Sareum Holdings

Healthcare

4 May 2021

Treading the TYK2 trail

Kinase inhibitor specialist Sareum develops small molecule therapeutics with application in oncology and autoimmune disease areas. Lead asset SDC-1801 targets the autoimmune space and is nearing an inflection point, with a planned clinical trial application (CTA) filing in mid-2021 and clinical progression in Q421. The other candidate, SDC-1802, is focused on cancer and holds first-in-class promise with value to be unlocked with clinical validation. The out-licensed assets, SRA737 and FLT3+Aurora kinase, are currently de-prioritised but offer upside potential on revived activity.

TYK2/JAK1, a novel therapeutic approach

SDC-1801/1802 are inhibitors of tyrosine kinase 2 (TYK2) and Janus kinase 1 (JAK1) enzymes – both part of the JAK family of proteins recognised for their role in immune regulation. An oral administration targeting multiple cytokine pathways could offer theoretical advantages over the incumbent biologics and a dual kinase approach accords applicability in a broad range of potential indications, a combined multi-billion-dollar opportunity. Pending clinical validation, market/out-licensing prospects remain attractive in the absence of approved TYK2 inhibitors.

Safer than predecessors?

By virtue of their TYK2 specificity, Sareum's lead candidates aim to circumvent the toxicity overhang associated with non-selective activity of first-generation JAK inhibitors. TYK2 class leader Deucravacitinib's (Bristol Myers Squibb) Phase III success in psoriasis (PS) offers encouraging read-across but we expect Pfizer's Brepocitinib, with its similar TYK2/JAK1 selectivity to SDC-1801 to be a better benchmark with Phase II read-outs in 2021 having a strong bearing on SDC-1801's market perception.

Decision on lead indications strategic

The autoimmune space is highly competitive (dominated by big pharma) and while PS will be the likely focus for SDC-1801's Phase Ia clinical study (easiest to recruit; potential c $40bn market, albeit a very crowded one), we expect Sareum to get better mileage from prospecting other, less explored, autoimmune conditions such as lupus ($1.9bn market but less crowded) and inflammatory bowel disease (IBD - $16bn market) where its dual action may offer greater therapeutic gains.

Limited funding headroom

Despite stringent resource management, Sareum's liquidity position remains constricted (cash runway lasting till Q421 at current run-rate) with valuation potential contingent on timely raising of funds to take SDC-1801 to the clinic.

Historical financials

Year end	Revenue (£m)	PBT (£m)	EPS (p)	DPS (p)	P/E (x)	Yield (%)
06/17	0.0	0.4*	0.02	0.0	N/A	N/A
06/18	0.0	(1.5)	(0.06)	0.0	N/A	N/A
06/19	0.0	(1.5)	(0.05)	0.0	N/A	N/A
06/20	0.04	(1.0)	(0.03)	0.0	N/A	N/A

Source: Company data. Note: *PBT includes £1.8m from share of profit of associates.

Price	2.25p
Market cap	£74m

Share price graph

Share details

Code	SAR
Listing	AIM
Shares in issue	3.27bn
Net cash at 31 December 2020	£1.3m

Business description

Sareum is a UK-based drug development company, specialising in small molecule kinase inhibitors. Its flagship programmes are its pre-clinical TYK2/JAK1 inhibitors, SDC-1801 for autoimmune diseases and SDC-1802 for cancer. SDC-1801 is undergoing advanced dose finding and toxicology studies with a target to file a CTA in mid-2021. Other programmes include the CHK1 inhibitor SRA737, out licensed to Sierra Oncology (Sareum holds a 27.5% stake of the economics of the licence agreement) and the de-prioritised FLT3+Aurora kinase.

Bull

- SDC-1801's novel TYK2 selectivity may be attractive to partners, pending clinical validation.
- First-in-class opportunity for SDC-1802 in multiple cancer indications.
- Possible COVID-19 opportunity with UK funding.

Bear

- SRA737 outlook uncertain following development hold by Sierra.
- Safety profile of combined TYK2/JAK1 inhibitor not certain or proved yet.
- Potential funding challenges delaying clinical progress of SDC-1801 and SDC-1802.

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Edison profile page

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Investment summary

Company description: 'SKIL'led in kinase inhibitors

Sareum is a development stage company specialising in oral formulations of small molecule kinase inhibitors using its drug discovery platform, Sareum Kinase Inhibitor Library (SKIL). Initial focus is on cancer and autoimmune diseases, with the potential to expand to other therapeutic areas. Listed on the AIM market of the London Stock Exchange in 2004, the company employs an asset-light, 'virtual' R&D model, outsourcing most of its development activities to global contract research organisations (CROs) as well as collaborating with partners for development work in return for a stake in future revenues. Sareum's lead product candidates are its proprietary TYK2/JAK1 inhibitors, SDC-1801 for autoimmune disease and SDC-1802 for cancer, both in late-stage pre-clinical studies. SDC-1801 is ahead in terms of development (maximum tolerated dose established through two toxicology studies) with a goal of undertaking final toxicology studies and filing a CTA in mid-2021, followed by an exploratory clinical trial towards the end of the year, contingent on formalising an out-licensing partnership and/or raising funding. Progress with SDC-1801 will also ascertain when the other TYK2/JAK1 candidate, SDC-1802, targeting multiple cancers, reaches the CTA stage. Development work on the other two portfolio constituents, SRA737 (stage I/II; CHK1 inhibitor targeting the DNA damage response (DDR) network for treatment of solid tumours) and Aurora+FLT3 Kinase (pre-clinical; targeting acute myeloid leukemia (AML) and other blood cancers) are temporarily stalled due to recent out-licensing setbacks.

Financials: Clinical transition contingent on fund raising

Prudent financial management has allowed Sareum to keep a strict check on its cash utilisation although periodic equity issues have been required to support the company's development programmes (c £16.5m raised since listing). The cash balance at the end of FY20 (June 2020) stood at £1.8m (£1.3m at the end of December 2020; £0.92m at the end of FY19), supported by a £1.02m equity issue in June 2020 and a 32% reduction in net loss (£0.99m vs £1.45m in FY19). Tight reins on working capital (including a 33% salary deferment by the directors) aided the improved operating performance, although the bulk of the cost saving appears to have emanated from R&D cuts (£0.55m in FY20 from £1.04m in FY18 and £0.94m in FY19). A narrowed focus on its proprietary TYK2/JAK1 candidates is the primary reason but can potentially raise the pipeline risk for the company. At the current run-rate (£0.6m operating loss in the six months ending December 2020), we expect the existing cash balance to provide a runway until Q421, but there is a near-term need for future funding. We expect the timing and ability of securing funds (either through partnerships or capital raising) to set the pace for clinical progress of the lead programmes.

Sensitivities: Partnerships key to development pathway

While exposed to the typical biopharma risks, the biggest near-term sensitivity for Sareum would be the ability to access adequate capital to progress its lead candidates to the clinic. With licensing setbacks on SRA737 and Aurora+FLT3, reliance on external sources of funding (notwithstanding the tight cash control) or, alternatively, urgency in seeking partners for the TYK2/JAK1 programmes have risen considerably. Delays in either could hinder the company's plans for a CTA filing and subsequent start of clinical trials for SDC-1801 in 2021. Given Sareum's out-licencing strategy, collaboration risk remains a major overhang, highlighted by the recent issues with SRA737 and Aurora+FLT3. Threat of competition is another risk, given Sareum's target markets for its TYK2/JAK1 programmes (autoimmune disease and cancer), while attractive, are fairly crowded and dominated by big pharma. Although it offers the advantages of an oral formulation, the lead TYK2/JAK1 candidates would have to showcase a superior safety/efficacy profile against incumbents (both biologics and first generation JAK inhibitors) and other candidates to create a

meaningful market for Sareum's products. Excessive reliance on its co-founders (given the absence of any other directly employed personnel) is another risk to be cognisant of.

Portfolio focused on kinase inhibitors

Sareum is a UK-based specialist drug discovery and development company with focus on small molecule therapeutics (specifically kinase inhibitors) for the treatment of cancer and autoimmune diseases. The company was listed on the AIM market of the London Stock Exchange in 2004 and its operating structure has since evolved from being a hybrid development and contract R&D provider to a pure-play drug development company (contract research assets were divested in 2008). The company operates an asset-light model, outsourcing its laboratory and development activities to third-party providers and/or collaborating with partners for a share of future revenues. This has allowed Sareum to efficiently manage its cost base. Another risk-mitigation strategy it uses is to develop candidates for targets that already have some clinical validation, and then leverage the background expertise of its founders to potentially develop 'improved' molecules. Management asserts that this materially reduces the development risk although the upside potential could be somewhat truncated. The strategy is to take its products into advanced pre-clinical or early clinical stage and then license them out for further development.

The focus for Sareum is its proprietary TYK2/JAK1 inhibitors, SDC-1801 for autoimmune disease and SDC-1802 for cancer, both in late-stage preclinical trials. SDC-1801 is the more advanced of the two, with dose finding toxicology studies complete (final pivotal toxicology studies to be undertaken) with a plan to file for a CTA in mid-2021. Potential indications for SDC-1801 include PS, rheumatoid arthritis (RA), IBD, lupus and multiple sclerosis (MS). The other candidate is SDC-1802, indicated for multiple cancer types (including T-cell acute lymphoblastic leukaemia (T-ALL), B-cell lymphoma plus solid tumours). The company is working to identify an optimal oncology application for SDC-1802, to be followed by pivotal toxicology studies in late 2021, contingent on the company being able to raise adequate funds. With the approval of the US patent grant for SDC-1802 in January 2021, Sareum now has patent protection for its TYK2/JAK1 cancer programme across the United States, Europe, Japan and China.

Other portfolio candidates include SRA737, a CHK1 inhibitor targeting the DDR network for the treatment of solid tumours. Developed in collaboration with the Institute of Cancer Research and the CRT Pioneer Fund (CPF), SRA737 was subsequently out-licensed by CPF to Nasdaq-listed Sierra Oncology (headquartered in Vancouver, Canada) in 2016. Sareum remains a passive partner in the programme with a 27.5% stake in the Sierra deal's potential future out-license fees. While the CHK1 programme is the most advanced of Sareum's portfolio in terms of clinical development (completed two Phase I/II trials, as monotherapy and as adjunct to low-dose gemcitabine (LDG), with encouraging headline data, Sierra has deprioritised development work (as of June 2019) on the product to refocus its resources on its lead candidate, Momelotinib. Sierra is assessing alternate options (including sub-licensing SRA737) to support further development of SRA737. The remaining pipeline product, Aurora+FLT3 Kinase (pre-clinical; targeting AML and other blood cancers), previously deprioritised, was out-licensed to a China-based specialty pharma company in March 2020 but the agreement was terminated in January 2021 on grounds of insufficient bioavailability and formulation challenges. We expect Aurora+FLT3 to remain low priority for Sareum in the absence of further out-licensing interests.

Exhibit 1: Sareum's product portfolio and pipeline

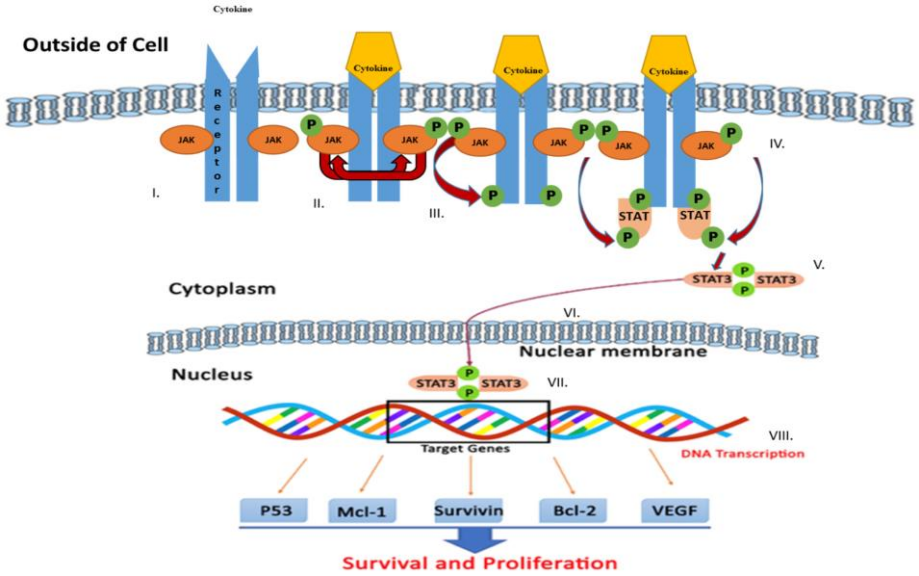
Product	Mechanism of action	Indications	Status	Comments
SDC-1801	TYK2/JAK1 inhibitor	Autoimmune diseases such as psoriasis, RA, lupus, ulcerative colitis, Crohn's disease and MS	Pre-clinical	Dose finding and longer-term toxicology studies ongoing. CTA filing planned for mid-2021.
SDC-1802	TYK2/JAK1 inhibitor	T-ALL, Anaplastic large cell lymphoma (ALCL), Kidney, colon, pancreatic and skin cancers, B-cell lymphoma	Pre-clinical	Showcased anti-tumour activity in multiple cancer disease models. Further toxicology studies planned in 2021 with an aim to file a CTA by 2022
SRA737	CHK1 inhibitor	Solid tumours, anogenital cancer, prostate cancer, squamous cell carcinomas – monotherapy/adjunctive therapy with chemotherapy or checkpoint inhibitors	Phase II	Development work currently suspended by partner Sierra Oncology. Assessing funding options (including sub-licensing) to restart studies.
SAR-20293	Aurora/FLT3 inhibitor	Acute myeloid leukaemia (AML), acute lymphoblastic leukaemia (ALL)	Pre-clinical	Licensing deal terminated by Chinese partner in 2021; development work deprioritised.

Source: Sareum company filings

TYK2/JAK1 inhibitors: Next-gen therapeutics family

TYK2 and JAK1 are two of the four isoforms of the JAK family of intracellular enzymes (the other two being JAK2 and JAK3) known for their role in facilitating downstream signalling of a number of extracellular, pro-inflammatory cytokines,[1] which lack their own enzymatic activity. The JAK family of inhibitors work by blocking this messaging pathway (aka the JAK-STAT pathway, schematic presented in Exhibit 2), in effect calming the immune system and relieving disease symptoms.

Exhibit 2: Cytokines downstream signalling using the JAK-STAT pathway



Source: Bose S et.al, Targeting the JAK/STAT Signaling Pathway Using Phytocompounds for Cancer Prevention and Therapy. *Cells*. 2020. Note: The binding of cytokines to their cell-surface receptors initiates an inflammatory signal which is transduced to the nucleus using the JAK-STAT (janus kinase signal transducer and activator of transcription) pathway. The four JAKs along with the seven STAT transcription proteins (STAT1, STAT2, STAT3, STAT4, STAT5A, STAT5B and STAT6) make up the JAK-STAT signalling pathway.

While there are only four JAKs, the number of currently identified cytokines stands at c 200, of which >50 signal via the JAK-STAT pathway (termed as type I and II cytokines). Clearly, each of the JAK isoforms can target multiple cytokines, an advantage over other targeted therapies, per initial assessment (see Exhibit 3). TYK2, for example is instrumental in mediating the downstream signalling of IL-6, IL-10, IL-12, IL-23 and type I IFNs, recognised for their role in driving autoimmunity and associated inflammation.

1 Cytokines are a broad group of signalling/communication proteins – including interleukins (ILs), interferons (IFNs), and growth factors – secreted by immune cells and are crucial for healthy immune system functioning.

Exhibit 3: JAKs and related cytokines

JAK	Related cytokines
JAK1	IL-2, IL-4, IL-6, IL-7, IL-9, IL-10, IL-11, IL-13, IL-15, IL-19, IL-20, IL-21, IL-22, IL-24, IL-26, IL-31, IFN-α, IFN0β, IFN-γ, IFN-λ, OSM, CNTF, LIF, CT1, TSLP
JAK2	IL-3, IL-5, IL-6, IL-11, IL-12, IL-13, IL-23, IL-27, IL-31, IL-35, IFNγ, GM-CSF, EPO, TPO, G-CSF, GH, PRL, Leptin, OSM, CNTF, LIF, CT1
JAK3	IL-2, IL-4, IL-7, IL-9, IL-15, IL-21
TYK2	IL-6, IL-10, IL-12, IL-19, IL-20, IL-22, IL-23, IL-24, IL-26, IL-27, IL-35, IFN-α, IFN-β, IFN-λ

Source: Various newsflow items and reports, Edison Investment Research

Finding application in the autoimmune landscape

Autoimmune diseases originate from an overactive immune system attacking healthy cells and are estimated to affect 3–5% of the world's population,[2] similar to the prevalence of cancer globally. The autoimmune disease area encompasses over 80 identified inflammatory diseases, of which the most common ones are RA, PS, psoriatic arthritis (PsA), MS, lupus and IBD. While genetics, gender, environmental factors and infections can all lead to an unregulated immune system, malfunctioning cytokines are believed to be at the core of the inflammatory response in all cases. Intuitively, therefore, therapies that regulate activity of proinflammatory cytokines, either by supplementation of anti-inflammatory, or neutralising inflammatory cytokines, have been the treatments of choice in the past two decades.

The treatment algorithm for autoimmune diseases includes anti-inflammatory drugs (NSAIDs), glucocorticoids and disease-modifying anti-rheumatic drugs (DMARDs). NSAIDs and glucocorticoids are effective in pain alleviation and inhibition of inflammation but are contraindicated for chronic use due to gastrointestinal and cardiovascular side effects. DMARDs have the capacity of reducing tissue and organ damage caused by inflammatory responses and are therefore the chosen option in advanced/progressed cases. The conventional DMARD methotrexate (MTX) has continued to be the anchor/first-line therapy (due to an acceptable toxicity profile, ease of administration and low cost) although 60–70% of patients show intolerance or inadequate response to this treatment. Conventional therapies are also hindered by their lack of selectivity (suppressing the immune system entirely rather than targeted areas, thereby increasing risk of diseases such as cancer). This issue was addressed with the approval of the first-generation targeted monoclonal antibody, J&J's anti-tumour necrosis factor (TNF) Remicade in 1998, followed by other anti-TNFs and second-generation biologics (such as IL-17, IL-12 and IL-23 blocking antibodies). Unlike traditional treatments, biologics target specific cellular pathways, promising higher selectivity, fewer side effects and an enhanced efficacy profile. The one exception here is the PDE4 inhibitor class of drugs, which have found broad application in dermatology-related inflammatory conditions. Otezla (Amgen) is a key player in this class (approved for PS, PsA and Bechet's disease) reporting revenue of $2.2bn in 2020.

JAK inhibitors are the latest novel class of targeted therapies to enter the autoimmune space, with the approval of Pfizer's pan-JAK inhibitor Xeljanz (tofacitinib) for RA in 2012. To date, four JAK inhibitors have been approved (termed first-generation and second-generation JAKs; see Exhibit 4) as either second- or third-line treatment after MTX and biologics, respectively.

2 Lifeng Wang, Fu-Sheng Wang et.al., Human autoimmune diseases: a comprehensive update. *Journal of Internal Medicine, 2015*

Exhibit 4: Approved and late-stage JAK inhibitors for autoimmune diseases

Company	Drug	Selectivity	Indications	2020 sales	Comments
First-generation					
Pfizer	Xeljanz (tofacitinib)	PAN JAK	Approved – RA (US-2012, EU-2017), PsA-2017, UC-2018, PcJIA -2020 Phase III – AS	$2,437m	Failed to meet primary endpoint (non-inferiority on cardiovascular events and malignancies) in post marketing study (Jan 2021) evaluating the safety of tofacitinib (5mg twice daily and 10mg twice daily) versus a TNF inhibitor.
Lilly	Olumiant (baricitinib)	JAK1/JAK2	Approved – RA (EU-2017, US-2018) Phase III – AD, AA, SLE Phase II – GCA	$639m	Reported positive headline data from Phase III study of baricitinib in AD in Dec 2020. Committee for Medicinal Products for Human Use (CHMP) positive recommendation for AD received in Sep 2020.
Second-generation					
AbbVie	Rinvoq (upadacitinib)	JAK1	Approved – RA (US and EU-2019), PsA (EU-2020), AS (EU-2020) Phase III – AD, UC, CD, AxSpA, GCA	$281m	Rinvoq beat market leader, Sanofi's Dupixent, in a Phase IIIb head-to-head study (data released in Dec 2020) for AD on both primary and secondary endpoints.
Galapagos	Jyseleca (filgotinib)	JAK1	Approved – RA (EU-2020, Japan-2020) Phase III – UC	N/A	Partner Gilead shelved its US marketing plans for Filgotinib after FDA rejection for RA in Aug 2020 over concerns on testicular toxicity. Deal with Galapagos scrapped.
Astellas	Smyraf (peficitinib)	PAN JAK	Approved – RA (Japan-2019, Korea-2020)	N/A	Currently being evaluated by the US FDA for RA showing inadequate response or intolerant to MTX
Pfizer	Abrocitinib	JAK1	Phase III – AD	N/A	PDUFA date pushed out by three months from the earlier indicated April 2021. Standard review ongoing in EMA. Approval possible by the end of H121.
Bristol Myers Squibb	Deucravacitinib (BMS-986165)	TYK2	Phase III – PS Phase II – PsA, UC, CD, lupus		Data from two pivotal Phase III studies in PS released in April 2021. Studies met both primary and secondary endpoints, convincingly beating both placebo and Otezla on PASI 75.

Source: Company filings and newsflow; Edison Investment Research. Note: UC, ulcerative colitis; AS, ankylosing spondylitis; AD, atopic dermatitis; CD, Crohn's disease; AA, alopecia areata; SLE, systemic lupus erythematosus; AxSpA, axial spondyloarthritis; PcJIA, polyarticular course juvenile idiopathic arthritis; GCA, giant cell arteritis.

Challenging the biologics monopoly

Since their initial approval two decades ago, biologics have revolutionised the autoimmune therapeutics landscape, cornering a major chunk of the market (90% in case of RA, including 68% held by anti-TNFs).[3] The domination of biologics in the autoimmune space can be gauged from Humira, AbbVie's anti-TNF drug, which raked in c $20bn in sales for the company in 2019 and has been the top-selling drug globally for years. In addition to anti-TNF, the other class of biologics include B-cell inhibitors (Pfizer's Rituxan), T-cell inhibitors (BMS's Orencia) and several interleukin inhibitors. Despite this, studies suggest that c 30% of patients with moderate to severe RA either fail to respond to biologic treatments or develop resistance over time.[4]

In comparison, JAK inhibitors capture only 5% of the RA market despite strong efficacy (although somewhat lower than the approved biologics) and several other potential advantages. Firstly, JAK inhibitors can block the function of multiple cytokines versus biologics, which target individual cytokines, theoretically increasing the disease coverage. They can also be administered orally as systemic drugs or in topical formulations versus the intravenous/subcutaneous administration required for biologics. Moreover, biologics, due to their nature, may trigger an immune system response leading to formation of neutralising antibodies, reducing their efficacy over time. This is unlikely to be the case with JAK inhibitors (Exhibit 5).

Exhibit 5: JAK inhibitors versus biologics characteristics

Characteristics	Biologics	JAK inhibitors
Size/molecular weight	Large (Humira 144,190 g/mol)	Small (Xeljanz 312g/mol)
Dosage frequency	Ranging from weekly or monthly	Once or twice daily
Mode of administration	Subcutaneous or intravenous	Oral or topical
Specificity/cytokine targeting	One or two cytokines	Multiple cytokines
Onset of action	Gradual (between two and four weeks)	Rapid (within one to two weeks)
Immunogenicity	Possible	Unlikely
Duration of effect	Long half-life	Short half-life

Source: Various newsflow items and reports; Edison Investment Research

3 www.prnewswire.com/news-releases/rheumatoid-arthritis-market-expected-to-increase-with-a-decent-cagr-of-approx-3-during-the-study-period-2017-30-301163029.html

4 www.hindawi.com/journals/bmri/2018/7492904/

Hindered by a questionable safety profile

Although approved JAK inhibitors have proven efficacious in their treatment areas, the uptake and outlook has been mired by questions around their safety and dose-limiting tolerability. All three of the US approved JAK inhibitors (Xeljanz, Olumiant and Rinvoq) come with a black box warning, highlighting the risk of thrombosis and malignancies. A post marketing study (January 2021) linking Xeljanz to increased risk of heart ailments and cancer versus an anti-TNF is likely to expose JAK inhibitors to even greater regulatory oversight. This has become even more apparent with the recent (April 2021) PDUFA extensions being imposed on multiple JAK inhibitors, including AbbVie's Rinvoq and Lilly's Olumiant, both in AD.

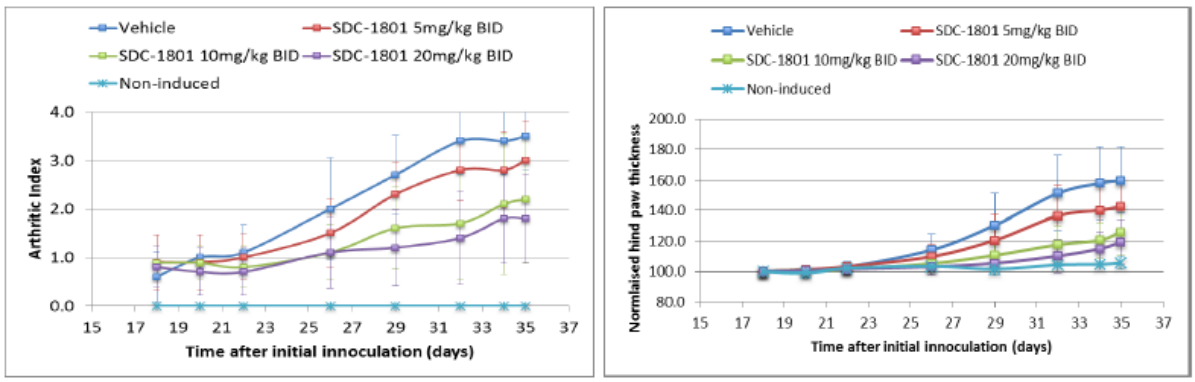
Although it is not entirely clear whether the toxicity issues stem from lack of selectivity, dosage or mode of administration, the key reason is widely believed to be the less-than-optimal isoform targeting by the first-generation JAK inhibitors,[5] resulting in broad level immunosuppression, in turn sparking higher incidence of adverse events. In particular, non-selective inhibition of the JAK2 and JAK3 proteins has been implicated in the toxicity profile of the approved inhibitors.

Learning from the experience of first-generation JAK inhibitors, second-generation compounds are being developed to showcase greater selectivity and, in theory, milder safety issues. However, the view that selective inhibition of JAK isoforms is associated with an increased clinical efficacy and/or better safety is debatable in the absence of more conclusive data. A case in point is Galapagos/Gilead's promising JAK1 inhibitor, filgotinib, which was shot down by the FDA in August 2020 on concerns over testicular toxicity associated with high doses of the drug. More recently (April 2021), the PDUFA extension of Pfizer's second-generation JAK1 inhibitor, Abrocitinib (for AD) highlights the high level of scrutiny on the safety profile of the JAK inhibitor class as a whole.

SDC-1801 – targeting autoimmune diseases

Sareum's lead product candidate, SDC-1801 is a JAK inhibitor engineered to selectively target the TYK2/JAK1 enzymes with the aim to circumvent the safety/toxicity issues related to the JAK2 and JAK3 isoforms. SDC-1801 had been initially developed in collaboration with co-development partner SRI International (undisclosed revenue sharing) and is undergoing advanced toxicology studies (following identification of the maximum tolerated dose) required to file a CTA for clinical trials. The goal is to apply for clinical trials in mid-2021, followed by a Phase Ia study towards the end of the year (either externally funded or through an out-licensing partnership). Pre-clinical data on the compound have been encouraging, based on disease models of PS and RA – good efficacy (Exhibit 6) and a strong tolerability signal (30x of the selected pre-clinical baseline dose administered without triggering a toxic reaction), with a potential for once-daily oral dosing in humans (twice-daily dosing employed in the rodent disease models).

Exhibit 6: SDC-1801 dose responsive effects on arthritic index and hind paw thickness



Source: Sareum corporate presentation, June 2020

5 https://rheumatology.medicinematters.com/rheumatoid-arthritis-/jak-inhibitors/jak-inhibitors-rheumatoid-arthritis/16934280

The TYK2 competitive landscape

While several JAK inhibitors are in development, Sareum is one of only a handful of companies active in the TYK2 space. None of the TYK2 inhibitors have made it to the market yet, although Bristol Myers Squibb (BMS) has got the head start with its selective TYK2 inhibitor Deucravacitinib (BMS-986165) in advanced Phase III studies for PS (positive data on two pivotal Phase III studies reported in April 2021). Deucravacitinib is also being assessed in mid-stage/Phase II studies for PsA, ulcerative colitis (UC), Crohn's disease (CD) and lupus. The drug holds promising prospects for BMS, convincingly beating Amgen's oral drug Otezla in two head-to-head Phase III studies for plaque PS. This accords validation to BMS/Celgene's decision to divest Otezla (sold to Amgen for $13.4m) while retaining its in-house asset Deucravacitinib to avoid anti-trust issues as part of their 2019 merger.

Another class leader is Pfizer, with two compounds under development: PF-06826647, a selective TYK2 inhibitor with ongoing Phase II studies in PS, UC and Hidradenitis suppurativa (HS) and brepocitinib (PF-06700841), a joint TYK2/JAK1 inhibitor being tested for PsA, UC, HS, lupus and vitiligo in Phase II studies. Brepocitinib is also being assessed for topical administration in mild-to-moderate PS and atopic dermatitis (AD). A list of TYK2 programmes under development is given in Exhibit 7.

Exhibit 7: TYK2 competitive landscape in autoimmune diseases

Company	Drug	Selectivity	Indications	Comments
Bristol Myers Squibb	Deucravacitinib (BMS-986165)	TYK2	Phase III – PS Phase II – PsA (Phase III in 2021), UC, CD, SLE, lupus nephritis	Showcased strong efficacy data in both Phase III studies for PS, convincingly beating both placebo and Amgen's oral drug Otzela on PASI75. Phase III studies on psoriatic arthritis to initiate in 2021.
Pfizer	PF-06826647	TYK2	Phase II – PS, HS	Phase II trial in ulcerative colitis discontinued as per pipeline report released in February 2021. Phase II study in Hidradenitis suppurativa a head-to-head study for PF-06650833, PF-06700841, and PF 06826647 against placebo.
Pfizer	Brepocitinib (PF-06700841)	TYK2/JAK1	Phase II (oral) – PsA, UC, HS, SLE, Vitiligo Phase II (topical) – PS, AD	Topical brepocitinib met both primary and secondary endpoints in a Phase IIb study (readout in January 2021) for mild to moderate AD.
Nimbus/ Celgene	NDI-031407	TYK2	Phase I – PS	BMS/Celgene holds the option to acquire Nimbus' TYK2 programme, based on a strategic agreement signed with Celgene in 2017. Plans to commence Phase II in 2021.
Galapagos	GLPG3667	TYK2	Phase I – PS	Phase Ib clinical trial in plaque PS commenced in November 2020. Based on study results, Phase II trials for psoriatic arthritis and ulcerative colitis will be initiated.
Galapagos	GLPG3121	TYK2/JAK1	Phase I	Discontinued due to an undesirable pharmacokinetic profile.

Source: Evaluate Pharma, Edison Investment Research. Note: PS, psoriasis; PsA psoriatic arthritis; UC, ulcerative colitis; AD, atopic dermatitis; SLE, systemic lupus erythematosus; HS, Hidradenitis suppurativa; PASI, Psoriasis Area and Severity Index; PASI75 denotes a 75% reduction from baseline in the PASI index.

BMS's efficacy with Deucravacitinib in PS trials (plus its showcased safety profile) has piqued the market's interest in the TYK2 assets under development. Note that none of the approved JAK contenders have found success with PS yet; Xeljanz's bid for a PS label was rejected in 2015 on grounds of inadequate safety. Moreover, in its latest released estimates, BMS pegs the non-risk-adjusted peak sales potential for Deucravacitinib at >$4bn by 2029[6] (including label expansion into other indications), indicating confidence on its treatment candidate. While BMS's data offer a compelling read-across for the other class assets under development, it is prudent to highlight that Deucravacitinib's high level of TYK2 selectivity may be attributable to its different mechanism of action,[7] allowing it to have a higher targeted selectivity for TYK2 over its other JAK counterparts (Exhibit 8).

6 BMS presentation, J.P. Morgan Healthcare Conference, January 2021

7 Allosteric approach, which allows it to bind to TYK2's non-active regulatory domain (vs the traditional ATP approach employed by Pfizer and Sareum).

Exhibit 8: Isoform selectivity (IC50) of TYK2 inhibitors versus other JAK inhibitors

Compounds	TYK2	JAK1	JAK2	JAK3
TYK2 selective inhibitors				
BMS-986165	0.2	>10,000	>10,000	>10,000
PF-06826647	17	383	74	>10,000
PF-06700841	23	17	77	6494
JAK selective inhibitors				
Xeljanz (tofacitinib)	34	3.2	4.1	1.6
Olumiant (baricitinib)	60	5.9	5.7	420
Rinvoq (upadacitinib)	4,100	45	109	2,100
Jyseleca (filgotinib)	110	10	28	810
Smyraf (peficitinib)	4.8	3.9	5.0	0.71

Source: Various newsflow items. Note: IC50 value in nM; a lower IC50 number denotes higher potency.

We expect SDC-1801 to be positioned closer to Pfizer's brepocitinib (due to its similar mechanism of action and TYK2/JAK1 selectivity) and consequently its Phase II readouts to have a stronger bearing on the market perception of Sareum's TYK2/JAK1 candidate. While market opinion is divided on the trade-off of having a super-selective TYK2 targeting versus a dual TYK2/JAK1 activity, head-to-head analysis of data released by both BMS and Pfizer from its clinical studies should provide some clarity on this aspect.

SDC-1801's market potential

Sareum's experience with kinase inhibitors along with takeaways from existing JAK inhibitors provide the company with an opportunity to address the issues plaguing this class of drugs. SDC-1801's strong toxicology profile in animal disease models to date is promising and more advanced toxicology studies should provide further validation. In terms of a lead indication, while Phase Ia trials would likely be conducted for PS (due to large market opportunity and ease of recruitment), Sareum's management has indicated that the decision on the lead indication(s) would be based on competitive positioning within each of the target disease areas. While the PS market looks attractive ($20.1bn market in 2019, expected to grow to $40.6bn by 2027, at a CAGR of 9.2%), it is also extremely competitive with >15 approved drugs, including more than 10 biologics (see Exhibit 9). Approved anti-TNF biosimilars increase the market competitiveness further.

Exhibit 9: Psoriasis competitive landscape (targeted therapies)

Drug	Company	Mechanism of action	PASI-75 score (%)	2020 sales for indication ($m)	Patent expiry
Biologics					
Stelara (ustekinumab)	Johnson & Johnson	IL-12/IL-23 antibody	67	4,816	2023
Humira (adalimumab)	AbbVie	Anti-TNF antibody	71	3,422	2023
Cosentyx (secukinumab)	Novartis	IL-17 antibody	82	2,925	2027
Skyrizi (Risankizumab)	AbbVie	IL-23 antibody	89	1,590	2031
Taltz (ixekizumab)	Eli Lilly	IL-17 antibody	89	1,456	2030
Tremfya (guselkumab)	Johnson & Johnson	IL-23 antibody	91	1,347	2031
Enbrel (etanercept)	Amgen	Anti-TNF antibody	49	671	2029
Remicade (infliximab)	Johnson & Johnson	Anti-TNF antibody	75	624	2016
Oral (small molecule)					
Otezla (apremilast)	Amgen	PDE4 inhibitor	33	1,876	2028
Deucravacitinib (BMS-986165)	Bristol Myers Squibb	TYK2 inhibitor	69	N/A	N/A

Source: Evaluate Pharma, various. Note: PASI 75 score at week 12–16 of treatment; list of companies not exhaustive.

It may make more sense for Sareum therefore to initially focus on other indications such as lupus where its TYK2/JAK1 candidates have reported encouraging observations from small disease model animal studies; this is a relatively smaller market but less crowded ($1.87bn in 2020, expected to reach $3.62bn by 2028 at a CAGR of 6.2%). IBD could be an attractive potential indication too ($15.9bn market in 2018 expected to grow at a CAGR to 4.4% to reach $22.5bn by 2026), given the role of IL-6 cytokine in its pathogenesis, which can be targeted by both TYK2 and JAK1 inhibitors.

Despite the conjecture around the efficacy versus toxicity profile of the new generation TYK2 inhibitors, market interest in the class as a whole remains high. Within the TYK2 landscape,

Sareum seems to be the only independent early-stage player as of date (both Nimbus and Galapagos are bound by acquisitive options from BMS and Gilead (ex-Europe) for their TYK2 drugs, respectively). We expect negotiations with prospective out-licensing partners for Sareum's SDC-1801 to pick up pace following culmination of the dose finding (in animal models) and advanced level toxicology studies in the next couple of months. Exhibit 10 lists some of the recent licensing deals in the space.

Exhibit 10: Selected licensing deals for JAK inhibitors in the autoimmune space

Date	Company	Partner	Asset	Clinical phase	Indication	Deal value
December 2019	Theravance	Pfizer	PAN JAK inhibitor	Preclinical	Topical treatment for mild-to-moderate skin diseases with minimal systemic exposure	Worldwide rights – $10m upfront + up to $240m milestone payment+ royalties
February 2018	Theravance	J&J	TD-1473/ Pan JAK inhibitor	Phase I	Gut selective oral drug for IBD	Ex-US rights – $100m upfront + up to $900m milestone payments + double-digit royalties; co-development in the US
October 2017	Nimbus Therapeutics	Celgene	TYK2+STING antagonist	Preclinical	Autoimmune conditions/cancer	N/D
December 2015	Galapagos	Gilead	Filgotinib/JAK1 inhibitor	Phase II	RA, CD, UC, AS, PsA, Lupus	Ex-European rights – $300m upfront+ $425m equity investment + up to $1.35bn milestone payment + royalties starting at 20% of sales; Co-promotion in European markets
September 2015	Rigel Pharmaceuticals	Aclaris	JAK inhibitor	Preclinical	AA and other dermatological conditions	Global rights – $8m upfront + up to $90m milestone payments+ tiered royalties

Source: Company newsflow; Edison Investment Research. Note: STING, stimulator of interferon genes.

The two deals involving Theravance just one year apart highlight the significant impact of clinical phase development on deal terms.

COVID-19 optionality

The pandemic has presented Sareum with an opportunity to test its TYK2/JAK1 inhibitor's immune-modulating properties in severe COVID-19 cases. Once the SARS-CoV-2 virus reaches the respiratory tract it can trigger a hyperactive immune response in some patients, leading to a cytokine storm, inflammation and pneumonia, which can eventually manifest into acute respiratory distress syndrome (ARDS; afflicting c 15% of all COVID-19 cases). COVID-19-related ARDS has mortality rates as high as 65.7–94.0% attached to it[8] and therefore presents a high unmet need for effective cytokine-targeting treatment options.

A number of pro-inflammatory cytokines implicated in COVID-19 (such as IL-6 and IFN-γ) signal via JAK-family kinases. This, along with convenient oral administration and relatively short half-lives could accord them a theoretical advantage over other therapeutics strategies in COVID-19. TYK2's role as a key causative genetic mechanism for the 'cytokine storm' in COVID-19 patients has also been highlighted in an Accelerated Article Preview by *Nature* in December 2020.[9]

Several clinical trials are ongoing, evaluating the therapeutic potential of JAK inhibitors in severe COVID-19. Some of the key ones include Pfizer's Xeljanz (tofacitinib, Phase II), CTI Pharma's pacritinib (Phase III) and Theravance's TD0903 (Phase II). Results from late-stage studies have, however, been mixed. While Lilly's JAK1 inhibitor Olumiant (baricitinib) was issued an emergency use authorisation in combination with remdesivir in November 2020, Novartis's Jakafi (ruxolitinib; JAK1) failed to show any benefits in Phase III studies. Even Olumiant has shown only limited efficacy, bringing recovery time down by just one day (from eight to seven days). This, along with the suspect safety profile of first-generation JAK's may impact their uptake in COVID-19.

Sareum's SDC-1801 promises TYK2 selectivity, while targeting the same cytokines as the other JAK family members. As per our understanding, SDC-1801 is the only compound with a TYK2

8 Gibson, Peter G et al. COVID-19 acute respiratory distress syndrome (ARDS): clinical features and differences from typical pre-COVID-19 ARDS. *The Medical journal of Australia* vol. 213,2 (2020): 54–56.e1. doi:10.5694/mja2.50674

9 Pairo-Castineira, E. et al. Genetic mechanisms of critical illness in Covid-19. *Nature,* 2020

selectivity currently vying for a COVID-19 indication. In October 2020, Sareum received a £174,000 UK Research & Innovation grant to investigate the therapeutic potential of SDC-1801 in severe COVID-19. The research project will be in-vitro and in-vivo studies of SDC-1801's effect on cells infected with the SARS-CoV-2 virus to evaluate its potential to block the immune pathway that leads to the cytokine storm. The study was initiated in December 2020 (with an additional £64,000 contribution from Sareum) and is expected to read-out by the end of H121. Sareum has reported encouraging initial results (details not disclosed) with plans to secure UK government funding from its AGILE development platform (launched in February 2021 to support novel COVID-19 treatments) to progress the treatment into clinical trials. A successful outcome will allow Sareum to expand SDC-1801's scope (although constant changes in the COVID-19 landscape make it difficult to ascribe a value to the asset) and should boost investor confidence/partnership interest for the company.

Sareum's TYK2/JAK1 programme: Oncology

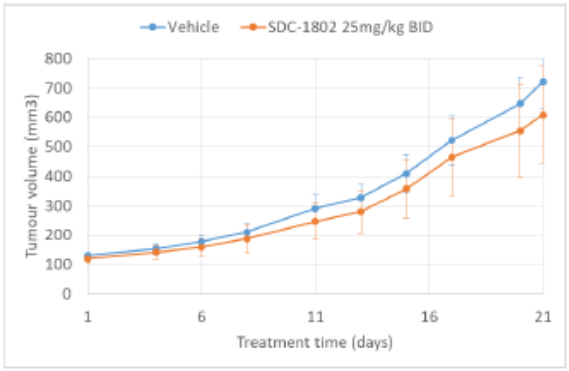
Sareum's other TYK2/JAK1 candidate SDC-1802 is being developed as a novel agent for multiple oncology indications, in both haematological (blood related) malignancies and solid tumours. The compound is lagging its autoimmune counterpart (SDC-1801) in terms of development progress, which could be due to Sareum's operational focus and funds being diverted towards SDC-1801. With limited financial headroom, SDC-1802's plans for a CTA filing and clinical progression will be contingent on the headway made with SDC-1801 as well as the company's success in raising additional funds.

Selected haematological indications being targeted by SDC-1802 include T-ALL and B-cell lymphoma, showing efficacy both in-vitro and in disease models. A 2013 study highlighted the role of the TYK2/STAT1/BCL-2 pathway in the pathogenesis of T-ALL where the inhibition of TYK2 resulted in T-ALL cell death.[10] Sareum is exploring this characteristic to develop a targeted therapy for T-ALL. T-ALL is a rare type of leukaemia, often occurring in late childhood and early adolescence and accounting for 12–15% of all newly diagnosed cases of ALL. The American Cancer Society estimates the number of newly diagnosed ALL cases in the United States will be 5,690 in 2021. This translates to 700–900 newly diagnosed cases of T-ALL in the US (we expect the European figure to be slightly higher). The current standard of care is chemotherapy followed by stem-cell transplant in cases where chemotherapy is not effective. The success rate with initial chemotherapy remains high, with 80–90% of patients achieving remission, although the cancer recurs in around half of cases. Moreover, chemotherapy does not work in 10–20% of patients (refractory cases). Treatment option for this set of patients remains limited, reflecting a high unmet need for a targeted therapy. Given the rarity of the disease, a chance of securing an orphan drug status remains high for any approved therapies.

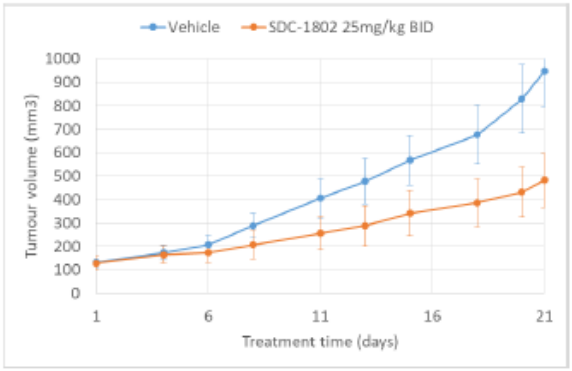
Another target area for SDC-1802 is solid cancers, where a mechanism of action via immunomodulation has been demonstrated in model studies. In a model of pancreatic cancer (Exhibit 11) SDC-1802 delivered a significant reduction in tumour growth in immunocompetent mice but had no significant effect against the same tumour type in immunocompromised mice. Markers of immunosuppression and populations of immunosuppressive cells were reduced in this model, and in models of kidney, colon and skin cancer. The action of SDC-1802 is being explored as a therapeutic option both as a monotherapy or in combination with chemotherapy or other immunotherapies.

10 Sanda T, Tyner JW, Gutierrez A, et al. TYK2-STAT1-BCL2 pathway dependence in T-cell acute lymphoblastic leukemia. *Cancer Discov*. 2013.

Exhibit 11: SDC-1802 effect in pancreatic tumours in rodent disease model



SDC-1802 has no significant effect against pancreatic tumour growth in immunodeficient mice



SDC-1802 gives significant reduction of pancreatic tumour growth in immunocompetent mice

Source: Sareum corporate presentation, June 2020

SDC-1802's TYK2 selectivity accords it a first-in-class potential for therapeutic treatment in cancer indications. Only two JAK inhibitors have been approved in oncology to date, Incyte/Novartis's Jakafi for myelofibrosis and polycythemia vera in 2011 and Celgene's Inrebic for myelofibrosis in 2019. While several other JAK inhibitors are undergoing clinical trials, none of them target T-ALL or solid tumours, as per our assessment. This creates an opportunity for Sareum but remains a risky undertaking nonetheless given several JAK inhibitors under development have terminated their studies on solid tumours either due to lack of clinical response or efficacy (including Jakafi). Exhibit 12 features the JAK inhibitors in clinical trials for oncology.

Exhibit 12: JAK inhibitors (approved and under development) for cancer indications

Company	Drug	Selectivity	Indications	Comments
Incyte/ Novartis	Jakafi (ruxolitinib)	JAK1/JAK2	Approved – MF, PV Phase III – acute GVHD, chronic GVHD Phase II – paediatric acute and chronic GVHD, MF (combination)	Stopped testing Jakafi in solid tumours in February 2016, citing lack of effectiveness. Discontinued late-stage studies on pancreatic cancer and mid-stage studies on colorectal, breast and lung cancers).
Celgene/ BMS	Inrebic (fedratinib)	JAK2	Approved – MF	Second drug approved for myelofibrosis, nearly a decade after Jakafi. Phase III trials ongoing to assess drug's efficacy on patients previously treated with ruxolitinib.
CTI BioPharma	Pacritinib	JAK2/IRAK1/SCR1 R	Phase III – MF	New drug application (NDA) filed with the FDA for myelofibrosis in September 2020. Clinical hold imposed by the FDA in 2016 on safety concerns before being released in 2017.
Sierra Oncolgy	Momelotinib	JAK1/JAK2/TBK1/ ACVR1	Phase III – MF (topline data from third Phase III study expected in H122)	Acquired by Sierra Oncology from Gilead Lifesciences in August 2018 for $198m ($3m upfront+ up to $195m in milestone payments+ tiered royalty payments (mid-teens to high twenties)).
Incyte	Itacitinib	JAK1	Phase III – MF, acute GVHD	Failed to meet primary end points in Phase III study for acute GVHD as a first line treatment in combination with corticosteroids.

Source: Newsflow, Edison Investment Research. Note: MF, myelofibrosis; PV, polycythemia vera; GVHD, graft-versus-host disease.

Toxicity remains an area of concern for JAK inhibitors in oncology too, highlighted by the discontinuation of several promising studies such as AstraZeneca's AZD1480 (neurological adverse events) and Cephalon's (acquired by Teva) lestaurtinib (gastrointestinal toxicity); both JAK inhibitors were being tested for solid tumours. While SDC-1802's TYK2 selectivity promises a potentially improved toxicology profile in the early pre-clinical setting, the data would have to be replicated in larger clinical studies to establish the safety of the compound. Sareum's interim report ending December 2020 suggests that the company will be identifying an optimal cancer indication and patient population before undertaking further toxicology studies later this year. While this seems to be a sensible approach, it is likely to push out the clinical entry of SDC-1802 well into 2022.

Sareum's out-licensed programme: SRA737

SRA737 is a highly selective CHK1 inhibitor targeting the DDR network for the treatment of solid tumours. The compound was developed by Sareum in collaboration with the Institute of Cancer Research and the CPF. It was subsequently out-licensed by CPF to Nasdaq-listed Sierra Oncology (headquartered in Vancouver, Canada) in 2016 for $328.5m (including development, regulatory and commercial milestones and royalties on sales), which was revised down to $290m in November 2020. Sareum remains a passive partner in the programme with a 27.5% stake in the economics from the Sierra deal (translating to $80m in milestone payments plus an estimated low- to mid-single-digit royalty).

Checkpoint kinases (CHK1 and CHK2) are key regulators of DNA damage (such as that caused by chemotherapy), allowing for DNA repair by temporarily pausing cell replication and division. Blocking this process, therefore, inhibits cancer cell survival. CHK1 inhibitors, consequently, find broad applicability across tumour types, particularly tumours with specific defects (such as TP53, CCNE1, BRCA1, BRCA2, MYC, RAS and ATM). Research indicates that TP53 is mutated in >50% of human malignancies, highlighting the significant scope for CHK1 inhibitor therapeutics.

Given their apparent properties CHK1 inhibitors have been explored as treatment for cancer indications for over two decades but have been unable to replicate their pre-clinical promise into larger clinical studies. While studies analysing CHK1 inhibitors as adjunct to chemotherapy have been hindered by off-target effects and toxicity issues, monotherapy trials have failed due to lack of sufficient efficacy. Development work on CHK1 inhibitors has been marred by a high failure rate and none of the candidates have reached Phase III trials. The most recent setback was the discontinuation of Eli Lilly's front-runner Prexasertib (reasons undisclosed). Given the high number of clinical and pre-clinical failures in CHK1 drug development, there is only one compound in active clinical development (Eli Lilly/Esperas Pharma's LY2880070) with a limited few in the pre-clinical stage (Exhibit 13). Targeting a subset of patients who have specific mutations (that respond to CHK1 inhibitors) has been suggested as a possible alternative and has been employed with some success in the Phase I/II clinical trials conducted for SRA737.

Exhibit 13: Selected CHK1 development programmes

Company	Drug	Phase	Comments
Clinical development			
LY2880070	Eli Lilly, Esperas Pharma	Active (Phase I/II)	Phase I/II trials ongoing in Canada as monotherapy and in combination with gemcitabine in patients with advanced or metastatic cancer.
SRA737	Sierra Oncology	Stalled (Phase I/II)	Positive read-out from studies in anogenital cancer (both monotherapy and in combination with low dose gemcitabine.
Prexasertib	Eli Lilly, Array	Abandoned (Phase II)	Discontinued development work in 2019 despite positive headline data.
LY2603618	Eli Lilly, Array	Abandoned (Phase II)	Variable PK profile, no benefit with Gemcitabine in pancreatic cancer
SCH-900776	Merck & Co.	Abandoned (Phase II)	7% response in solid tumours, cardiac dose-limiting toxicities.
RG-7602	Roche, Array	Abandoned (Phase I)	Low tolerability and enhanced bone marrow toxicity.
AZD-7762	Astrazeneca	Abandoned (Phase I)	Cardiac dose-limiting toxicities
PF-477736	Pfizer	Abandoned (Phase I)	Response in mesothelioma, lung cancer, squamous cell carcinoma.
Pre-clinical			
VER250840	Cumulus Oncology, Ligand Pharma	Pre-clinical	Out licensed to Cumulus Oncology in May 2019.
SOL578	Sentinel Oncology, PharmaEngine	Pre-clinical	PharmaEngine purchased exclusivity rights in December 2020.
V158411	Vernalis	Pre-clinical	Acquired by Ligand Pharmaceuticals in October 2018.

Source: Evaluate Pharma, Edison Investment Research

SRA737 has several properties that position it attractively among its peers, including a convenient oral route of administration and high selectivity for CHK1 (a thousand times or more selective for CHK1 compared to CHK2, CDK1 and CDK2). In comparison, the now discontinued Prexasertib showed less than 10x selectivity for CHK2 and had to be administered intravenously on a bi-weekly basis. The CHK1 programme is the most advanced of Sareum's portfolio, two Phase I/II trials have been completed on a treatment cohort with pre-selected genetic markers expected to confer higher sensitivity to CHK1 inhibitors. The two clinical programs are:

- A monotherapy study evaluating SRA737 in patients in ovarian, prostate, non-small cell lung, head and neck, and anus and colorectal cancers with specific genetic aberrations.
- A drug combination study evaluating SRA737 alongside chemotherapy drug LDG in four cancer indications, including ovarian, small cell lung, sarcoma, and cervical/anogenital.

While the two studies were read-out in December 2019 and April 2020, respectively, with encouraging results, Sierra has decided to stall further development work, given a shift in its strategic priorities towards momelotinib, a JAK1/JAK2 inhibitor for treatment of myelofibrosis. Sierra is assessing options for either in-house development or for sub-licensing but there is no clarity in terms of timelines. Given its minority ownership in the licensing deal, we expect Sareum to have limited decision-making powers on the future action plan for SRA737.

Sensitivities

Sareum's risks mirror those of a typical development-stage pharma company, including clinical development delays or failures, regulatory risks, competitive landscape and partnering issues. However, the biggest near-term sensitivity for the company remains access to adequate funding to facilitate the progression of its development programs into the clinic Sareum will have to rely on external sources of financing to pursue development work on its TYK2/JAK1 products, at least in the near term. Inability to raise adequate funds (notwithstanding its tight cost control) could hinder the company's plans for a CTA filing and subsequent start of clinical trials for SDC-1801 in 2021. Extensive R&D cuts to manage the cash runway (such as the one undertaken in FY20) would also be counterintuitive, resulting in further delay in developing the company's candidates and increasing the pipeline risk.

Fostering partnership deals and/or out-licensing opportunities will also be critical. Given its limited financial resources, Sareum will have to resort to partnerships and out-licensing agreements to further develop and commercialise its lead pre-clinical programmes. Collaboration risk remains a major overhang as well, highlighted by the recent issues with SRA737 and Aurora+FLT3. Operating a 'virtual' business model entails complete reliance on the founders for both operational and scientific decision making. Loss of any of these key personnel could jeopardise the company's future plans.

Another key risk comes from competing therapeutics. Sareum's target autoimmune market for SDC-1801, while attractive, is highly competitive and also crowded with several classes of drugs showing strong efficacy (particularly biologics, anti-TNFs and anti-interleukins as well as first-generation JAK inhibitors). Although the newer generation TYK2/JAK1 inhibitors promise advantages of an oral formulation, greater selectivity and potentially a better safety profile, it may face stiff competition from incumbents and TYK2 class leaders BMS and Pfizer. SDC-1801 would have to showcase a clear advantage over the two to create a meaningful market for its product.

Financials

An asset-light business model combined with prudent financial management has allowed Sareum to keep a strict check on its cash utilisation (annual average cash burn of £1.2m in the past three years) although periodic equity issues have been required to support the company's development programmes (c £16.5m raised since listing). The cash balance at the end of FY20 stood at £1.8m (£1.3m at the end of half-year ending December 2020; £0.92m at the end of FY19), supported by a £1.02m equity issue in June 2020 and a 32% reduction in net loss (£0.99m in FY20 versus £1.45m in FY19). Tight reins on working capital (including a 33% salary deferment by the directors) aided the operating performance although the bulk of the cost saving appears to have emanated from R&D cuts (£0.55m in FY20 from £1.04m in FY18 and £0.94 in FY19). A narrowed focus on its

proprietary TYK2/JAK1 candidates is the primary explanation but can potentially raise the pipeline risk for the company. Net loss for the half-year ending December 2020 stood at £0.55m, slightly lower than the half-year ending December 2019 figure of £0.61m. At the current run-rate, we estimate the existing cash balance to provide a runway until Q421, but we also anticipate the near-term need for further financing to support clinical progression of its lead candidate. The timing and ability of securing funds (either through partnerships or capital raising) should set the pace for clinical progress of the lead programmes.

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