EDISON

Viralytics

Initiation of coverage

Cancer immunotherapy goes viral

Pharma & biotech

Viralytics' investment case centres on the successful development and commercialisation of lead product Cavatak, for advanced melanoma. Solid initial efficacy data from the Phase II CALM study bode well for the trial meeting its primary end point in H114. A positive final CALM readout could potentially attract an out-licensing deal. We value Viralytics at A$61m or A$0.69/share (undiluted), based on peak sales of A$646m in 2024.

Year end	Revenue (A$m)	PBT* (A$m)	EPS* (c)	DPS (c)	P/E (x)	Yield (%)
06/11	1.4	(2.1)	(3.7)	0.0	N/A	N/A
06/12	0.9	(4.3)	(6.4)	0.0	N/A	N/A
06/13e	1.5	(4.0)	(4.9)	0.0	N/A	N/A
06/14e	1.6	(4.9)	(6.0)	0.0	N/A	N/A

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

Novel oncolytic virus targeting melanoma

Lead product Cavatak is a proprietary formulation of Coxsackievirus A21 (CAV21), a common cold-producing virus that selectively binds to ICAM-1, a cell adhesion molecule on the surface of many cancer cell types. It targets local (primary) and distant (metastatic) tumour cells, by infecting and destroying them (direct cytolysis) and activating a tumour-specific immune response (adaptive response).

Encouraging interim Phase II efficacy data…

The US Phase II CALM study of intratumoural Cavatak in late-stage melanoma needs to deliver at least 10 patients with immune-related progression free survival (irPFS), a measure that recognises the inherent lag in response of immunotherapy treatments from 54 evaluable patients to achieve its primary end point. Notably, eight of 23 evaluable patients at the interim look have already achieved irPFS at six months, which augurs well for the final study readout in H114.

…and favourable safety profile

Intratumoural (direct injection) and intravenous (systemic) formulations of Cavatak have shown good safety and tolerability across five Phase I studies. Moreover, interim CALM data suggest multi-dose intratumoural therapy with Cavatak is well tolerated, with relatively mild adverse events (grade 1 or 2) and no serious AEs.

Financed to data readout

Viralytics has net cash of A$5.1m (at end-June 2013), which provides a cash runway into mid-2014. This should allow completion of the Phase II CALM trial and commencement of a Phase I/II (STORM) study of intravenous Cavatak in the UK.

Valuation: A$0.69/share (undiluted)

We value Viralytics at A$61m, or A$0.69/share (undiluted), using a risk-adjusted net present value method in only the lead indication of metastatic melanoma, and end-June 2014 net cash of c A$150k.

12 August 2013

Price	**A$0.30**
Market cap	**A$26m**

Net cash (A$m) as At end-June 2013	5.1
Shares in issue	87.2m
Free float	100%
Code	VLA
Primary exchange	ASX
Secondary exchange (*ADR = 3 ordinary shares)	OTCQX*

Share price performance

%	1m	3m	12m
Abs	(8.3)	(5.2)	(3.5)
Rel (local)	(4.2)	(2.4)	(20.4)
52-week high/low	A$0.46		A$0.23

Business description

Viralytics is an ASX listed biopharmaceutical developing virus applications using a common cold producing virus to target late stage melanoma. The Phase II CALM trial is evaluating intratumoural administration of lead candidate Cavatak in patients with metastatic melanoma.

Next events

Start STORM trial	H213
Fiscal 2013 results	H213
CALM trial full-enrolment	H213

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Edison profile page

Investment summary: Targeting metastatic melanoma

Company description: Oncolytic virotherapy developer

Viralytics is focused on developing oncolytic virotherapy to treat a range of cancers. Lead candidate, Cavatak, is a proprietary formulation of a common cold producing virus Coxsackievirus A21 in clinical development for metastatic melanoma and a range of other solid tumours. An ongoing US Phase II study (CALM) is evaluating intratumoural injection of Cavatak in late-stage melanoma, with final data anticipated in H114. A planned UK Phase I/II study (STORM) of intravenous (IV) Cavatak in advanced solid tumours (melanoma, prostate, lung, bladder) is expected to start in H213. Preliminary results from STORM are possible in H214. Since 2009 Viralytics has raised c A$16m via secondary offerings, rights issues and a US$6m convertible note facility issued in June 2009, fully drawn down and converted to equity by November 2011.

Valuation: A$0.69/share (undiluted)

We value Viralytics at A$61m, or A$0.69/share (undiluted), using a risk-adjusted net present value method to discount future cash flows through to 2032 in metastatic melanoma only. Our approach assumes a partnering deal or out-licensing of Cavatak post-release of the final Phase II data in 2014, with all costs of subsequent clinical development borne by the partner/licensee. Of note, our model does not include upfront payments or milestones from a potential licensing deal. Product launch is assumed in 2020 with peak market share of 20% in 2024, before tapering off for the remaining term of market exclusivity under the Biologic Licence Approval of 12 years. A 30% probability of success has been applied to reflect Cavatak's phase of clinical development with projected cash flows discounted at 12.5%. There is additional upside to our base case valuation since Cavatak could be developed for a range of cancers other than melanoma, given positive preclinical data and the prospect of new indications identified in the upcoming STORM trial.

Sensitivities: CALM trial outcome the key

Viralytics is subject to typical biotech company development risks, including the unpredictable outcome of trials, regulatory decisions, success of competitors, financing and commercial risks. In particular, it has a very high single-product risk, with the entirety of its value residing in Cavatak. The investment case hinges on the outcome of the CALM study and, assuming data are positive, the company's ability to secure a partnership (or further capital) to advance Cavatak into late-stage trials. Ideally, a partner would have an established oncology franchise with the resources and experience to evaluate Cavatak in multiple cancer indications. Another key sensitivity is the rapidly evolving treatment landscape for melanoma, which means that future trials of Cavatak will likely be in combination with targeted agents and/or immunotherapies – selection of the appropriate therapy to combine with Cavatak could be critical to future clinical and commercial success.

Financials: Cash runway to mid-2014

Viralytics reported cash of A$5.1m at end of June 2013. Deferred tax credits under the Australian R&D tax incentive scheme provide a 45% cash rebate in the following fiscal year and are recognised as revenue. Cash burn is expected to remain c A$1.2m per quarter for FY14 given operating cash outflows in Q413 of A$1.2m, which included R&D expense of A$0.8m, with a cash runway extending to mid-2014 and that coincides with the expected CALM study readout. If a partner or licensee is not secured for Cavatak, Viralytics intends to conduct a further Phase II trial, which could require additional capital of between A$10m and A$20m. However, given the positive signs of efficacy to date and the potential of a significant readout, the prospects for attracting a big pharma partner appear promising.

Outlook: CALM trial readout ahead

Viralytics' investment case centres on the successful development and commercialisation of its lead product Cavatak to treat advanced melanoma and potentially other solid cancers. Solid initial efficacy data from the Phase II CALM study for intratumoural Cavatak in melanoma bode well for the trial meeting its primary end point in H114. A positive final readout from the Phase II CALM trial could be a catalyst for a rerating of the stock and potentially trigger a partnering or out-licensing deal. With net cash of A$5.1m as at end-June 2013, Viralytics has sufficient cash to fund clinical programmes through to mid-2014.

Exhibit 1: Active clinical trials

Product	Mode of administration	Indication	Stage	Development notes
CAVATAK	Intratumoural	Melanoma	Phase II	Phase II CALM study in malignant melanoma (n=63, results due in Q114).
				Phase II CALM extension study to 48 weeks.
	Intravenous	Melanoma, prostate, lung	Phase II	Phase I/II STORM trial planned in in H213 in two stages.

Source: Edison Investment Research

Oncolytic viruses – approaching prime time

Dual mechanism of anti-cancer activity

Oncolytic virotherapy is an emerging class of anti-cancer therapy that harnesses viruses to eradicate tumour cells while sparing their normal counterparts. Oncolytic viruses exert anti-cancer effects against both local (primary) and distant (metastatic) tumour cells, by preferentially infecting and destroying cancer cells (direct cytolysis) while simultaneously activating a tumour-specific immune response (adaptive response). The idea that viruses can be harnessed as anti-cancer agents is not new, but only recently have clinical data emerged to support oncolytic virotherapy as a valid treatment alternative. Recent positive mid- to late-stage clinical data (including Viralytics' Cavatak) suggest that oncolytic virotherapy may soon become a commercial reality (Exhibit 4). Oncolytic viruses could offer a broad yet targeted anti-cancer activity that address the limitations of current treatment or, more likely, provide additive efficacy when combined with existing agents. Traditional chemotherapy is an effective first-line treatment for various cancers, but has cytotoxic effects on normal cells that can cause significant side effects. The introduction of targeted anti-cancer drugs (ie Roche's Zelboraf) has considerably improved survival in certain cancers, but its therapeutic benefits are limited by its specificity. The latter includes use in specific patient subgroups due to restricted expression of the drug target (eg mutated protein), and potential development of resistance as cancer cells adapt to selective pressures. The recently introduced cancer immunotherapies (BMS's Yervoy) are effective, but not for all patients, and have unique and sometimes serious side effects.

TVEC Phase III data – potentially first-in-class in the US market

Recent positive Phase III data for Amgen's TVEC (talimogene laherparepvec) in metastatic melanoma represents a landmark for the field of oncolytic virus therapy. TVEC comprises a herpes virus (HSV1) backbone containing the gene for GM-CSF, a potent immune stimulator. A positive readout from a single, open-label Phase II study in 50 late-stage melanoma patients triggered Amgen's acquisition of Biovex, TVEC's developer, in 2011, in a deal valued at up to US$1bn (US$425m upfront, US$575m potential milestones). Presented at ASCO 2013, preliminary Phase III results for TVEC in Stage III-IV melanoma showed a significant increase in durable response rate (DRR) vs GM-CSF alone (the primary end point) and interim data pointing to an overall survival (OS) benefit. Final OS data are expected in H114 that could, if still positive, trigger regulatory filings, which would represent a significant catalyst for the entire category.

Viralytics datasheet

Exhibit 2: R&D programmes (active and pending)

Product	Mode of administration	Indication	Stage	Development notes
CAVATAK	Intratumoural	Melanoma	Phase II	Phase II CALM study in malignant melanoma (n=63, results due H114). Monotherapy. Phase II CALM extension study with dosing up to 48 weeks in total.
	Intravenous	Mel, breast, lung, prostate	Phase II	Phase I/II STORM trial planned in H213 in two stages (test indication, Chemo-combo).
	Intratumoural	Head and neck	Phase I	On hold. Phase I head and neck cancer complete.
	Intratumoural	Prostate	Preclinical	On hold. Oncolytic activity in xenograft tumour models in mice.
	Intratumoural	Glioma	Preclinical	On hold. Oncolytic activity in athymic mice bearing malignant glioma tumours.
	Intravenous	Pancreatic	Preclinical	On hold. Oncolytic activity in xenograft tumour models in mice.
	Intravenous	Multiple myeloma	Preclinical	On hold. Promising data from study in multiple myeloma (MM) cell lines.
		Bladder	Discovery	On hold. Signs of synergy of CVA21 and radio/chemotherapy in bladder cell lines.
		Mesothelioma	Discovery	On hold. ICAM-1 over-expressed by cultured cells of all mesothelioma cell lines.
EVATAK		Ovarian	Preclinical	On hold. Therapeutic dose-response demonstrated in SCID mouse model.
		Prostate	Preclinical	On hold. Therapeutic dose-response demonstrated in SCID mouse model.
		Gastric	Preclinical	On hold. Therapeutic dose-response demonstrated in SCID mouse model.

Source: Edison Investment Research. Note: SCID = Severe combined immunodeficiency.

Exhibit 3: Approved treatment for malignant melanoma

Product	Company	Mechanism of action	Notes
Zelboraf (vemurafenib)	Roche	BRAF inhibitor	FDA (2011)/EU (2012) approved for unresectable or metastatic melanoma in patients with the BRAF V600E mutation.
Yervoy (ipilimumab)	BMS	T-cell mediated immune response	FDA (2011)/EU (2011) approved for unresectable or metastatic melanoma.
Tafinlar (dabrafenib)	GSK	BRAF inhibitor	FDA approved (May 2013) for unresectable melanoma or metastatic melanoma in adult patients with BRAF V600E mutation.
Mekinist (trametinib)	GSK	MEK inhibitor	FDA approved (May 2013) for unresectable or metastatic melanoma in adult patients with BRAF V600E or V600K mutation.

Source: Edison Investment Research

Exhibit 4: Competing development programmes for malignant melanoma

Product	Company	Mechanism	Development stage/notes
TVEC (talimogene laherparepvec/ OncoVEXGM-CSF)	Amgen	Oncolytic virus	439-pt Phase III trial comparing intratumoural TVEC to subcutaneous GM-CSF in previously treated unresectable Stage IIIb/c and IV melanoma. Results: met primary end point of durable response rate (DRR: rate CR or PR lasting continuously for ≥6 months). Statistically significant difference in DRR: 16% in the TVEC arm vs 2% in the GM-CSF arm. OS analysis, a secondary end point, is event driven; interim analysis showed an OS trend in favour of TVEC as compared to GM-CSF. The OS data is expected to mature in H114.
Ipilimumab	BMS	Immunotherapy	950-pt Phase III trial vs placebo after complete resection of high-risk Stage III melanoma. Results: Q213.
			700-pt Phase III trial of ipilimumab at 3mg/kg vs 10mg/kg in metastatic melanoma. Results: Q415.
Nivolumab /ipilimubab	BMS	Immunotherapy	915-pt Phase III trial of nivolumab vs nivolumab + ipilimumab vs ipilimumab in previously untreated unresectable or metastatic melanoma. Results: Q416.
Nivolumab	BMS	Immunotherapy	410-pt Phase III trial of nivolumab vs dacarbazine in previously untreated, unresectable or metastatic melanoma. Results: Q415.
			390-pt Phase III trial of nivolumab vs dacarbazine, carboplatin or paclitaxel in advanced melanoma progressing post anti-CTLA-4 therapy. Results: Q215.
Vemurafenib	Roche	BRAF inhibitor	3,300-pt Phase III trial in surgically resected, BRAF mutant metastatic melanoma. Results: Q215.
			725-pt Phase III trial in resected, BRAF mutant melanoma at high risk for recurrence. Results: Q316.
Vemurafenib/ GDC-0973	Roche	BRAF/MEK inhibitor	500-pt Phase III trial of vemurafenib ± GDC-0973 in untreated BRAF mutant unresectable advanced or metastatic melanoma. Results: Q316.
Dabrafenib	GSK	BRAF inhibitor	200-pt Phase III trial of dabrafenib vs dacarbazine (DTIC) in previously untreated BRAF mutant advanced (Stage III) or metastatic (Stage IV) melanoma. Results: Q313.
Dabrafenib/ trametinib	GSK	BRAF/MEK inhibitor	694-pt Phase III trial of dabrafenib + trametinib to vemurafenib in BRAF mutant unresectable (Stage IIIc) or metastatic (Stage IV) melanoma. Results: Q214.
			340-pt Phase III trial of dabrafenib + trametinib vs dabrafenib first-line in BRAF mutant unresectable (Stage IIIc) or metastatic (Stage IV) melanoma. Results: Q213.
MEK162	Novartis	MEK inhibitor	393-pt Phase III trial of MEK162 vs dacarbazine in KRAS mutant advanced unresectable or metastatic melanoma. Results: Q414.
LGX818	Novartis	BRAF inhibitor	900-pt Phase III trial of LGX818 ± MEK162 vs vemurafenib in BRAF mutant melanoma. Results: Q217.
Lambrolizumab	Merck	Anti PD-1	510-pt Phase II trial of lambrolizumab vs chemotherapy (carboplatin + paclixatel, paclitaxel alone, decarbazine or temozolomide) in advanced melanoma after previous therapy.

Source: Edison Investment Research

Cavatak – CALM before STORM

New role for a common cold-producing virus

Cavatak is a proprietary formulation of the Coxsackievirus A21 (CVA21), a wild-type (genetically unaltered) common cold-producing enterovirus, which is in Phase II development for advanced melanoma and, shortly, a range of other cancers. The ongoing CALM (Cavatak in Late stage Melanoma) Phase II study is evaluating efficacy and safety of intratumoural Cavatak in late-stage malignant melanoma. The planned STORM (Systemic Treatment Of Resistant Malignancies) Phase I/II trial, which should commence in H213, will evaluate the safety and efficacy of intravenous Cavatak in patients with a range of cancers (melanoma, prostate, lung) when administered alone and in combination with chemotherapy, mostly docetaxel.

Beyond Cavatak, Viralytics is investigating three other Group A Coxsackieviruses: A13 (CVA13), A15 (CVA15), A18 (CVA18) and one ECHOvirus 1 (EVATAK). These programmes are all in preclinical stage and currently on hold.

Identification of anti-cancer activity – ICAM-1 target on cancer cells

Cavatak is a proprietary formulation of the unmodified Coxsackievirus A21 (Kuykendall strain), or CVA21, a naturally-occurring non-enveloped (naked) RNA human enterovirus C genus of the family Picornaviridae that is often associated with mild upper respiratory tract infections in humans. CVA21 was one of several viruses identified by Professor Darren Shafren, Viralytics' chief scientific officer, as having oncolytic activity against *in vitro* cultures of cancer cells and *in vivo* xenografts of human cancers in mouse models of melanoma, multiple myeloma, prostate and breast cancer, all of which exhibit high surface expression of the receptor intercellular adhesion molecule-1 (ICAM-1). Immunohistochemical tissue studies suggest CVA21 preferentially infects cells with high surface levels of the intercellular adhesion molecule-1 (ICAM-1), a process enhanced by Decay-accelerating factor (DAF). As noted above, numerous different types of cancers express high levels of ICAM-1 and, therefore, represent target indications for Cavatak.

The basic IP covering Cavatak originates from the University of Newcastle, Australia, where Professor Darren Shafren conducted research in the late 1990s into how cross-linked DAF and ICAM-1 facilitate cellular attachment and internalisation of human picornaviruses.

Favourable profile of Cavatak

Cavatak's appeal as an anti-cancer agent is based on its safety profile, potentially high therapeutic index at low viral doses, the lack of requirement for genetic modification, and the relatively low prevalence of 'background' neutralising antibodies in the general population. Cavatak is highly stable in neutral and acid environments, which allows simple preparation from highly purified culture in mammalian cells according to established live viral vaccine protocols and the development of formulations for multiple routes of administration (intratumoural, intravenous and intraperitoneal).

Preclinical data – positive findings in multiple cancers

Intratumoural, intraperitoneal or intravenous administered CVA21 was found equally effective in reducing volumes in xenografts of malignant melanoma in immunodeficient (SCID) mice supporting a role against malignant melanoma and the choice of lead indication. Oncolytic activity has also been reported in preclinical studies of CVA21 in cell lines of head/neck, pancreatic, breast, lymphoma, primary brain cancer (GBM), lung cancer, multiple myeloma and bladder cancer. Recent positive preclinical data suggesting synergy between CVA21 in combination with radiotherapy and chemotherapy in bladder cancer cell lines presented at a leading oncolytic virus meeting in Canada[1] raises the prospect for this indication to advance into animal models.

[1] The Seventh International Meeting on Replicating Oncolytic Virus Therapeutics, 15-18 June 2013.

Phase I data – safe, tolerated and hints of anti-tumour activity

Viralytics has already conducted five open-label Phase I studies in various late-stage cancer indications (Exhibit 5) with the results incorporated in the IND application for the current Phase II trials. Four studies evaluated intratumoural injections (single- and multiple-dose), while one assessed single intravenous dosing as monotherapy in a total of 28 patients that had progressed on prior therapy. The primary end point of each study was to establish safety and tolerability, while secondary objectives included direct measures of tumour response, indirect measures of efficacy using biomarkers and tumour biopsies, and characterisation of anti-CVA21 antibody response.

Exhibit 5: Cavatak - Phase I trials in advanced cancer

Administration	Frequency	Indication	Disease stage	Patients
Intratumoural	Single dose	Melanoma	Stage IV	2
Intratumoural	Single dose	Melanoma	Stage IV	3
Intratumoural	Multi-dose escalation*	Melanoma	Stage IV	9
Intravenous	Single dose	Melanoma, colorectal, breast, prostate	Stage IV	10
Intratumoural	Multi-dose	Head and neck	Stage IV	4
			Total	**28**

Source: Viralytics. Note: *Two doses of CAVATAK separated by 48 hours.

Exhibit 6 outlines the key efficacy findings, which included c 36% of injected tumour patients demonstrating tumour shrinkage and c 21% showing disease stabilisation. No clinically significant safety or tolerability issues were reported. Two patients also showed overall disease stabilisation.

Exhibit 6: Cavatak- Phase I results

Injected tumour response	Single intratumoural injection (n=5)	Multiple intratumoural Cavatak injections (n=9)*	% patients
Reduction	2	3	35.7
Stable	1	2	21.4
Progressive	2	4	42.9
Reduction and stable			57.1

Source: Viralytics. Note: *Two doses.

CALM – US Phase II trial in advanced melanoma

The ongoing US, single-arm, open-label, multi-centre Phase II CALM study is evaluating intratumoural (IT) injections of Cavatak, administered as monotherapy over 18 weeks, in up to 63 patients with advanced melanoma (Exhibit 7). In a two-stage study design, up to 35 evaluable patients were treated in the first stage. Provided three or more patients showed objective responses (interim futility clause), the study could proceed to the second stage, with up to 63 patients being enrolled. The trial passed the futility milestone in December 2012 and recently delivered promising interim efficacy data from the first 35 patients. To date, CALM has enrolled 38 subjects with stage IIIc (26%) or IV (74%) disease that have failed previous therapy (average of three treatments), but have no active brain, bone or widespread visceral metastases. With the study adding around four new patients per month, we expect the enrolment target of 54 evaluable patients required will be reached by December 2013. Final data are expected in H114.

The primary end point of CALM is stable disease (or better) at six months after the first dose of Cavatak, as measured by irPFS; this includes patients with a complete response (CR), partial response (PR) or stable disease. The choice of irPFS at six months as the primary end point was based on prognostic benchmarks developed in a meta-analysis of 42 Phase II trials in metastatic melanoma[2] and recognises the lag in therapeutic response inherent in immunotherapy treatments. Tumour assessments are conducted in accordance with Response Evaluation Criteria in Solid Tumors criteria (RECIST 1.1). To meet its primary end point, the study has to deliver at least 10 patients with irPFS at six months from 54 evaluable patients. Secondary end points include DRR at six months, one-year survival, OS, disease control rate, safety and tolerability.

[2] Korn *et al*; J Clin Oncol 26: 527-534 (ASCO 2008)

The CALM study includes an open-label extension, which allows enrolled patients achieving the primary end point of irPFS (partial, stable, complete) at six months after the first dose for a further nine doses over six months (48 weeks in total).

Encouraging interim efficacy data – closing in on primary end point

Interim results from the first 35 patients were presented at the World Congress of Melanoma, which revealed that CALM is close to achieving its primary end point (Exhibit 8). Encouragingly, eight of 23 evaluable patients (35%) at the interim look have achieved six-month irPFS, only two short of the target of 10. Moreover, 18 of 30 (60%) assessable patients have achieved three-month irPFS, with seven of these patients currently between the three and six month assessment time point – this points to CALM meeting its primary end point well before target enrolment is completed.

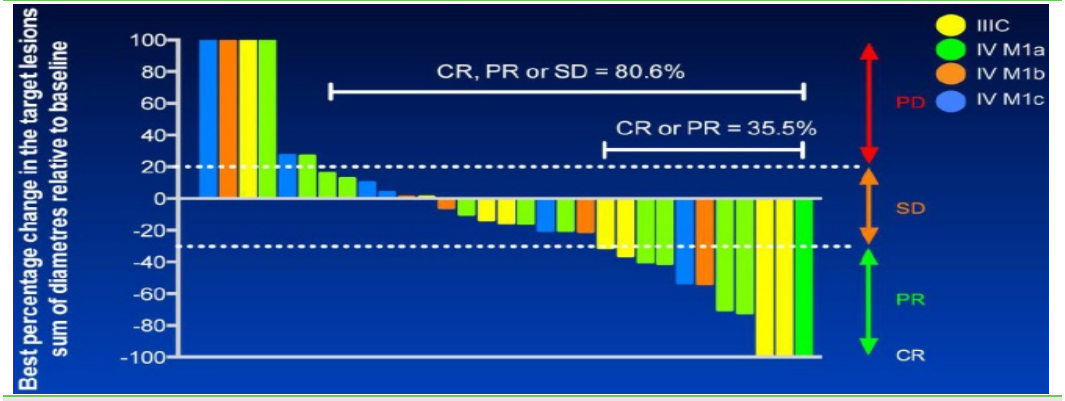
Exhibit 7: Phase II CALM study – interim efficacy data

Efficacy end point	Patient number (%)	Comment
irPFS six months	8/23 (35%)	Primary end point is at least 10 patients with six-month irPFS from 54 evaluable patients. This irPFS analysis excludes 15 patients (out of 38) currently being treated but not on study long enough for six-month evaluation.
irPFS three months	18/30 (60%)	Analysis excludes eight patients (out of 38) currently being treated but not on study long enough for three-month evaluation.
Complete response (CR)	2/30 (1%)	Response analysis (CR, PR, OR) excludes eight patients (out of 38) currently being treated but not on study long enough for six-week tumour response assessment.
Partial response (PR)	6/30 (7%)	
Overall response (OR)	8/30 (27%)	Interim futility end point of at least three CR or PR achieved in first 35 patients. Ongoing overall response continually assessed beyond 12 weeks up to 48 weeks.

Source: Viralytics

Six of the eight patients that met the primary irPFS end point achieved a PR with two showing a CR (Exhibit 8). The ongoing OR is c 27% (eight of 30 patients). Consistent with Cavatak's MOA, tumour responses were observed in both injected and distant non-injected lesions.

Exhibit 8: CALM Phase II trial – current analysis of % change in target lesions



Source: Viralytics, Hunstman Cancer Institute

To date, five patients have entered the extension study, with two reaching the 12-month timepoint and both achieving a partial response. Further surgery to resect the residual injected tumour resulted in a surgical complete response in both patients.

Despite the inherent limitations of cross-trial comparisons, we note previous primary end point data for approved and key Phase III drugs in malignant melanoma (Exhibit 9). Notably, Cavatak has reported promising initial efficacy data, in an albeit small cohort of patients compared to Yervoy, TVEC and Reolysin on both PR (%) and CR (%) measures (revised RECIST 1.1).

Cavatak is well tolerated, with no reports of adverse drug-related side effects (grades 3 or 4) reported and a comparatively low incidence of low grade drug-related side effects (1 or 2).

Exhibit 9: Key efficacy results for approved and key Phase III drugs in malignant melanoma

Product	Treatment	Study	No (n)	PR (%)	CR (%)	Median OS (m)	Median PFS (m)	BORR (%)	Notes
CAVATAK*	Mono	Phase II	23	20	7	N/A	N/A	N/A	Interim results
TVEC (OncoVEX)***	Mono	Phase III	295	16	11	23	8.2	26 (ORR)	ASCO 2013
Reolysin (Reovirus)**	Combo	Phase II	43	21	0	N/A	N/A	21 (ORR)	Stage one complete
Zelboraf (vemurafenib)	Mono	Phase III	675	47	6	77	5.3	52	FDA access data
Yervoy (ipilimumab)	Combo+	Phase III	502	14	2	64	2.1	15	Weber et al 2009
Tafinlar (dabrafenib)	Mono	Phase III	250	48	3	18 (OIRR)	5.1	52 (ORR)	FDA access data
Mekinist (trametinib)	Mono	Phase III	322	25	2	16 (OIRR)	4.8	NR	FDA access data

Source: Edison Investment Research Note: BORR = best objective response rate) using RECIST Version 1.1 criteria for metastatic melanoma. OS = overall survival, PFS = progression-free survival, PR = partial response, CP = complete response. *Interim results (World Congress of Melanoma presentation 18 July 2013: R. Andtbacka). **At six months. ***At 12 months.

STORM – intravenous Cavatak Phase I/II planned

A UK, two-stage Phase I/II intravenous Cavatak study in approximately 30 late-stage melanoma, prostate, lung and metastatic bladder cancer patients is planned to start in H213; the STORM (Systemic Treatment Of Resistant Malignancies) trial is subject to UK regulatory approval of clinical protocols. Stage one, the 'signal seeking' Phase I part, will evaluate the impact of intravenous administration of Cavatak in a range of cancers including melanoma, prostate, lung and metastatic bladder, to identify the most responsive cancer type for Stage two. Stage two (Phase II) will then focus on the 'preferred' cancer identified in Stage one and investigate multiple intravenous dosing of Cavatak in combination with or without standard chemotherapy, most likely docetaxel. We expect STORM to render initial data in 2014. Advancement into Phase II is supported by Phase I data (Exhibit 5), which showed good tolerability and initial efficacy (two patients with stable disease) following IV Cavatak in 10 patients with advanced solid tumours.

Metastatic melanoma – rapidly evolving treatment landscape

Malignant melanoma has an incidence of around 0.02% and c77,000 Americans are diagnosed each year with an estimated 9,500 deaths. Surgical resection is often curative in early, limited-stage disease but no effective treatment exists for metastatic melanoma. Until recently, the standard agents for metastatic melanoma were limited to dacarbazine (DTIC) and interleukin-2 (IL-2) and neither of these agents led to a significant prolongation in survival; with median OS at 8.5 months and the probability of surviving five years from diagnosis less than 5%. Various therapeutic strategies including immunotherapies, tyrosine kinase inhibitors, angiogenesis inhibitors and vaccines have been pursued in metastatic melanoma without success. The challenging nature of development in this indication has once again been highlighted by the failure of a Phase III study with Vical's DNA-based immunotheraptic Allovectin. However, oncologists are currently excited by four newly approved therapies: the anti-CTLA-4 antibody ipilimumab, the BRAF inhibitors, vemurafenib and dabrafenib, and the MEK inhibitor, trametinib.

Emergence of targeted agents and immunotherapy

Yervoy (ipilimumab), which was launched in 2011, is a monoclonal antibody that blocks CTLA-4. It was the first new agent to be approved by the FDA for the treatment of advanced melanoma in over a decade. Results of three follow-up studies showed a five-year survival rate of between 12% to 28% in previously treated patients and 38% to 50% in treatment-naïve patients. This compares with a historical five-year survival rate of about 15% in patients with distant metastasis. Yervoy's approval has expanded the available treatment options and boosted OS rates despite its relatively modest efficacy and concerns over severe immune-mediated adverse events. Two Phase III trials are currently evaluating the benefit of ipilimumab as an adjuvant therapy for Stage III melanoma. Subsequent FDA approvals of targeted therapy agents Zelboraf (vemurafenib) and Tafinlar (dabrafenib), and Mekinist (trametinib) for BRAF-mutant melanoma, address specific sub-

populations of affected patients (BRAF mutant melanomas). GSK recently filed a New Drug Application (NDA) to the FDA for use of dabrafenibin combined with trametinib.

Oncolytic virotherapy – TVEC and Reolysin

The most advanced immunotherapy product in late-stage clinical development is Amgen's TVEC, the first oncolytic virotherapy to show therapeutic benefit against melanoma in a Phase III trial. TVEC is an oncolytic herpes virus that encodes granulocyte macrophage-colony-stimulating factor (GM-CSF) and is administered intratumourally. Final readout from the OPTiM Phase III pivotal trial comparing TVEC with sc administered GM-CSF in 430 patients with unresectable advanced melanoma (Stage IIIb/c or IV) will be a major determinant of the commercial viability of the category. OS data should be available in H114. Another oncolytic virotherapy relevant to Cavatak, Oncolytics' Reolysin, is a proprietary formulation of reovirus. Oncolytics has obtained promising preliminary Phase II data in melanoma and lung cancer, but has paused development in melanoma while it evaluates its strategy in light of potential combinations with new targeted agents.

PD-1 and PD-L1 inhibitors – lambrolizumab and nivolumab

Lambrolizumab and nivolumab, now in Phase II and I trials respectively for a range of advanced cancers, are humanised monoclonal IgG4 antibodies that act against the programmed death 1 (PD-1) receptor and its primary ligand PD-L1 respectively. There is much interest in these programmes given the impressive median two-year OS of 43%, coupled with long-term safety and response data reported from Phase I trials of nivolumab in melanoma patients at ASCO 2013.

Potential role for Cavatak – in combination

The discovery that BRAF was a major contributor to c 40% of the incident population, and the subsequent development of targeted agents, has shifted the metastatic melanoma treatment paradigm and created an impetus for the identification of other oncogenic targets. Similarly, increased understanding of regulatory checkpoints of the immune system that led to the development of Yervoy has raised the prospect of targeted immunotherapies addressing the remaining incident population, alone or in combination with other novel agents. Oncolytic virotherapy is one such novel approach under consideration as evidenced by the ongoing 149-patient Phase I/II trial of Yervoy and TVEC. Assuming it can demonstrate a competitive safety/efficacy profile vs TVEC and/or Reolysin (if these agents reach the market), the most likely role for Cavatak will be in combination with immunotherapy. At this stage it is difficult to know which immunotherapies will emerge as standard of care by the time Cavatak is ready to enter late-stage development (2015). Nonetheless, choice of immunotherapy backbone for this trial could be critical to Cavatak's clinical and commercial success in reaching the market by 2020.

Valuation

We value Viralytics at A$61m, or A$0.69/share (undiluted), using a risk-adjusted net present value method to discount future cash flows through to 2032 in metastatic melanoma only. Our approach assumes a partnering deal or out-licensing of Cavatak post-release of the final Phase II data in 2014, with all costs of subsequent clinical development borne by the partner/licensee, for a royalty stream of 15% to Viralytics upon launch of the product in 2020. We assume peak sales of A$646m in 2024 or 20% of the metastatic melanoma market, before tapering off for the remaining term of market exclusivity under the Biologic Licence Approval of 12 years. Our model assumes simultaneous product launches in Europe and RoW with cost of drug c 60% of the price achieved in the US market. Forecast cash flows are taxed at an effective tax rate of 10% with a 30% probability of success applied to reflect Cavatak's phase of clinical development, with projected cash flows discounted at 12.5% as per Edison's standard approach. There is additional upside to our base case valuation since Cavatak could be developed for a range of cancers other than melanoma

given positive preclinical data and the prospect of new indications being identified in the signal seeking phase of the upcoming intravenous STORM trial.

Exhibit 10: Valuation and assumption metrics (base case)

Value driver	rNPV A$000s	rNPV per share (A$)	Probability of success	US launch	Peak Mt**	Key assumptions
CAVATAK	74,625	0.86	30%	2020	20%	Out-license CAVATAK end of Phase II
R&D expense	-4,267	-0.05				Market exclusivity of 12 years under BLA
Admin	-2,491	-0.03				Royalty stream of 15%
Tax	-7,416	-0.09				One cycle of treatment per patient
Net cash*	137	0.00				Average price of US$75k
Total	**60,588**	**0.69**				Australian corporate tax of 30%
						Shares in issue 87.2m + options 5.9m

Source: Edison Investment Research. Note: *At end-June 2013. **Maximum penetration achieved by year five after launch (2024).

Exhibit 11: rNPV/share with different CAVATAK price and penetration assumptions

		CAVATAK price* in US market (US$)		
		50,000	75,000	100,000
Market penetration	15%	0.26	0.43	0.59
	20%	0.44	0.69	0.95
	30%	0.77	1.19	1.61
	40%	1.08	1.66	2.24

Source: Edison Investment Research. Note: *Base case. Assumes cost of CAVATAK in Europe and RoW is 60% of US.

Exhibit 11 highlights both the sensitivity of market penetration at a steady state and the ultimate average price of Cavatak to our risk adjusted NPV based on a 30% probability of success in clinical trials.

Sensitivities

Viralytics is subject to typical biotech company development risks, including the unpredictable outcome of trials, regulatory decisions, success of competitors, financing and commercial risks. In particular, it has a very high single product risk, with the entirety of its value residing in Cavatak. The investment case hinges on the outcome of the CALM study and, assuming data are positive, the company's ability to secure a partnership (or further capital) to advance Cavatak into late-stage trials. Another key sensitivity is the rapidly evolving treatment landscape for melanoma, which means that future trials of Cavatak will likely be in combination with targeted agents and/or immunotherapies – selection of the appropriate therapy to combine with Cavatak could be critical to future clinical and commercial success.

Financials

Viralytics reported cash of A$5.1m at end of June 2013. Deferred tax credits under the Australian R&D tax incentive scheme provide a 45% cash rebate in the following fiscal year and are recognised as revenue. Cash burn is expected to remain c A$1.2m per quarter for FY14e, given operating cash outflows in Q413 of A$1.2m, which included R&D expense of A$0.8m, with a cash runway extending to mid-2014 and that coincides with the expected CALM study readout. In the event a partner or licensee is not secured for Cavatak, Viralytics intends to conduct a randomised intratumoural Phase II trial, which could require additional capital of between A$10-20m. However, given the positive signs of efficacy to date and the potential of a significant readout, the prospects for attracting a partner appear promising. Of the 5.9m unlisted options in issue, 3.5m are with the board and the remainder with the executive team, vesting equally on the first, second and third anniversaries of issue.

Exhibit 12: Financial summary

A$'000s	2010	2011	2012	2013e	2014e	2015e
30-June	IFRS	IFRS	IFRS	IFRS	IFRS	IFRS
PROFIT & LOSS						
Revenue	0	1,406	875	1,536	1,570	2,160
Cost of Sales	0	0	0	0	0	0
Gross Profit	0	1,406	875	1,536	1,570	2,160
EBITDA	(3,664)	(2,246)	(4,621)	(4,282)	(5,160)	230
Operating Profit (before amort. and except.)	(3,765)	(2,302)	(4,659)	(4,324)	(5,189)	210
Intangible Amortisation	(390)	(390)	(390)	(390)	(390)	(390)
Exceptionals	(20)	0	0	0	0	0
Other	0	0	0	0	0	0
Operating Profit	(4,175)	(2,693)	(5,049)	(4,714)	(5,579)	(180)
Net Interest	23	240	317	294	254	8
Profit Before Tax (norm)	(3,742)	(2,063)	(4,342)	(4,029)	(4,935)	218
Profit Before Tax (FRS 3)	(4,152)	(2,453)	(4,732)	(4,419)	(5,325)	(172)
Tax	0	0	0	0	0	0
Profit After Tax (norm)	(3,742)	(2,063)	(4,342)	(4,029)	(4,935)	218
Profit After Tax (FRS 3)	(4,152)	(2,453)	(4,732)	(4,419)	(5,325)	(172)
Average Number of Shares Outstanding (m)	362.3	55.3	67.5	82.4	82.4	82.4
EPS - normalised (c)	(1.0)	(3.7)	(6.4)	(4.9)	(6.0)	0.3
EPS - normalised and fully diluted (c)	(1.0)	(3.7)	(6.4)	(4.9)	(6.0)	0.3
EPS - (IFRS) (c)	(1.1)	(4.4)	(7.0)	(5.4)	(6.5)	(0.2)
Dividend per share (c)	0.0	0.0	0.0	0.0	0.0	0.0
Gross Margin (%)	N/A	N/A	N/A	N/A	N/A	N/A
EBITDA Margin (%)	N/A	N/A	N/A	N/A	N/A	N/A
Operating Margin (before GW and except.) (%)	N/A	N/A	N/A	N/A	N/A	N/A
BALANCE SHEET						
Fixed Assets	4,077	3,675	3,267	2,856	2,456	2,066
Intangible Assets	3,998	3,607	3,217	2,827	2,436	2,046
Tangible Assets	79	68	50	29	20	20
Investments	0	0	0	0	0	0
Current Assets	5,463	6,365	7,039	6,234	1,309	1,527
Stocks	137	365	0	0	0	0
Debtors	200	995	1,154	1,154	1,154	1,154
Cash	5,126	5,005	5,884	5,080	154	372
Other	0	0	0	0	0	0
Current Liabilities	(925)	(981)	(746)	(746)	(746)	(746)
Creditors	(613)	(664)	(746)	(746)	(746)	(746)
Short term borrowings	(312)	(317)	0	0	0	0
Long Term Liabilities	0	0	0	0	0	0
Long term borrowings	0	0	0	0	0	0
Other long term liabilities	0	0	0	0	0	0
Net Assets	8,614	9,058	9,560	8,344	3,019	2,846
CASH FLOW						
Operating Cash Flow	(3,811)	(3,190)	(3,561)	(4,282)	(5,160)	230
Net Interest	219	159	5	294	254	8
Tax	0	0	0	0	0	0
Capex	(4)	(49)	(20)	(20)	(20)	(20)
Acquisitions/disposals	506	0	0	0	0	0
Financing	6,899	2,959	4,455	3,204	0	0
Dividends	0	0	0	0	0	0
Net Cash Flow	3,810	(121)	880	(804)	(4,926)	218
Opening net debt/(cash)	(1,049)	(4,814)	(4,688)	(5,884)	(5,080)	(154)
HP finance leases initiated	0	0	0	0	0	0
Other	(45)	(5)	317	0	0	(0)
Closing net debt/(cash)	(4,814)	(4,688)	(5,884)	(5,080)	(154)	(372)

Source: Edison Investment Research, Viralytics accounts

EDISON

Contact details	Revenue by geography
Suite 305, Level 3 66 Hunter Street Sydney 2000 Australia +61 2 9988 4000 www.viralytics.com/	N/A

CAGR metrics		Profitability metrics		Balance sheet metrics		Sensitivities evaluation	
EPS 2011-15e	N/A	ROCE 14e	N/A	Gearing 14e	N/A	Litigation/regulatory	●
EPS 2013-15e	N/A	Avg ROCE 2011-15e	N/A	Interest cover 14e	N/A	Pensions	○
EBITDA 2011-15e	N/A	ROE 14e	N/A	CA/CL 14e	N/A	Currency	◖
EBITDA 2013-15e	N/A	Gross margin 14e	N/A	Stock days 14e	N/A	Stock overhang	○
Sales 2011-15e	11.3%	Operating margin 14e	N/A	Debtor days 14e	N/A	Interest rates	◖
Sales 2013-15e	18.6%	Gr mgn / Op mgn 14e	N/A	Creditor days 14e	N/A	Oil/commodity prices	○

Management team

CEO: Dr Malcolm McColl	CSO: Professor Darren Shafren
Appointed CEO in November 2012. Previously VP business development at Starpharma and responsible for partnering activities and programmes. Previous roles include director of business development for Hospira (formerly Mayne Pharma) and CSL, where he was Global VP business development for the Animal Health Division.	Dr Shafren is associate professor of virology in the faculty of health, University of Newcastle, and the inventor of the technology acquired by Viralytics. He is responsible for research, development and intellectual property management.
CFO : Robert Vickery	
Mr Vickery is a chartered accountant with over 20 years' experience in industry and professional practice. During the past decade he has held senior finance roles with several biotech and innovation based businesses.	

Principal shareholders	(%)
Dr Nicholas Smith	2.4
Newcastle Innovation	1.8
Getty Minerals Pty	1.4
Asian Investment Holdings	0.9
Mr Stephen Richard Barrett	0.9
National Nominees	0.8
Ignatius Lip Pty	0.7

Companies named in this report

Amgen, Oncolytics Biotech, GlaxoSmithKline, Roche, Bristol-Myers Squibb

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