Initiation | Healthcare

7 November 2018

Sareum Holdings

TYKing the boxes

Sareum Holdings' (Sareum's) investment case centres on the development of a therapy for the treatment of solid tumours (SRA737, a Chk1 inhibitor – see page 6 for an explanation) and the potential licensing of internally-generated candidates for the treatment of autoimmune disease and cancer (TYK2/JAK1 inhibitors – see page 8).

Sareum is effectively a passive investor in SRA 737, which is licensed for development to Sierra Oncology. QuotedData's model values Sareum's 27.5% economic interest in this licensing deal at £20.3m. This figure could rise by £2-3m a year over the next two years, as development progresses, before doubling to around £52m in 2021. By contrast, Sareum's enterprise value (market cap less cash, EV) is £22m.

In addition, Sareum's TYK2/JAK1 assets represent potentially highly attractive licensing opportunities. These could become increasingly valuable as their development progresses. In view of their early development stage, QuotedData's model places an indicative value of £7-15m on these assets. However, the model suggests that their value could double with a small incremental investment (in the region of £1-2m) and rise a further fivefold to about £150m in the early 2020s on reaching clinical proof of concept.

With normal assumptions for research and development (R&D) spending, overheads and tax, QuotedData's model suggests a current value for Sareum of £25-33m (0.87-1.14p/share), which offers up to 35% upside to the share price.

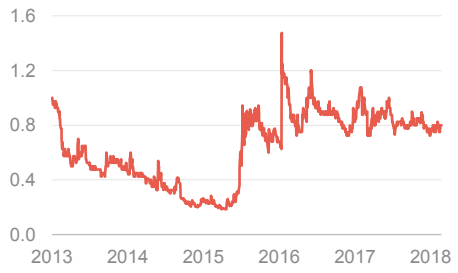
Year ended	Revenue (£m)	Profit before tax (£m)	Earnings per share (p)	Dividend per share (p)
30/06/16	0.0	(1.2)	(0.05)	0.0
30/06/17	0.0	0.4	0.02	0.0
30/06/18	0.0	(1.7)	(0.06)	0.0
30/06/19	0.0	(1.7)	(0.06)	0.0

Source: Marten & Co

Sector	Healthcare
Ticker	SAR LN
Base currency	GBP
Price	0.80p
Daily volume (1-year average)	6.5k shares
1-year high	1.075p
1-year low	0.725p
1-year performance	(8.8%)
5-year performance	(3.0%)
Yield	0.0%

Share price

Time period 06/11/2013 to 06/11/2018



Source: Bloomberg

Domicile	England and Wales
Market cap	£23.3m
Shares outstanding	2.88bn
Net cash*	£1.7m

* estimated as of 31 December 2018 – see page 16.

Many of the terms used in this note are explained in the glossary on the QuotedData website, which is accessed through the search box.

Contents

Virtual drug development

UK biotech focused on tyrosine kinase inhibitors

Sareum is a UK-based biotech company that operates on a virtual basis (in that most of its activities are outsourced to third parties) and specialises in the early-stage development of compounds that inhibit a class of cell signalling molecule known as receptor tyrosine kinases.

Tyrosine kinase inhibitors (TKIs) are a well-established drug class, particularly in cancer where more than 50 have been approved and many more are in development. TKIs are also used to treat autoimmune /inflammatory conditions, albeit with only a small number of approved products to date.

Founded in 2003 as spin out from Millennium

Sareum was originally formed in 2003 as an management buy-out from Millennium Pharmaceuticals, a large US biotech company (now a subsidiary of Takeda). The company originally operated a hybrid business model, in contract R&D, based on its expertise in solving the 3D structure-activity relationships of "challenging" drug targets (hence the "S-A-R" in its name). This provides a basis for the optimisation of molecules that could selectively block those targets without affecting other mechanisms.

Sareum's structure-based approach particularly lends itself to kinases as the large number of these targets and their closely-related nature means that prior knowledge of 3D structure is often required to achieve adequate levels of selectivity. Its internal discovery efforts focussed on "difficult" drug targets, such as TYK2 (see page 8).

Moe information is available on the company's website www.sareum.com

Sareum listed on the AIM market of the London Stock Exchange in 2004 and has funded its activities through periodic share issues, which have totalled £12m to date. The company took a strategic decision to sell its contract research activities in 2008 and evolved into a pure drug-development business, based on the expertise of its two principals and founders.

Since then, it has focused purely on advancing its portfolio with the aim of reaching recognised value inflection points, such as demonstrating desirable pharmacological properties and activity in animal models. The company expects to licence out its compounds after reaching key inflection points, typically to larger biotech or pharmaceutical companies, for further development and commercialisation.

A well-established business model

This is a well-established business model for biotech companies and, indeed, pharmaceutical companies typically source as much as half of their R&D pipeline in this way. Returns from licensing deals come in the form of an upfront payment, milestones (payments on successful completion of key development stages; regulatory filings or approvals; or achievement of sales thresholds) and royalties (a percentage of sales) payable on a territory-by-territory basis until the expiry of the licensed intellectual property.

It is, however, difficult to predict the level of interest on the part of potential licensees as well as the timing and outcome of licensing negotiations. Nevertheless, assets that are likely to be most attractive to potential partners would be expected to be those with the strongest competitive position among those with the same or a similar mechanism. This should be an important consideration for investors.

One of a handful of companies with TYK2 inhibitors in development

Sareum is one of a handful of companies that have identified a TYK2 inhibitor – and effectively the only one that is unpartnered – so there is reason to believe it could find a partner, which it would seek to do on economically attractive terms. Typically, autoimmune-condition market opportunities appear to support at least four compounds in the same class, as is the case with JAK1 inhibitors for rheumatoid arthritis (RA).

Figure 1: Sareum's research and development (R&D) pipeline

Compound	Mechanism[1]	Indication(s)[2]	Stage[3]	Notes
SRA737	CHK1 inhibitor	High-grade serous ovarian cancer other solid tumours particularly with the CCNE1 mutation, which is thought to confer sensitivity to Chk1 inhibition.	Phase I/II	Licensed to **Sierra Oncology** in a deal with an upfront payment, milestones of $328.5m and royalties on sales. Sareum has a 27.5% economic interest, with 72.5% held by **CRT Pioneer Fund**.
SDC-1801	TYK2/JAK1 inhibitor	Potential indications include psoriasis, RA, lupus, IBD and multiple sclerosis.	Preclinical	Efficacy demonstrated in psoriasis, RA and colitis models. Entering non-GLP tox studies. Joint development agreement with **SRI International.**
SDC-1802	TYK2/JAK1 inhibitor	T-cell acute lymphoblastic leukaemia (T-ALL); anaplastic large cell lymphoma (ALCL), solid tumours.	Preclinical	Efficacy demonstrated in model of T-ALL.
N/D	Aurora/FLT3 inhibitor	Acute myeloid leukaemia (AML)/ acute lymphoblastic leukaemia (ALL).	Preclinical	**HMUBEC** is entitled to a low-mid single digit royalty.

Source: Sareum, Marten & Co. Notes: 1) Each of these describes a means of inhibiting receptors on cells that are responsible for intra-cellular signalling. 2) These are the disease areas that it is believed the inhibitors can target. 3) Please see QD's 'Phase – in drug trials' glossary note for an explanation.

Figure 2: The TYK2/JAK inhibitor landscape in autoimmune disease: clinical development summary

Company	Drug	Selectivity	Development status	Notes
Pfizer	Xeljanz (tofacitinib)	pan-JAK	Approved (RA, PsA, UC (US, Canada)). Phase III (AS, sJIA). Phase II (atopic dermatitis, diffuse scleroderma). Phase I (dermatomyositis).	FDA rejection in psoriasis. Discontinued (asthma; Crohn's, dry eye; IBS, therapy rejection).
Lilly	Olumiant (baricitinib)	JAK1/2	Approved (RA). Phase III (atopic dermatitis, SLE, AA). Phase II (giant cell arteritis).	Originated at Incyte. FDA only approved lower 2mg dose.
Incyte	ruxolotinib (topical)	JAK1/2	Entering Phase III (atopic dermatitis). Phase II (vitiligo).	Discontinued (AA, psoriasis). Positive Phase II data.
Abbvie	upadacitinib	JAK1	Pre-registration (RA), Phase III (atopic dermatitis; Crohn's; PsA, UC). Entering Phase III (giant cell arteritis). Phase II (AS).	Four positive Phase III trials in RA.
Gilead	filgotinib	JAK1	Phase III (RA, Crohn's, UC). Phase II (AS; cutaneous lupus erythematosus; lupus nephritis; PsA, Sjogren's syndrome; uveitis).	Originated at Galapagos. First Phase III in RA positive and pos. best in class activity in RA.
Pfizer	abrocitinib	JAK1	Phase III (atopic dermatitis).	Holds breakthrough therapy designation. Phase II in psoriasis (results).
Pfizer	PF-06651600	JAK3	Entering Phase III (AA). Phase II (Crohn's, RA, UC, vitiligo).	Holds breakthrough therapy designation.
Astellas	peficitinib	pan-JAK	Phase III (RA).	Phase II studies by J&J in UC, psoriasis.
Incyte	italcitinib	JAK1	Phase II (UC).	Phase II for haem cancers.
Incyte	INCB54707	JAK1	Phase II (hidradenitis suppurativa).	-
Theravance/ J&J	TD-1473	JAK	Phase III (UC), Phase II (Crohn's).	Drug is intestinally restricted.
Concert	CTP-543	JAK1/2	Phase II (AA)	Deuterated ruxolitinib.
Aclaris	ATI-502	JAK1/3	Phase II (atopic dermatitis, AA, androgenetic alopecia).	Topical. Phase II in AA interim results.
Aclaris	ATI-501	JAK1/3	Phase II (AA).	-
Reistone Biopharma	SHR-0302	JAK	Phase II (Crohn's, UC).	Originated at Jiangsu Hengrui.
Bristol-Myers Squibb	BMS-986165	TYK2	Phase III (psoriasis). Phase II (Crohn's, SLE); Phase II planned (UC, PsA). Phase I (autoimmune disorders; IBD, PsA).	Showed near biologic efficacy in Phase II in psoriasis.
Pfizer	PF-06700841	TYK2/ JAK1	Phase II (psoriasis, UC, Crohn's, vitiligo). Phase I (IBD).	Positive Phase II in AA.
Asana	ASN002	JAK/SYK	Entering Phase II (atopic dermatitis).	Topical.

Source: Marten & Co. RA = Rheumatoid arthritis, PsA = psoriatic arthritis, SJIA = systemic juvenile idiopathic arthritis, AS = ankylosing spondylitis, SLE = systemic lupus erythematosus, UC = ulcerative colitis, IBD = inflammatory bowel disease; AA= alopecia areata.

Investment summary

- The investment case for Sareum centres on development of the Chk1 inhibitor, SRA737, by its partner Sierra Oncology, together with the early development and potential out-licensing of Sareum's internal TKY2/JAK1 candidates for autoimmune disease and cancer. Sareum's R&D pipeline is summarised in Figure 1.
- Sareum holds a 27.5% interest in the $328.5m licensing deal that covers SRA737, with the majority interest held by CRT Pioneer Fund[1]. SRA737 is one of two compounds in active development with the Chk1 mechanism. QuotedData's model values Sareum's interest at £20.3m and suggests that this figure to rise by £2-3m a year over the next two years, before doubling to £52m in 2021.
- Sareum's enterprise value (market cap less cash) of £22m suggests investors either undervalue SRA737 or ascribe little value to its TYK2/JAK1 assets.
- Although the value of its interest in SRA737 has potential to grow as development progresses, Sareum is effectively a passive investor in that asset. However, its TYK2/JAK1 assets have – based on judicious R&D investment over the next two - three years – the potential to deliver a more significant return. These have the potential to become the main driver of the investment case.
- Two JAK1 inhibitors, developed by competitors, have been approved to date for autoimmune indications. Xeljanz and Olumiant have or are projected to have sales of $1-2bn/year, despite significant safety issues. Other, more selective JAK1 agents, upadacitinib and filgotinib, are approaching the market and have greater peak sales potential.
- Sareum is one of only a handful of companies active in the TYK2 space. Competing agents have shown impressive efficacy in psoriasis and alopecia areata, and are in development for multiple additional indications. QuotedData's evaluation of the competitive landscape for TYK2/JAK in autoimmune disease (summarised in Figure 2) and cancer (shown later) suggests there are multiple, high-value development opportunities available to Sareum or a potential licensee.
- QuotedData's model places an indicative value[2] on the TYK2 assets of £7-15m ($10-20m) but highlights their potential for value creation through judicious R&D investment. It suggests that the value could double with a relatively small R&D spend (£1-2m), which would be required to reach pre-IND-stage, while an investment in the range of around £10m could generate early clinical proof of concept data in 2022 and could support a further fivefold increase in value to £150m or more.
- Licensing on the back of early clinical data should allow Sareum to realise highly attractive economic terms in a potential licensing deal. Although Sareum's cash reach currently extends into 2020, further funds will be needed to exploit the full potential of the TYK2/JAK1 inhibitors, pending a partnership.
- The company is exposed to the risks normally associated with drug development, including the uncertain outcome of clinical trials and the success or failure of competitors. Sierra's ability to fund further development of SRA737 and/or its strategic priorities represent additional risk factors.
- With normal assumptions for R&D spending, overheads and tax, QuotedData's model suggests an indicative valuation for Sareum of £25-33m (0.87-1.14p/share), which offers up to 35% upside to the share price.

Notes: 1) A £70m fund established by Cancer Research UK and funded by the European Investment Bank and Syncona, which is managed by Sixth Element Capital. 2) Stock-market valuations are typically well below values that might be realised in licensing or M&A transactions, as the market tends to discount heavily financing and deal risk.

SRA737 – CCNE1 driven cancers

Developed in collaboration with CR UK and CRT Pioneer Fund

Sareum originated SRA737 and developed it in collaboration with Institute of Cancer Research (now CR UK) with financial support from CRT Pioneer Fund. Sareum originally held a 50% economic interest in the product, but this was reduced to 27.5% through the co-funding arrangements. Sareum was responsible for the compound's early development up to the licensing deal with Sierra Oncology (then called ProNAi Therapeutics).

SRA737 is a highly selective inhibitor of Checkpoint kinase 1 (Chk1), a serine/threonine protein kinase that is a key regulator of cell-cycle progression and DNA damage response. In addition to regulating DNA damage checkpoints, Chk1 plays a central role in normal DNA replication, resolving replication stress, the progression to mitosis and cytokinesis. Inhibition of CHK1 in the absence of DNA damage can cause impaired DNA replication; loss of DNA damage checkpoints; premature entry into mitosis with highly fragmented DNA; and cell death via replication catastrophe.

One of just two Chk1 inhibitors in development

SRA737 is one of just two Chk1 inhibitors in clinical development, Roche having just discontinued its agent, RG7741[1]. Eli Lilly's prexasertib is the leader in this class and has shown positive results in women with BRCA wild-type high-grade serous ovarian carcinoma[2].

Phase I/II studies are underway as a monotherapy and in combination with low-dose gemcitabine

SRA737 is being evaluated in two Phase I/II trials in patients with advanced cancer. The first study is testing the compound's activity as a monotherapy, while the second is in combination with a sub-therapeutic dose of gemcitabine with/without cisplatin. Both studies originally recruited patients with various solid tumour types, as is common for early signal finding studies, but have since been focussed more on high-grade serous ovarian cancer. This includes patients with the CCNE1 mutation, which is thought to confer sensitivity to Chk1 inhibition.

Figure 3: SRA737 trial schedule

Indication	No. of patients	Design	Study ID	Data
Ovarian/ other	170	Monotherapy: 145 patients in five indication cohorts: high-grade serous ovarian cancer with 65 patients with/without CCNE1 mutation and four smaller cohorts of 20 patients each in prostate, non-small-cell lung carcinoma, head & neck/anal and colorectal. See here.	NCT02797964 / SRA737-01	Sep-19
Ovarian/ other	140	Combination with low-dose gemcitabine +/- cisplatin. Expansion cohort consists of four cohorts of 20 patients with prioritised enrolment of 20 genetically defined high-grade serous ovarian cancer. See here.	NCT02797977 / SRA737-02	Oct-19
Prostate	N/A	Combination study of SRA737 + niraparib.	SRA737-03	N/A

Source: Marten & Co

Preliminary data from both the monotherapy and combination studies are expected to be reported in the first half of 2019, with final results due later that year. Meanwhile, a third study of SRA737 in combination with niraparib, a PARP inhibitor (and possibly other DNA damage repair-targeted agents) is expected to start shortly.

Meanwhile, Lilly's prexasertib is in three Phase II trials, although all are single arm, as well as several pilot Phase I studies examining combinations with other agents. Data from these studies are due from the middle of 2019 and would presumably, if positive, support a move into registration trials.

Notes: 1) Roche conducted a single Phase I study (NCT01564251) with GDC-0575, alone and in combination with gemcitabine (results). 2) https://www.ncbi.nlm.nih.gov/pubmed/29361470

Figure 4: Phase I/II studies underway with prexasertib

Indication	No. of patients	Design	Study ID	Data
Squamous cell carcinoma of the head and neck	70	Combination with cisplatin or cetuximab with radiation.	NCT02555644	Jan-19
Platinum-resistant/refractory recurrent ovarian cancer	180	Four cohorts: BRCA negative, ≥3 lines of prior treatment; BRCA-negative <3 lines of prior treatment; BRCA positive, prior PARP inhibitor; and platinum refractory.	NCT03414047	Apr-19
BRCA1/2 mut. breast or ovarian, TNBC, HGSOC and mCRPC	153	Pilot study of monotherapy.	NCT02203513	Jun-19
Adv solid tumours*	205	Five arms test prexasertib in combination with cisplatin, cetuximab, G-CSF, pemetrexed, fluorouracil and LY3023414 (a PI3K/mTORi).	NCT02124148	Feb-20
Adv solid tumour	50	Three cohorts: HR deficiency, replicative stress, and CCNE-1 amplification.	NCT02873975	Apr-20

Source: Marten & Co. Note: * Phase I, TNBC = triple negative breast cancer.

After a strategic review last year, Lilly selected prexasertib as one of six cancer R&D pipeline projects to be prioritised, which suggests its confidence in the mechanism. Lilly also has a second, earlier-stage Chk1 inhibitor in Phase I, which was de-prioritised and allocated to partnering or external development.

Investment sensitivities specific to SRA737

Additional risk arises from Sierra's relative early-stage biotech and dependence on capital markets

Investors should be aware of the specific risks/sensitivities related to SRA737 that are present, over and above the normal risks associated with any drug development. These largely arise from the fact that Sierra Oncology is still a relatively early-stage company (market capitalisation approximately $140m) and is itself dependent on raising capital to support development of SRA737 and its other programmes. The company's cash of $125m as of June 30, gives it a reach into mid-2020.

Furthermore, there is also a risk that Sierra's acquisition of a Phase III-stage asset, momelotinib, a JAK1/JAK2 and ACVR1 inhibitor, could cause a change in strategic priorities, with resources directed towards development of this later-stage asset to the detriment of SRA737. And as Sierra is relatively cash constrained and obligated to make milestone payments on SRA737, it might alternatively delay milestone triggering events (presumed to include the start of registration studies).

Changes in development priorities are, however, not uncommon and, ultimately, the licensing arrangements can be changed by negotiation (or even terminated, if the licensee materially fails to perform against its best endeavours obligations). However, if such circumstances were to occur, Sareum may have only limited influence over the outcome as it is the junior party to CRT Pioneer Fund.

Sierra would, presumably, at some point seek to sub-license SRA737 either globally or outside the US, although it is also possible that the company may also be acquired either for the Chk1 inhibitor or its other assets. In either case, SRA737 would then fall into the hands of a third party that may have different objectives in terms of development.

TYK2 – autoimmune disease

TYK2 is one of four JAK kinases

TYK2 (Tyrosine kinase 2) is one of four members of the Janus kinase family, the others being JAK1, JAK2 and JAK3, all of which modulate the JAK pathways that play a critical role in the signalling of cytokines that have been implicated in the pathogenesis of inflammatory and autoimmune diseases. TYK2 is critical in transducing signals downstream of the IL-12 and IL-23 receptors, via activation of the transcription factors STAT4 and STAT3. IFN-gamma production by T cells, mediated by IL-12 signalling, is also highly dependent on TYK2. These cytokines and receptors are often involved in proinflammatory responses associated with immunological diseases and thus inhibition of TYK2 has potential to be beneficial in conditions such as multiple sclerosis, rheumatoid arthritis, psoriasis and inflammatory bowel disease (see link for a further discussion).

Pfizer's Xeljanz, a pan-JAK inhibitor, is the lead product in the broad JAK class, gaining approval in 2012 for rheumatoid arthritis and subsequently for psoriatic arthritis and ulcerative colitis. Xeljanz has sales of more than $1.6bn/year despite carrying a "black box" warning for serious infections and lymphoma (the product was rejected for psoriasis on the grounds of benefit/risk).

Lilly's Olumiant, the second JAK inhibitor to be approved, has peak sales forecast of $2bn/year and it also carries a black-box warning for serious infections, lymphoma and thrombosis. Olumiant is in late-stage development for other indications including atopic dermatitis and lupus. Two other companies have selective JAK1 inhibitors in late development, both initially targeting rheumatoid arthritis. These are Abbvie (updacitinib, due to be filed shortly) and Gilead (filgotinib, which is likely to be filed next year).

Sareum is perhaps one of only five companies that have TYK2 inhibitors (see Figure 5 below). In terms of this space, Bristol-Myers Squibb is in the lead with BMS-986165, which has just entered Phase III trials for psoriasis. This agent is also in mid-stage studies for systemic lupus erythematosus and Crohn's with plans for two more indications – in ulcerative colitis and psoriatic arthritis. Pfizer's TYK2/JAK1 is in Phase II studies in psoriasis, ulcerative colitis and Crohn's disease.

Figure 5: TYK2 landscape

Company	Compound	Specificity	Indications/stage	Notes
Bristol-Myers Squibb	BMS-986165	TYK2	Phase III (psoriasis). Phase II (lupus, Crohn's, ulcerative colitis, psoriatic arthritis).	Phase II in psoriasis showed near biological levels of efficacy.
Pfizer	PF-06700841	TYK2/ JAK1	Phase II (Crohn's disease, psoriasis, ulcerative colitis).	Positive Phase II in alopecia areata. Phase I study suggests possible QT prolongation.
BMS	N/A*	TYK2	Phase I	
Nimbus Therapeutics	N/A	TYK2	Preclinical studies underway in Crohn's disease, multiple sclerosis, ankylosing spondylitis and cancer.	Under option to Celgene. Activity shown in psoriasis and IBD models. Activity shown in T-ALL for NDI-031301.
Sareum	SDC-1801	TYK2/ JAK1	Preclinical. Lead indications may include psoriasis, RA, lupus, IBD and multiple sclerosis.	Candidate SAR-20347 showed activity in models of psoriasis, RA and colitis. US DoD funding for lupus model.
Sareum	SDC-1802	TYK2/ JAK1	Preclinical. Lead indications may include T-cell acute lymphoblastic leukaemia (T-ALL); anaplastic large cell lymphoma (ALCL) and solid tumours.	Innovate UK funding award for T-ALL model.
Origenis	N/A	TYK2	N/A	Lead optimisation.

Source: Marten& Co. * Note: possibly BMS-986235

Both TYK2 and JAK1 are validated mechanisms

Both TYK2 and JAK1 inhibition can be considered validated mechanisms: JAK1 via the approved products in rheumatoid arthritis (Xeljanx and Olumiant) as well as multiple positive studies in other indications (psoriasis, atopic dermatitis, Crohn's and ulcerative colitis), while TYK2 has positive studies in psoriasis and alopecia areata.

There is an ongoing debate about the merits of selectivity just for TYK2 in this area, as the BMS and Nimbus compounds are pure TYK2 inhibitors while Pfizer and Sareum's are conventional ATP-competitive inhibitors that hit both TYK2 and the closely-related JAK1. The dual activity on JAK1 may confer an efficacy advantage over pure TYK2 inhibition.

Competitor data due from Pfizer may shed light on possible advantages of dual TYK2/JAK1 inhibition in psoriasis

Pfizer should shortly see Phase II results of its TYK2/JAK1 in psoriasis and any decision it takes to move into Phase III would be highly informative. The study results will obviously be compared with BMS-986165 and potentially give a read-across as whether the dual approach offers some advantages over pure TYK2 inhibition.

Recently published data also validate the mechanism in alopecia areata, an autoimmune condition that causes patchy or complete hair loss, usually on the scalp (but, importantly, is different to male pattern baldness). Pfizer published positive Phase II results for its TYK2/JAK1 inhibitor, PF-06700841 in a study that tested the drug in parallel with the JAK3 inhibitor, PF-06651600 (a similar study testing the two compounds in parallel is also underway in psoriasis). Pfizer selected the latter compound for further development, even though the efficacy for the TYK2/JAK1 was arguably slightly better.

Figure 6: Ongoing later-stage clinical studies with the Pfizer and BMS' TYK2 inhibitors

Molecule	Indication	Stage	Number of patients	Design	Endpoint(s)	NCT ID
BMS-986165	plaque psoriasis	III	600	Double blind, 3 arm (one dose vs placebo vs aprelimast).	Co-primary: sPGA score of 0 or 1 at week16 and PASI 75 at 16 weeks.	NCT03624127 /POETYK-PSO-1
BMS-986166	plaque psoriasis	III	1,000	Double blind, 3 arm (one dose level vs placebo vs apremilast) with rand withdrawal and retreat.	Co-Primary: sPGA score of 0 or 1 and PASI 75, both at week 16.	NCT03611751 /POETYK-PSO-2
BMS-986167	SLE	II	360	3 dose levels vs placebo.	SLE Responder Index at 24 weeks.	NCT03252587
BMS-986168	Crohn's disease	II	240	3 dose levels vs placebo.	Co-primary: CDAI at 12 weeks and endoscopic response.	NCT03599622
PF-06700841	plaque psoriasis	II	212	7 diff. doses (some with higher induction) vs placebo.	PASI index score at week 12	NCT02969018
PF-06700841 & PF-06651600 (JAK3i)	Crohn's disease	II	250	4 arms: both actives vs placebo for 12 weeks, followed by OLE drug for up to 52 weeks.	Endoscopic improvement (>3patients) at week 12.	NCT03395184
PF-06700841 & PF-06651600	ulcerative colitis	II	360	12 arm: (3 doses vs placebo for each drug) for 8 and 24 weeks.	Total Mayo Score (week 8).	NCT02958865
PF-06700841 & PF-06651600	vitiligo	II	300	12 arm (induction and maintenance) for 20 weeks.	VASI index at week 24.	NCT03715829

Source: Marten & Co. Note: SLE = systemic lupus erythematosus

Sareum's candidates, SDC1801 and SDC-1802, were selected from a novel series of compounds for either first or best-in-class potential. The selection was based on five characteristics: potency/selectivity for TYK2 and JAK1 (and avoidance of JAK2/JAK3); activity in disease models; predicted once or twice daily oral dosing; a good toxicological profile; and a straightforward synthesis route.

Sareum aims to reach IND stage in 2020. The company will have to fund non-GLP toxicology studies; GLP production and stability; preclinical efficacy; and pharmacology and toxicology studies before it can start first-in-man studies (single ascending dose and multiple ascending dose) in volunteers. Sareum expects to use early clinical data as the basis for securing a licensing deal.

SLE/lupus – a possible first indication

Sareum is considering lupus or lupus nephritis (the kidney damage caused by advanced lupus) as possible first indication(s) for SDC-1801. If this decision is confirmed, it would mean SDC-1801 following Bristol-Myers Squibb's Olumiant (Phase III) and BMS-986165 (Phase II) and Gilead's JAK1 filgotinib (Phase II for cutaneous lupus and lupus nephritis). Results of these studies should become available in 2020 and will potentially inform a future decision by Sareum.

There are relatively few competing molecules with oral availability in mid/late stage development for main autoimmune diseases, most of which are listed in the table below. There are also a larger number of biologicals under development in all of the indications (not shown).

Figure 7: Oral agents in mid/late development for autoimmune disease (non-TYK2/JAK inhibitor).

Company	Compound	Mechanism	Indications/stage
Celgene	ozanimod	S1P1 antagonist	Phase III (Crohn's, MS, UC). Refusal to file letter in MS, refiling planned in 2019
Novartis	siponimod	S1P1 antagonist	Filed (MS)
Corbus	lenabasum	CB2 agonist	Phase III (systemic sclerosis, dermatomyositis), Phase II (SLE).
Vanda	tradipatant	NK-1R antagonist	Phase III (atopic dermatitis)
CanFite	CF101	A3AR	Phase III (psoriasis), Phase II (RA)
Celgene	AJM300	alpha4 integrin antag	Phase III (UC)
RedHill	RHB104	triple antibiotic combo	Phase III (Crohn's)
J&J	ponesimod	S1P1 antagonist	Phase III (MS, psoriasis)
Biogen	diroximel fumarate	MMF prodrug	Phase III (MS)
BMS	BMS-986142	BTK inhibitor	Phase II (RA)
Rottapharm	CR6086	EP4 antagonist	Phase II (RA).
AstraZeneca	AZD9567	glucocorticoid receptor modulator	Phase II (RA)
Novartis	ZPL389	H4 antagonist	Phase II (atopic dermatitis)
Roche	Fenebrutinib/GDC-0853	BTK inhibitor	Phase II (RA, SLE, urticaria)
Abbvie	ABBV-599	BTK/upadacitinib combo	Phase II (RA, lupus)
GlaxoSmithKline	GSK2982772	RIP1 kinase inhibitor	Phase II (RA, UC)
Merck KGaA	evobrutinib	BTK inhibitor	Phase II (RA, SLE). Positive phase II in MS.
Kadmon	KD025	ROCK inhibitor	Phase II (psoriasis, IPF, GvHD)
Celgene	iberdomide	Cereblon modulator	Phase II (SLE)
Arena	etrasimod	S1P1 antagonist	Phase II (UC)
Lycea	LYC 30937	adenosine triphosphatase	Phase II (psoriasis, Crohn's)
Syntrix	aminopterin		Phase II (psoriasis)
Asahi Kasei	mizoribine	immunosuppression	Phase II (lupus nephritis)
Gilead/Ono	tirabrutinib	BTK inhibitor	Phase II (Sjögren's)
Roche	petesicatib	Cathepsin-2 inhibitor	Phase II (Sjögren's)
Principia	PRN1008	BTK inhibitor	Phase II (pemphigus vulgaris)

Source: Marten& Co. Note: may not be exhaustive. Excludes all JAK/TYK2 inhibitors shown in tables earlier.

JAK licensing deals

There have been a number of licensing deals in the JAK space, details of which are shown in Figure 8. Sareum would probably need to have some data from early human studies – preferably showing some proof of concept – to achieve the most attractive terms in a licensing agreement.

Figure 8: Licensing deal in the broad JAK space for cancer/autoimmune disease

Originator/ Licensor	Date	Product(s)	Indications	Stage at licensing	Notes
Gilead/Sierra Oncology	Aug-18	momelotinib	myelofibrosis	Phase III (failed)	Upfront = $3m, milestones of $195m (largely sales based) and royalties from mid-teens to high-twenties percent. Failed in Phase III.
Theravance/ Janssen (J&J)	Jan-18	TD-1473 + back-ups	UC and Crohn's	Phase I	Upfront = $100m. Milestones of $900m. Joint dvt/commercial in US with costs shared (67: 33 to Theravance). J&J has rights ex-US.
Celgene/ Impact Biomedicines	Jan-18	federatinib	myelofibrosis	Phase III	Acquired for $1.1bn, contingent payments of $1.4bn and sales-based milestones of $4.5bn.
Nimbus/ Celgene	Nov-17	Tyk2	N/A	Preclin	Celgene acquires option to Tyk2 and STING antagonist (also preclin). Financial terms not disclosed.
Galapagos/ Gilead	Dec-15	filgotinib	RA, Crohn's, UC, AS; PsA, Lupus, Sjogren's; uveitis	Positive Phase II in RA & Crohn's	Upfront = $300m, $425m equity invest at 20% premium. Milestone payments of up to $1.35bn and tiered royalties starting at 20% and a profit split in co-pro territories.
Rigel/Aclaris Therapeutics	Sept-15	ATI-501/2	alopecia areata/ dermatology	Preclin	Upfront = $8m, milestone payments of up to $90m and tiered royalties on sales.
CTI Biopharma/ Baxter	Nov-13	pacritinib	myelofibrosis	Phase III	Upfront = $30m and $30m equity investment, plus milestones of up to $112m. Rights returned by Baxalta after its acquisition by Shire.
Gilead/YM Biosciences	Dec-12	momelotinib	myelofibrosis	Phase I/II	Acquired for $385m, net of cash.
Astellas/J&J	Oct-12	perfectinib	RA	Phase II	Upfront = $65m for global, ex-Japan rights. Milestones of $880m and double-digit royalty. Now discontinued by J&J.
Galapagos/ Abbott (now Abbvie)	Feb-12	filgotinib	RA	Phase II in RA underway	Upfront = $150m, with option to license on completion of RA Phase II trials for $200m, with milestone payments of $1.0bn and tiered double-digit royalties. AbbVie subsequently declined option to licence.
Rigel Pharma/ AstraZeneca	Feb-10	fostamatinib disodium	RA	Phase II in RA completed.	Upfront = $100m. $345m in R&D milestones, $800m in sales-related milestones and double-digit royalties on sales. Oral SYK inhibitor. Rights returned by AZ and discontinued in RA. Since approved for ITP (as Tavalisse).
Incyte/Novartis	Nov-09	ruxolitinib	myelofibrosis	Phase III	Upfront = $150m plus initial $60m milestone for ex-US rights for ruxolitinib, up to $1.1bn in R&D and sales milestones plus double-digit royalty. Deal also provides global rights to capmatinib (a cMET inhibitor.
Cytopia/'YM Biosciences	Oct-09	momelotinib	myelofibrosis	Entering Phase II	Acquisition for C$14m in stock.

Source: Marten & Co.

Cancer indications

Sareum's SDC-1802 has shown efficacy in cellular and disease models of T-cell acute lymphoblastic leukaemia (T-ALL) and B-cell lymphoma. T-cell ALL is a rare cancer that largely affects children and accounts for 10-15% of newly diagnosed cases of ALL. Sareum estimates there may be 2,000 cases/year in Europe and a similar number in the US. The condition is currently treated with chemotherapy and stem-cell transplant, but no targeted therapies (or chimeric antigen T-cell therapies) have yet been developed.

T-ALL development could qualify for pediatric rare disease voucher.

One major attraction of developing a product in this indication is that it may, if successful, be rewarded with a pediatric rare disease voucher (PRV) in the US. This is an incentive to develop products for rare childhood conditions and allows the holder to receive fast-track review for another product at the FDA. Importantly these can be transferred, i.e. sold. The current transfer value is about $80-100m.

Sareum molecules are validated in various solid tumour disease models

Sareum has also generated evidence in disease models of kidney, colon, skin and pancreatic cancer that suggests that TYK2 inhibition can modulate the host's immune system to block tumour-cell proliferation. Further work may elucidate a strategy in solid-tumour indications, possibly with immune checkpoint inhibitors.

So far, only one JAK inhibitor, Incyte/Novartis's Jakafi, has been approved for cancer indications, namely myelofibrosis and polycythemia vera. It is also in development for Graft vs host disease, a serious complication of stem-cell transplantation, with an exploratory study underway in ALL. Ongoing studies in cancer with other JAK inhibitors are shown in Figure 9 below. The only development programme that seems to include T-ALL is a Phase II study involving J&J's Darzalex.

Figure 9: Ongoing studies of JAK inhibitors in cancer

Compound	Company	Indication	Stage	Design/notes	Study ID	Data
Italcitanib	Incyte	r/r DLBCL.	Phase I/II	In combination with ibrutinib	NCT02760485	Sep-18
Itacitinib	Incyte	B-cell malignancies	Phase I/II	3 arms: INCB050465 (PI3Ki) +/- itacitinib and INCB050465 + chemo	NCT02018861/ CITADEL-101	Dec-18
Italcitinib	Incyte	myelofibrosis	Phase II	itacitinib +/- low-dose ruxolitinib	NCT03144687	Jan-19
Italcitinib	Incyte	NSCLC (EGFRmut).	Phase I/II	In combination with Tagrisso	NCT02917993	Jan-19
INCB052793	Incyte	Adv solid tumours	Phase I/II	3 stages: (Ia) monotherapy; (Ib) comb with various single agent chemo; and (II) comb with azacitidine +/- itacitinib	NCT02265510	May-19
Pacritinib	CTI Biopharma	myelofibrosis	Phase I/II	Dose ranging study in myelofibrosis after failure on ruxolotinib.	NCT03165734	Dec-18
Jakafi	Incyte	B-ALL	Phase II	Single arm study of Jakavi plus chemo	NCT02723994	Feb-24

Source: Marten & Co. Note: Pacritinib is a JAK2/FLT-3 inhibitor. DLBCL = relapsed/refractory diffuse large B-cell lymphoma.

Investment thesis

Valuation

QuotedData's model considers SRA737 and the two TYK2/JAK1 compounds to form the core of the investment case and treats other projects in Sareum's R&D portfolio (principally its dual aurora kinase/FLT-3 inhibitor) as potential upside.

Valuation of Sareum's interest in SRA737 reflects assumptions on size and timing of milestones and royalties

Within the model, assumptions have been made about the size and timing of future milestones under the licensing deal (as these have not been disclosed). The main assumptions are that the remaining $319.5m comprises $195m in development and regulatory milestones and $125 of sales milestones, a roughly 60:40 split. It is assumed that SRA737 is launched in 2022 (in the US only, accelerated approval) with a broader worldwide launch in 2023. For the purposes of modelling royalties, it has been assumed that the product has a commercial life until 2034, when the intellectual property may expire (unless extended).

Milestone and royalty income from SRA 737 has been modelled broadly on the basis that Sierra continues development with a focus on HGSOC and on a site-agnostic approach for tumours driven by CCNE1 (or similar) mutations. CCNE1 mutations are thought to be present in 21% of ovarian cancers.

Figure 10: SRA737 modelling assumptions - summary

Assumption	Detail	Notes
R&D milestones	$45m on entry into pivotal trials	$20m (2019), $25m (2022)
Regulatory milestones	$150m on approval and launch	$50m (2022), $100m (2023).
Sales milestones	$125m on key thresholds	$50m when sales >$250m/year (2025), $75m when global sales >$500m/year (2027)
Royalties	9-12%	9% on sales up to $500m/year, 12% on sales >$500m/year
Peak sales	$922m in 2034	Not specifically modelled based on incidence, pricing but by reference to other TKIs using a tumour agnostic approach
Key indication	HGSOC	Monotherapy in CCNE1 mutant/wild type/combination with low-dose gemcitabine
Key indication	CCNE1 mutant solid tumours	CCNE1 (or similar) mutations are present in other solid tumour types such as bladder (25%), endometrial (21%), colorectal (14%) and non-small cell lung (9%)[1]

Source: Marten & Co.

The model assumes that peak sales of SRA737 of $920m/year are achieved in the late 2020s. This is clearly a rough estimate given the product's potential indications, pricing, duration of use and competition are all unknown at this point. However, the figure would be in line with projections for sales of Zejula in ovarian cancer (one of three PARP inhibitors approved in this indication) and, also is in line with sell-side estimates for other developmental cancer drugs that target specific driver mutations across several tumour types.[2]

Notes: 1) Source: Sierra Oncology Investor presentation. (p19). 2)For example, Blueprint Medicines' BLU-667 and Loxo Oncology's LOXO-292, both for RET mutant cancers; Loxo/Bayer's larotrectinib and Ignyta (now Roche)'s entrectinib for Trk mutant cancers.

This approach values Sareum's interest in SRA737 at £20.2m based on a risk-adjusted net present value, assuming a 25% probability of success, a 12.5% discount rate and a USD/GBP exchange rate of 1.3. The sensitivity of the value of the interest in SRA737 to adjustments in probability of success and discount rate is shown in the table below. The 25% probability is in line with industry norms and a cost of capital of 12.5% would also be typical for stock-market investors in early stage biotech.

Figure 11: Sareum's interest in SRA737- sensitivity to probability/cost of capital

Probability of success	Change in £m for given discount rate		
	10%	12.5%	15%
20%	£19.6	£16.3	£13.6
25%	£24.5	**£20.3**	£17.0
30%	£29.4	£24.4	£20.4

Source: Marten & Co

The valuation approach for the TYK2 assets within the model is less sophisticated. It would be unrealistic to use a risk-adjusted NPV to value early preclinical projects as this would produce a misleading figure.[1] An alternative is to use a non-risk adjusted net present value with a higher cost of capital (say 25%), but given the potential indications are still unknown, the model instead uses common benchmarks to value Sareum's TKY2/JAK1 assets, yielding a figure of £7-15m ($10-20m).

Sensitivities

Sareum is exposed to the risks typical of biotech drug development, including the uncertain outcome of clinical trials and reliance on third parties (notably Sierra) to advance the development of SRA737 and its TYK2 assets. Specific sensitivities related to Sierra have been noted earlier. Sareum will also have to raise further funds to advance its TKK2 assets, particularly SDC-1801.

The value of these may be affected by the success or failure of competitors, both within the TYK2/JAK class and, to a lesser extent, for other oral molecules addressing autoimmune/inflammatory indications. In order to be commercially successful, oral agents will need to show levels of efficacy that approach or match those of biological agents while offering side-effect advantages, such a lower tendency for immunosuppression. Oral agents are often preferred by dermatologists (eg for atopic dermatitis and psoriasis). The value of SDC-1801 could see a step change upwards if the competitive landscape for TYK2 inhibitors were to shift in its favour if, for example, the development of a competitor molecule were to be discontinued for some reason.

Note: 1) This tends to produce a misleadingly low or negative value, as undiscounted development costs weigh against heavily discounted and risk-adjusted future revenues.

Management & Shareholders

Sareum has 2,745m shares in issue. Management owns 3.2% of the company and there are no other substantial or disclosable (>3%) shareholdings. Further information on the company's management is provided in the table below.

Figure 12: Sareum director profiles

Executive	Role	Biographic details
Dr Tim Mitchell	CEO	Co-founder. CEO (2004-date) 30+ years of experience in the life science industry. Prior to leading buy-out of Sareum, was director, structure based discovery at Millennium Pharmaceuticals (2000-2003), and scientific team leader in R&D at SmithKline Beecham. He holds a PhD in computational chemistry and a BSc in chemistry. He holds a 1.54% shareholding.
Dr John Reader	CSO	Co-founder. VP chemistry (2004-2009, CSO 2009-date). Formerly associate director chemical technologies at Millennium Pharmaceuticals, prior to which he worked with Pharmacopeia and Cambridge Discovery Chemistry. He has a PhD in chemistry and a BSc in applied chemistry. He holds 1.58% shareholding.
Dr Stephen Parker	Chairman*	Chairman (2016-date). Formerly a partner with Celtic Pharma (2005-2011), CFO of OxfordGlycoSciences and investment banker focusing on pharma/biotech with Barings, Warburg and Apax Partners. Non-executive director of Silence Therapeutics Plc.

Source: Sareum, Marten & Co. Note: * non-executive role

Stock catalysts

Figure 13: Potential Sareum stock catalysts involving Sierra Oncology and TKY2/JAK1 competitors

Time	Catalyst	Comment/notes
Imminent	Results of PF-06700841 Phase II in psoriasis	Efficacy data will allow comparison of TYK2/JAK1 vs TYk2.
Imminent	Confirmation of FDA filing of upadacitinib in RA	Approval possible in late 2019.
Nov-18	Phase II results of prexasertib in small cell lung cancer due	Unlikely to be disclosed immediately.
Dec-18	Results of Phase III FINCH-3 filgotinib in RA	Second phase III study.
H1 2019	Preliminary data from monotherapy and combination therapy studies of **SRA737**	Likely to target ASCO for presentation.
1-5 Mar 2019	American Academy of Dermatology	Potential venue for competitor data presentations (eg PF-06700841 in psoriasis).
Q1 19	Potential approval of ruloxitinib in Graft vs host disease	Based on estimated PDUFA date.
Mar-19	Results of abrocitinib Phase III in atopic dermatitis (JADE Mono-1)	First Phase III study with this JAK1 inhibitor.
Apr-19	Results of Phase III FINCH-1 of filgotinib in RA	Third Phase III trial needed for registration.
April-19	Phase II data on prexasertib in ovarian cancer	Important given focus on SDRA737 on HGSOC.
31 May-4 Jun 2019	American Society of Clinical Oncology	Venue for updates on SRA737 and prexasertib.
Mid-2019	Filing of filgotinib in RA	Gilead expected to use priority voucher, approval possible in mid-2020.
Jun-19	Phase II data on prexasertib in breast and ovarian cancer.	
Aug-19	Results of abrocitinib Phase III in atopic dermatitis (JADE-Mono-2)	Second Phase III trial of JAK1 inhibitor.
9-13 Oct 2019	European Academy of Dermatology and Venerology	Possible venue for presentation of PF-06700841/abrocitinib data.
Nov-19	First Phase III results of filgotinib in Crohn's and UC.	
H2 19	Final data on mono and combo studies of **SRA737**	Will inform selection of indications for further development.
Jul 2020	Phase III data on BMS-986165 in psoriasis	Likely first registration data with TYK2 inhibitor.
2020	Phase II data on PF-06700841 in UC and Crohn's, BMS-986166 in SLE	
2020	Potential registration trial(s) of **SRA737**	
Oct 2020	Results of Phase II of Darzalex in T-ALL.	
2020	Potential IND submission for **SDC-1801**	Sareum may disclose its first indication at this time.
2021	Results of baricitinib Phase III in systemic lupus erythematosus	Potentially important new indication for this JAK1.

Source: Marten & Co

Financials

Sareum reported cash of £1.3m at its financial year end (30 June), and has just completed a £850k fundraising (estimated £790k net) which if current spending levels are maintained should provide a runway in 2020, in the absence of any milestones from Sierra. However, the company operates on a prudent basis and reviews R&D expenditures items carefully.

Historic and forecast financials, extracted from the QuotedData model, are shown in Figures 14, 15 and 16.

Figure 14: Income statement

Year ending Jun £'000	2016	2017	2018	2019e	2020e
Revenue	123	20	0	0	0
Cost of sales	(1,328)	330	(1,722)	(1,722)	(1,722)
EBITDA	(1,203)	354	(1,717)	(1,717)	(1,717)
Depreciation	(2)	(4)	(5)	(5)	(5)
Operating profit	(1,205)	350	(1,722)	(1,722)	(1,722)
Net financials	4	3	4	3	0
Profit before tax	(1,201)	353	(1,718)	(1,719)	(1,722)
Tax	0	153	47	47	47
Net income	(1,201)	505	(1,671)	(1,672)	(1,675)

Source: Marten & Co

Figure 15: Balance sheet

Year ending Jun £'000	2016	2017	2018	2019e	2020e
Cash	1,253	2,306	1,375	156	35
Receivables	79	80	138	138	138
Other	155	48	254	254	254
Total current assets	1,487	2,434	1,767	548	427
Tangible assets	1	13	8	5	4
Other	475	54	41	29	29
Total fixed assets	476	67	49	34	33
Total assets	1,963	2,501	1,816	582	460
Accounts payable	(100)	(156)	(183)	(183)	(183)
Short-term debt				(500)	(1,600)
Total current liabilities	(100)	(156)	(183)	(683)	(1,783)
Shareholder equity	1,864	2,346	1,633	(102)	(1,324)

Source: Marten & Co

Figure 16: Cash-flow statement

Year ending Jun £'000	2016	2017	2018	2019e	2020e
Operating profit	(1,205)	350	(1,722)	(1,722)	(1,722)
Depreciation	2	4	5	3	1
Change in debtors	(79)	(1)	(57)	0	0
Change in creditors	100	56	28	0	0
Other	321	281	110	0	0
Net operating cash inflow/(outflow)	(862)	690	(1,636)	(1,719)	(1,721)
Capex	0	(16)	0	0	0
Tax	184	154	43	43	43
Financial income (charge)	4	3	4	0	0
Free cash flow	(674)	831	(1,589)	(1,675)	(1,678)
Acquisition spend	(597)	0	0	0	0
Net cash flow before financing	(1,271)	831	(1,589)	(1,675)	(1,678)
Equity issues	0	0	656	791	0
Other	0	229	0	0	0
Net cash inflow/(outflow)	(1,271)	1,060	(933)	(885)	(1,678)
Other	0	(7)	3	(43)	0
Change in net debt	(1,271)	1,053	(930)	(928)	(1,678)

Source: Marten & Co

QuotedData

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