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Pharmaceuticals & Biotechnology

Source: Eikon Thomson Reuters

Market data	
EPIC/TKR	VAL
Price (p)	1.70
12m High (p)	11.49
12m Low (p)	1.62
Shares (m)	143.81
Mkt Cap (£m)	2.44
EV (£m)	3.18
Free Float*	97%
Market	AIM

**As defined by AIM Rule 26*

Description

ValiRx is a clinical-stage biopharmaceutical company focused on novel treatments for cancer and associated biomarkers. It currently has two products in Phase I/II and Phase II clinical trials. Its business model focuses on out-licensing or partnering drug candidates after clinical trials

Company information

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Key shareholders

Directors	1.4%
Yorkville	1.8%

Diary

4Q-17	Read-out VAL201, VAL401
Nov-17	Interims

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ValiRx

GeneICE and VAL101 progress

ValiRx is a clinical-stage biopharmaceutical company focused on the development of therapeutics for the treatment of cancer, associated biomarkers and companion diagnostics. The company's two leading assets are in clinical trials: VAL201 (Phase I/II) – a peptide for advanced prostate cancer and potential to treat other hormone-induced indications; and VAL401 (Phase II) – a novel reformulation of risperidone, in trials for lung cancer. Optimisation of the manufacturing process for its GeneICE technology platform has enabled the development of a commercially viable process and acceleration of the development of VAL101 towards the clinic.

- **Strategy:** ValiRx operates as a virtual business, out-sourcing most of its activities. The core strategy is to develop its therapeutic assets through the clinical pathway and seek a partner/licensing deal to complete the development programme and regulatory submissions to commercialise the products.
- **GeneICE update:** Through a consortium of partners, led by ValiRx, the manufacturing process for the GeneICE platform has been optimised. This has paved the way for accelerated pre-clinical development of VAL101 and all future products derived from this proprietary gene silencing technology.
- **VAL101:** VAL101 targets directly the Bcl-2 gene that helps cancer cells to proliferate. The second-generation product has shown similar results compared to the original version, with a commercially viable manufacturing process. ValiRx aims to get VAL101 into the clinic fast via an accelerated pre-clinical programme.
- **Risks:** New and/or first-in-class drugs carry the risk that they might fail in clinical trials. However, the substantial safety history of the active ingredient in VAL401 and the consistent safety record to date in the VAL201 trial mitigate these risks. More capital is needed to further its proprietary assets along the value chain.
- **Investment summary:** ValiRx is undervalued. The reason for this is certainly its need for more capital to advance its clinical programmes, thereby building shareholder value. Given the clinical and pre-clinical progress seen to date, the company should be attracting potential commercial partners and/or institutional investors in order to achieve the real value of its assets.

Financial summary and valuation

Year end Dec (£000)	2014	2015	2016	2017E	2018E	2019E
Sales	88	83	0	0	0	0
SG&A	-1,514	-1,645	-1,666	-1,750	-1,837	-1,929
R&D	-1,772	-1,543	-2,375	-2,850	-3,421	-4,105
EBITDA	-2,958	-2,877	-3,939	-4,502	-5,155	-5,936
Underlying EBIT	-2,958	-2,888	-3,949	-4,508	-5,165	-5,941
Reported EBIT	-3,138	-3,029	-3,987	-4,734	-5,399	-6,182
Underlying PBT	-2,952	-2,889	-5,531	-4,622	-5,292	-6,092
Statutory PBT	-3,641	-2,567	-5,569	-4,848	-5,525	-6,332
Underlying EPS (p)	-10.5	-7.7	-8.2	-3.4	-3.3	-3.8
Statutory EPS (p)	-13.5	-6.7	-8.2	-3.6	-3.5	-3.9
Net (debt)/cash	453	232	-734	-3,224	-8,073	-13,564
Capital increases	2,510	2,681	2,615	1,090	0	0

Source: Hardman & Co Life Sciences Research

GeneICE progress

Background

Gene Inactivation by Chromatin Engineering (GeneICE) is a novel proprietary epigenetic gene silencing platform being developed by ValiRx that involves changes in gene function without changing the DNA sequence. ValiRx is investigating the efficient silencing of targeted genes, with a potential to halt and reverse tumour growth. The technology uses natural biological mechanisms that are present within living cells.

In-licensed technology

ValiRx acquired the world-wide exclusive licence from Imperial College

ValiRx acquired a worldwide and exclusive licence for GeneICE technology from Imperial College London. The licence agreement covers any resulting products generated by the GeneICE technology with ValiRx owning all the subsequent intellectual property rights generated from future GeneICE developments.

Development consortium

Being developed through a consortium of high profile partners

ValiRx is leading the GeneICE development through collaboration with a consortium of high profile partners:

- Deutsche Krebsforschungzentrum, Germany
- Institute of Oncology, Heidelberg, Germany
- Pharmatest Services Ltd, Finland
- Undisclosed academic and commercial partners

Grant funding

This consortium has attracted two Eurostars grants from the European Commission. The first was for €1.4m to progress the further development of the GeneICE technology platform; with a second of up to €1.6m specifically to progress the pre-clinical studies of VAL101, the company's lead candidate.

GeneICE platform

Potential application in inflammatory, autoimmune and neurological diseases

One of the main characteristics of cancer cells is the overexpression and/or the aberrant expression of certain genes that promote cell growth. This condition could also be found in other conditions such as inflammatory, Alzheimer's and autoimmune diseases.

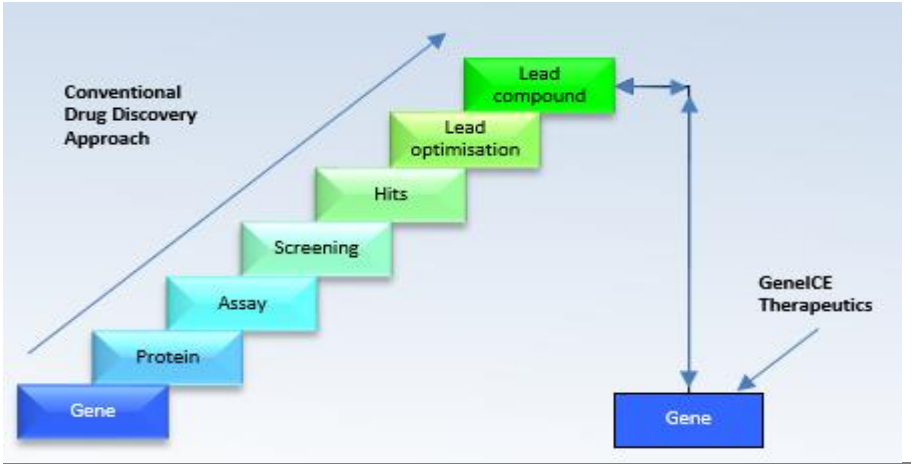
GeneICE uses the natural gene regulation process in cells

GeneICE technology utilises the natural gene regulation process that cells use in order to express or halt the expression of a gene. GeneICE enables the selective silencing of specific genes by mimicking the process of histone deacetylation by histone deacetylases (HDACs).

Unlike the traditional lengthy and costly drug discovery approach in finding a protein inhibitor, GeneICE silences directly the selected gene. In addition, a key advantage of GeneICE is that products are expected to be cheap and relatively easy to manufacture.

The platform is currently in late stage pre-clinical evaluation. Once completed, its potential use as a therapeutic would be complicated by a complex regulatory environment. Therefore, ValiRx is in active discussions with the appropriate regulatory bodies to address any issues prior to applying for first-in-man studies.

GeneICE approach



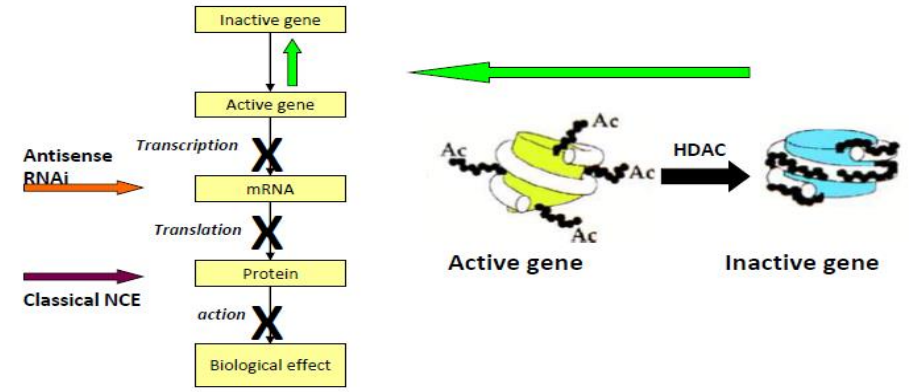
Source: ValiRx

Mechanism of action

GeneICE inhibits directly gene expression

As depicted in the following schematic, GeneICE is thought to mimic a natural process used by cells to silence genes. By targeting upstream, at the gene expression level, the technology may enable improved inhibition compared to existing therapeutics acting at the protein or post-transcriptional levels.

GeneICE mechanism

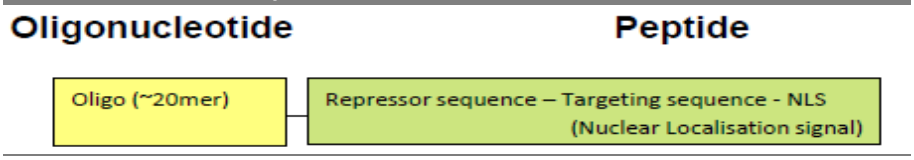


Source: ValiRx

The GeneICE construct is an epigenetic alternative to anti-sense and RNAi technologies. It consists of two synthetic molecules with two distinct functions:

- **Oligonucleotide:** This component targets directly the gene of choice by binding to it in a complementary manner
- **Peptide:** This component attracts the HDAC proteins. By doing so, the de-acetylation process stops the gene to be expressed and prevent the transcription

GeneICE molecular representation



Source: ValiRx

VAL101 update

Importance of Bcl-2

Bcl-2 is a well-known oncogenic protein over-expressed in cancer cells

Bcl-2 is an oncogenic protein that plays a crucial role in cell death regulation. When Bcl-2 is overexpressed in cancer cells, it may inhibit pro-apoptotic signals and cause resistance to chemotherapy, allowing the cancer cell to survive under stressful conditions. It is believed that alteration in the expression of Bcl-2 occurs in nearly half of all human cancers[1].

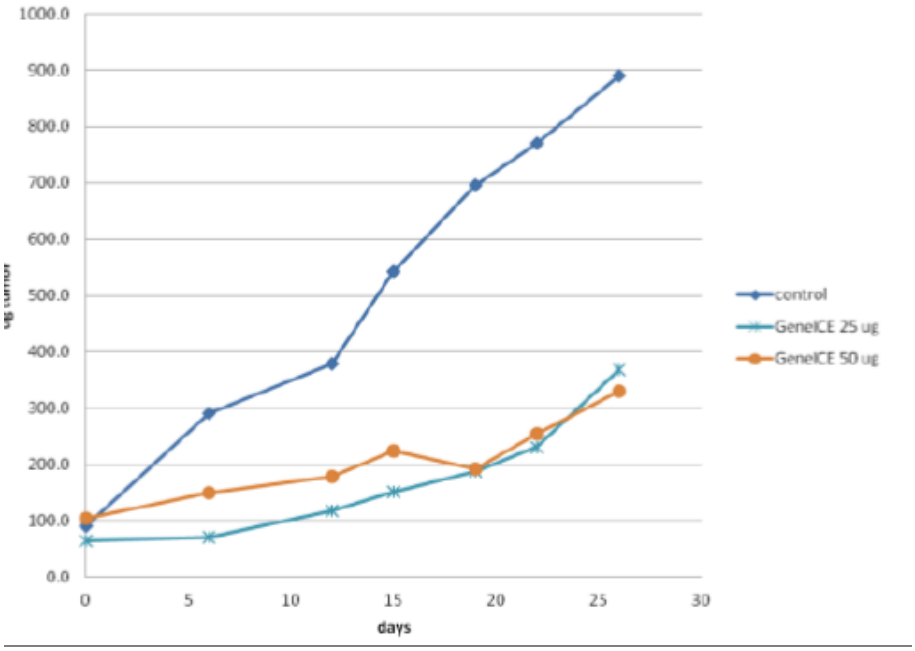
Despite its important role in blocking cell apoptosis, Bcl-2 is not considered as causing cancer. In lung cancer, it is actually a sign of good prognosis[2]. In contrast, over expression of Bcl-2 in hematologic cancers like B-cell chronic lymphocytic leukaemia (CLL) is associated with chemotherapy-resistant disease, aggressive clinical course and poor survival.[3]

VAL101 – proof-of-concept

VAL101 is a gene silencing therapeutic in pre-clinical evaluation in cancer

ValiRx is developing VAL101, a novel therapeutic using GeneICE technology, that targets and silences the gene that expresses Bcl-2. In an *in vivo* pre-clinical study in mice, VAL101 was shown to slow down tumour growth in saturated dose

VAL101 triggers tumour growth inhibition



Source: ValiRx

In subsequent studies, GeneICE-based products have been shown to be effective in prostate, ovarian, pancreatic, lung and other cancer cell lines. ValiRx is currently developing and testing VAL101 in several cancer models including pancreatic and ovarian tumours.

[1] K W Yip; J C Reed Oncogene, 2008, **27,** 6398–6406.
[2] Daniel J. Renouf; Richard Wood-Baker; Diana N. Ionescu; Samuel Leung; Hamid Masoudi; Cyril B. Gilks; Janessa Laskin Thorac Oncol. 2009;4: 486–491.
[3] T. Robak Leukemia, 2015, BCL-2 inhibitors for Chronic Lymphocytic Leukemia. J Leuk 3: e114. doi:10.4172/2329-6917.1000e114

VAL101 – pre-clinical update

Second generation VAL101 generated similar results to the non-commercial first generation molecule

The results shown above were generated using a first generation version of VAL101. While this structure was sufficient to demonstrate that Bcl-2 was reduced and that cancer cell death occurred, it was not considered to be commercially viable from a manufacturing stand-point. Therefore, in conjunction with its partners, ValiRx has been working on developing a second generation molecule that has the same level of gene silencing activity but is also commercially viable.

Further late stage pre-clinical studies are being prepared...

... with the aim to enter first-in-man trials

ValiRx has announced that considerable progress has been made regarding the optimisation of the GeneICE platform, overcoming some of the technical manufacturing issues. An optimised VAL101 has been demonstrated to have the same gene silencing properties compared to the first generation product, but with a more efficient manufacturing process. Consequently, the company is looking to accelerate it pre-clinical evaluation of VAL101 with a view to getting the drug into the clinic as soon as possible.

Improved manufacturing process

Beneficial for all products coming from the GeneICE platform

The manufacturing improvements that have been made will not only benefit VAL101 but also any other product that will be derived from the GeneICE platform. This potentially paves the way for the technology platform to be out-licensed to third parties.

Competitive environment

AbbVie is the most advanced and competitive company in the field of Bcl-2 inhibition. In April 2016, it received accelerated approval of its first-in-class Bcl-2 inhibitor, venetoclax, for patients diagnosed with chronic lymphocytic leukaemia (CLL). AbbVie is also pursuing other clinical trials of venetoclax for multiple indications, despite serious adverse reactions observed in nearly 44% of patients, such as pneumonia and tumour lysis syndrome. The following table shows the most advanced competitors to ValiRx in this field.

Bcl-2 inhibitor marketed and in clinical development

Name	Company	Stage	Selectivity	Indications
Venetoclax	AbbVie	Approved in US Submitted in EU	Selective Bcl-2	Chronic lymphocytic leukaemia, multiple myeloma, acute myeloid leukaemia, Diffuse large B cell lymphoma
Obatoclax	Teva	Phase III*	Pan Bcl-2	Acute myeloid leukaemia, small cell lung cancer, Hodgkin's lymphoma, myelodysplastic syndromes
Navitoclax (ABT263)	Abbott	Phase II	Pan Bcl-2	Chronic lymphocytic leukaemia, Platinum-resistant or refractory ovarian cancer, prostate cancer, refractory lymphoid malignancy
AT-101	Ascentage	Phase II	Pan Bcl-2	Chronic lymphocytic leukaemia, Lung cancer, prostate cancer, B-cell malignancies, Follicular lymphoma, Squamous cell carcinoma, laryngeal cancer, adrenocortical carcinoma
ABT-737	AbbVie	Phase II	Pan Bcl-2	Ovarian cancer
R-(-)-gossypol	Ascentage	Phase II	Pan Bcl-2	Non-Hodgkin's lymphoma, prostate cancer, NSCLC
Oblimerson	Genta	Phase I/II	Antisense therapeutic	Chronic lymphocytic leukaemia
S055746 (BCL201)	Servier	Phase I	Selective Bcl-2	Acute Myeloid leukaemia, Myelodysplastic syndrome
APG-1252	Ascentage	Phase I	Pan Bcl-2	Solid tumour, NSCLC

**Phase III halted due to business decision*

Source: www.clinicaltrials.gov, Hardman & Co Life Sciences Research

Financial summary

Financial forecast summary						
Year end Dec (£000)	**2014**	**2015**	**2016**	**2017E**	**2018E**	**2019E**
Profit & Loss						
SG&A	-1,362	-1,514	-1,645	-1,750	-1,837	-1,929
R&D	-1,622	-1,772	-1,543	-2,850	-3,421	-4,105
Other income	0	211	203	0	0	0
Underlying EBIT	**-2,856**	**-2,958**	**-2,888**	**-4,508**	**-5,165**	**-5,941**
Share based costs	0	-89	-49	-134	-141	-148
Statutory EBIT	-2,911	-3,138	-3,029	-4,734	-5,399	-6,182
Net financials	5	-503	462	-114	-126	-150
U/L pre-tax profit	**-2,850**	**-2,952**	**-2,889**	**-4,622**	**-5,292**	**-6,092**
Reported pre-tax	-2,906	-3,641	-2,567	-4,848	-5,525	-6,332
Tax liability/credit	308	397	391	744	893	1,072
Underlying net income	-2,647	-2,470	-2,440	-3,877	-4,399	-5,020
Underlying basic EPS (p)	**-19.1**	**-10.5**	**-7.7**	**-3.2**	**-3.1**	**-3.5**
Statutory Basic EPS (p)	-19.5	-13.5	-6.7	-3.4	-3.2	-3.7
Balance sheet						
Share capital	6,359	7,282	8,121	8,166	8,166	8,166
Reserves	-3,129	-4,520	-3,667	-9,920	-14,552	-19,812
Short-term loans	0	0	0	1,294	1,294	1,294
less: Cash	960	453	232	-1,930	-6,779	-12,270
Invested capital	**1,502**	**2,335**	**2,837**	**1,490**	**1,707**	**1,937**
Cashflow						
Underlying EBIT	-2,856	-2,958	-2,888	-4,508	-5,165	-5,941
Change in working capital	620	-366	-105	563	0	0
Company op cashflow	**-2,233**	**-3,317**	**-2,977**	**-3,939**	**-5,155**	**-5,936**
Capital expenditure	-134	-1	-32	0	0	0
Free cashflow	**-3,002**	**-2,622**	**-4,196**	**-4,196**	**-4,462**	**-5,104**
Capital increases	896	2,510	2,681	1,090	0	0
Change in net debt	**-1,301**	**-507**	**-220**	**-2,491**	**-4,849**	**-5,491**
Opening net cash	960	453	232	-734	-3,224	-8,073
Closing net cash	**453**	**232**	**-734**	**-3,224**	**-8,073**	**-13,564**

Source: Hardman & Co Life Sciences Research

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