat is currently undergoing a Phase III study in combination with hormone therapy for advanced hormone receptor positive (HR+) breast cancer, in indication for which it has been granted Breakthrough Therapy Designation. Preclinical models have shown that entinostat reduces the number and function of host immune suppressor cells, thereby enhancing the anti-tumour activity of immune checkpoint blockade. Keytruda is an antibody that works as an immune checkpoint inhibitor, blocking the interaction between PD-1 (programmed death receptor-1) and its ligands, PD-L1 and PD-L2. These checkpoint inhibitors (which also include Bristol-Myers Squibb's nivolumab, Opdivo) represent a major recent advance in the treatment of cancer, and consensus estimates for both products are in the $4-6bn range.

In this context, 4SC's recent presentation on the immunotherapeutic effects achieved with resminostat at the ITOC conference (Munich) is a potentially significant development. The preclinical data demonstrated the immunomodulating effects of resminostat by re-programming cancer cells and enhancing the immune system's defence mechanism against cancer cells. The data indicate the ability of resminostat to improve the effect of checkpoint inhibitors (PD1/PDL1, CTLA4 inhibitors), other immunotherapeutic agents such as antibodies (eg rituximab), and other immunostimulating agents (eg TLR ligands).

Specifically, in hepatocellular (HepG2, Huh7, SNU475) and adenocarcinomic (A549) cellular models, resminostat reduced the expression of immunosuppression mediating enzymes, IDO1 and ARG1. This renders the tumour microenvironment more sensitive to attack from natural immune cells, which could therefore increase the number of patients responding to immunotherapeutic treatments, such as PD1 and CTLA4 inhibitors. In addition, resminostat was shown to enhance the expression of several cancer antigens and MHC class I molecules on multiple tumour cell lines, thus making the cancer cells more visible for recognition by T-cells. Resminostat was also shown to upregulate NK-cell ligands and therefore boost the production of NK cells (natural killer cells of the immune system).

Valuation

Our overall valuation for 4SC has increased to €115m (vs €102m), or €11.32 per share after the recently completed 1-for-5 share consolidation (previously €10.00 on an equivalent basis). 4SC now has 10.2m shares outstanding, compared to 50.8m prior to the consolidation. The increase in overall valuation is the result of adding China to resminostat's potential in HCC (€250m peak sales at 20% probability) following the Menarini deal, and raising the probability in NSCLC to 40% to match HCC. Our valuation model is summarised in Exhibit 1 and is based on a risk-adjusted NPV analysis of the key products and lead indications, and uses a 12.5% discount rate. We now split out resminostat's potential by indication and territory.

Resminostat is the primary valuation driver, so securing the finance and/or partner to advance this programme is key to the investment case. This may be for HCC or niche haematological indications, although our current valuation is primarily based on development for HCC (globally) and NSCLC (Japan).

4SC also has options to finance and/or partner its Phase I cancer candidates, 4SC-202/4SC-205, for further development. 4SC-202 is perhaps the most advanced in terms of supporting data in haematological tumours. We look forward to final study reports on these compounds in 2015.

Exhibit 1: 4SC valuation model and key assumptions

Product	Indication	Region	Status	Partner	NPV (€m)	Prob. of success	rNPV (€m)	rNPV/ share (€)	Launch	Peak sales (€m)	Net royalty estimate
Resminostat	1st-line HCC	Japan	Phase II	Yakult Honsha	83.9	40%	33.6	3.30	2021	200	17.5%
		China	Phase I	Menarini	74.3	20%	14.9	1.46	2022	250	15%
		USA	Phase II	-	46.4	40%	18.5	1.82	2021	200	20%
		EU	Phase II	-	49.1	40%	19.7	1.93	2021	200	20%
Resminostat	2nd-line NSCLC	Japan	Phase II	Yakult Honsha	54.9	40%	22.0	2.16	2021	200	17.5%
4SC-202/ 4SC-205	Haematological/ solid tumours	WW	Phase I	-			25.0	2.46			
R&D expenses							(10.0)	(0.98)	50% risk-adjusted		
Admin expenses							(5.3)	(0.52)	95% risk-adjusted		
Net debt at end-2014							(3.2)	(0.32)			
Total							**115**	**11.32**			

Source: Edison Investment Research

With the Menarini deal and Yakult's ongoing clinical studies with resminostat in Japan, the development of this compound for HCC is now possible in the key global markets for HCC.

In addition, we note that Yakult's Phase II trial in HCC is similar in design to 4SC's proposed Phase II study in HCC, which will also seek to properly validate the potential predictive biomarker ZFP64. As a reminder, results from the Phase IIa Shelter study indicated a greater survival benefit for those resminostat-treated patients that had a higher level of ZFP64 (blood-based biomarker) at baseline. However, results from a prospectively designed study are required before conducting a Phase III trial with ZFP64-based patient stratification. Data from the Yakult study, potentially in 2016, should therefore help to confirm resminostat's effectiveness in HCC and the relevance of ZFP64 to any treatment effect. In terms of advancing resminostat for HCC in the EU/US, it may therefore seem logical for 4SC to await the outcome of Yakult's study before confirming next development steps for the compound in Western markets.

Sensitivities

4SC is subject to sensitivities typical of biotech drug development, including the unpredictable nature of clinical trials, the success or failure of competitors, changing market dynamics and a reliance on partnerships to commercially exploit its products. The main investment case hinges on 4SC's ability to secure financing and/or a deal for resminostat (excluding Japan/Asia-Pacific) to advance the product for HCC or niche haematological indications. Related to HCC, a key sensitivity is the outcome of the Phase III trial of Eisai's lenvatinib in front-line HCC in 2015/16; positive data versus sorafenib could shift the standard of care in advanced HCC. 4SC has a limited free float (c 36%) with a large single shareholder, Santo Holding, having a 49% share.

Financials

4SC reported net debt of €3.2m as of 31 December 2014, with €3.2m in cash offset by €6m drawn from the €10m Santo shareholder loan and €0.32m in Yorkville convertible bonds.

In June 2014, 4SC agreed a shareholder loan of up to €10m with Santo Holding, its largest shareholder (which now holds a 49% stake). As of March 12, 2015, three tranches of €2m each have been drawn from this loan, leaving up to €4m still available. 4SC can draw down credit lines in tranches until 31 December 2015. The loan carries interest of 8% pa and runs until the end of 2016 (the maturity date, when the principal and interest must be paid). 4SC also has the option to draw up to €15m from a convertible note agreement with Yorkville (signed in February 2014), until December 2016. The Yorkville bonds can be issued in tranches of €0.5m (gross). To date, two

tranches have been issued (in February and September 2014), generating €0.95m (after 5% discount) to 4SC and resulting in notes being converted into a total of 477,392 new shares in 2014.

The existing cash, coupled with the Santo and Yorkville facilities, should therefore provide 4SC with the funding to support current operations into H116, based on expected revenue and cost development in 2015. This guidance includes preparing for the resminostat Phase II HCC study, but not the actual costs of running the trial (direct costs estimated at €15m). We have added the estimated €1m upfront fee from Menarini to our revenue forecast for FY15e (now €8.5m vs €7.5m previously), but we note that 4SC has not revised its financial guidance following the deal. As such, excluding the potential cost of new clinical trials, the company is guiding an average monthly cash burn rate of €0.2m in 2015. This assumes a significantly reduced R&D spend in 2015, following completion of the Phase I trials with 4SC-202 and 4SC-205 in 2014.

However, our current model includes the assumption that funding and/or a partner is secured in 2015 to start the Phase II liver cancer study for resminostat, such that R&D expenses are estimated at €10m and €13.3m in FY15e and FY16e, respectively. Admin expenses are expected to be roughly flat with c €4m in 2015. The proposed R&D investment creates a significant financing requirement over the next 24 months, which we nominally assign to debt and we model as follows: €12m in 2015 and €10m in 2016 (in fresh finance). We note these figures are indicative and purely for financial modelling purposes, and acknowledge that the actual amounts may vary significantly. We assume that the remaining €4m Santo loan is fully drawn in 2015, but again this is for illustrative purposes and the actual amounts may vary significantly.

The additional funds still required for the resminostat clinical trial could come from debt, equity, partners, or a combination of all three. In terms of a potential equity raise, we note that 4SC recently completed a 1-for-5 share consolidation (approved at an EGM in March), which has lowered the shares in issue from 50.8m to 10.2m. This has re-priced 4SC's shares to approximately €6.00, which is now well above the €1.00 minimum required by German regulators to issue fresh equity. This is purely a technical transaction and in theory should not have a material impact on 4SC's market capitalisation. We also note that although the shares outstanding have been reduced by a factor of 5, the company's authorised share capital of up to 25.2m shares (approved until 1 May 2018) remains unchanged, underlining the financial flexibility that 4SC now has.

Our financial model is summarised in Exhibit 2.

Exhibit 2: Financial summary

€'000s	2012	2013	2014	2015e	2016e
Year end 31 December	IFRS	IFRS	IFRS	IFRS	IFRS
PROFIT & LOSS					
Revenue	**4,353**	**4,904**	**7,055**	**8,500**	**6,800**
Cost of sales	(327)	(1,474)	(4,080)	(4,250)	(3,060)
Gross profit	**4,026**	**3,430**	**2,975**	**4,250**	**3,740**
R&D expenditure	(12,909)	(10,243)	(8,504)	(10,000)	(13,300)
Administrative, distribution and other	(4,483)	(3,779)	(3,908)	(4,028)	(4,092)
Operating profit	**(13,366)**	**(10,592)**	**(9,437)**	**(9,778)**	**(13,652)**
Intangible amortisation	(1,403)	(1,593)	(819)	(819)	(819)
Exceptionals (impairment / restructuring costs)	0	(862)	0	0	0
Share-based payments	(130)	(53)	(3)	(15)	(20)
EBITDA	**(11,522)**	**(7,804)**	**(8,339)**	**(8,694)**	**(12,588)**
Operating profit (before GW and except.)	(11,833)	(8,084)	(8,615)	(8,944)	(12,813)
Net interest	126	48	(228)	(802)	(859)
Other (profit/loss from associates)	33	19	39	39	39
Profit before tax (norm)	**(11,707)**	**(8,036)**	**(8,843)**	**(9,746)**	**(13,672)**
Profit before tax (FRS 3)	**(13,207)**	**(10,525)**	**(9,626)**	**(10,541)**	**(14,472)**
Tax	(10)	0	(70)	0	0
Profit after tax (norm)	**(11,684)**	**(8,017)**	**(8,874)**	**(9,707)**	**(13,633)**
Profit after tax (FRS 3)	**(13,217)**	**(10,525)**	**(9,696)**	**(10,541)**	**(14,472)**
Average number of shares outstanding (m)	9.2	10.1	10.1	10.2	10.2
EPS - normalised (€)	**(1.27)**	**(0.80)**	**(0.88)**	**(0.95)**	**(1.34)**
EPS - FRS 3 (€)	**(1.43)**	**(1.04)**	**(0.96)**	**(1.04)**	**(1.42)**
Dividend per share (€)	0.0	0.0	0.0	0.0	0.0
BALANCE SHEET					
Fixed assets	**13,326**	**11,591**	**10,639**	**9,673**	**8,732**
Intangible assets	12,223	10,651	9,836	9,020	8,204
Tangible assets	787	602	425	275	150
Investments and other	316	338	378	378	378
Current assets	**15,741**	**6,114**	**4,295**	**5,506**	**4,068**
Stocks	22	23	25	25	25
Debtors	3,084	346	652	652	652
Cash	12,064	4,899	3,202	4,436	2,998
Other current assets	571	846	393	393	393
Current liabilities	**(3,499)**	**(3,587)**	**(4,842)**	**(5,579)**	**(4,829)**
Creditors	(584)	(675)	(993)	(993)	(993)
Short-term borrowings	0	0	(317)	(317)	(317)
Deferred revenue (short term)	(2,021)	(1,589)	(2,638)	(3,375)	(2,625)
Other current liabilities	(894)	(1,323)	(894)	(894)	(894)
Long-term liabilities	**(3,755)**	**(2,836)**	**(8,042)**	**(21,254)**	**(30,729)**
Long-term borrowings	0	0	(6,131)	(18,131)	(28,131)
Deferred revenue (long term)	(3,575)	(2,682)	(1,788)	(3,000)	(2,475)
Other long-term liabilities	(180)	(154)	(123)	(123)	(123)
Net assets	**21,813**	**11,282**	**2,050**	**(11,654)**	**(22,758)**
CASH FLOW					
Operating cash flow	**(15,327)**	**(7,052)**	**(8,302)**	**(10,643)**	**(11,313)**
Net interest	163	66	0	(20)	(21)
Tax	(10)	0	(70)	0	0
Capex	(50)	(99)	(100)	(100)	(100)
Expenditure on intangibles	(51)	(21)	(3)	(3)	(3)
Acquisitions/disposals	10	10	0	0	0
Financing	11,367	0	477	0	0
Other	0	0	0	0	0
Net cash flow	(3,898)	(7,096)	(7,998)	(10,766)	(11,438)
Opening net debt/(cash)	**(15,820)**	**(12,064)**	**(4,899)**	**3,246**	**14,012**
HP finance leases initiated	0	0	0	0	0
Other	142	(69)	(147)	0	0
Closing net debt/(cash)	**(12,064)**	**(4,899)**	**3,246**	**14,012**	**25,450**

Source: Edison Investment Research, 4SC accounts. Note: historical EPS and shares outstanding amounts have been adjusted to reflect the 1-for-5 share consolidation completed on 27 April 2015, with the total shares in issue reduced from 50,849,206 to 10,169,841.

Frankfurt +49 (0)69 78 8076 960
Schumannstrasse 34b
60325 Frankfurt
Germany

London +44 (0)20 3077 5700
280 High Holborn
London, WC1V 7EE
United Kingdom

New York +1 646 653 7026
245 Park Avenue, 39th Floor
10167, New York
US

Sydney +61 (0)2 9258 1161
Level 25, Aurora Place
88 Phillip St, Sydney
NSW 2000, Australia

Wellington +64 (0)48 948 555
Level 15, 171 Featherston St
Wellington 6011
New Zealand