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Biotron (BIT)

Benefiting from the Hepatitis C gold rush

Recommendation
Buy (Initiation)
Price
$0.145
Target (12 months)
$0.40
Risk
Speculative

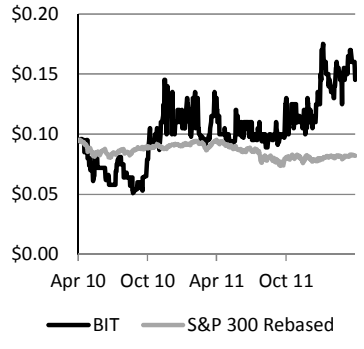
Expected Return	
Capital growth	176%
Dividend yield	0
Total expected return	176%
Company Data & Ratios	
Enterprise value	$24.0m
Market cap	$33.1m
Issued capital	228.3m
Free float	100%
Avg. daily vol. (52wk)	184,520
12 month price range	$0.089-$0.19
GICS sector	
Healthcare Equipment and Services	

Disclosure: Bell Potter Securities acted as partial underwriter in the recent exercise of the December 2011 BITO listed options and received fees for that service.

Price Performance

	(1m)	(3m)	(12m)
Price (A$)	0.13	0.14	0.14
Absolute (%)	16.00	7.41	7.41
Rel market (%)	12.49	4.78	20.27

Absolute Price



SOURCE: IRESS

This note represents a re-initiation on Biotron. Southern Cross Equities previously published a note on the company on 25 March 2011.

Biotron (BIT) is an early stage company developing new anti-viral drugs. We like the clinical data so far in Hepatitis C, the potential for a favourable clinical outcome in HIV, and the opportunity for early licensing of the BIT225 compound on the back of Phase II, particularly given the extraordinary change now underway in the treatment landscape for Hepatitis C. We have a favourable regard for Biotron management. With this note we are re-initiating on Biotron with a price target of $0.40.

An HCV compound with good Phase II data that also appears to work in HIV

Biotron's proprietary BIT225 compound has looked good in pre-clinical studies in Hepatitis C (HCV) and HIV, as well as shown encouraging early stage clinical data in HCV in two Phase I/II trials. In the most recent trial, for which data was reported in December 2011, the drug performed well as an add-on to conventional interferon/ribavirin therapy, generating, 12 weeks after initial dosing, a cure in 87% of patients versus 63% for placebo. This was after only four weeks of BIT225 treatment, an encouraging result which bodes well for future trials involving 12-week dosing.

Hepatitis C is generating some strong commercial interest

Chronic Hepatitis C infection is an area of large unmet medical need, with 2-3 million patients in the US alone that, until recently, had only interferon and ribavirin as treatment options in spite of this drug regimen's drawbacks. The FDA approvals of Vertex's Incivek and Merck & Co.'s Victrelis in 2011 have begun a revolution in HCV treatment in which direct-acting antivirals markedly improve cure rates. With other pharma companies looking to access the new, larger marketplace, which is expected to grow from US$3bn to US$11bn globally by 2018, the race is on to put together the best drug regimen. In recent days this has seen Gilead Sciences pay a massive US$11bn to acquire Pharmasset while Bristol-Myers Squibb paid US$2.5bn to acquire Inhibitex. In this sort of environment, we see strong licensing interest emerging for BIT225, particularly since Biotron's drug, which targets HCV's p7 protein, has a different target to most HCV drugs in clinical development today.

A well-managed company

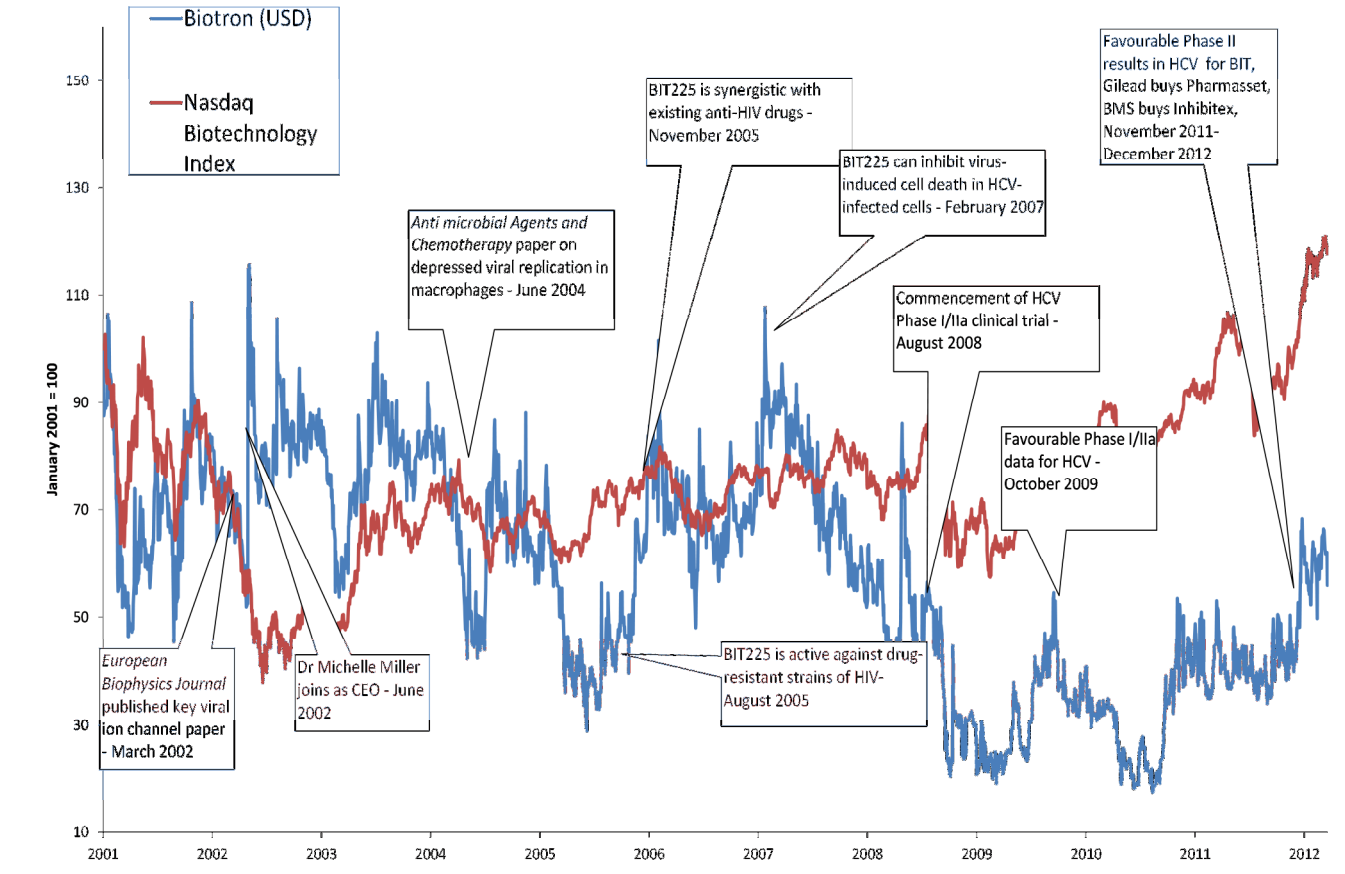
Dr Michelle Miller has done an excellent job in focusing Biotron on anti-viral drug discovery, getting compounds ready for the clinic, and marketing the opportunity to potential licensing partners. Backing Michelle is a strong board chaired by the former Fairfax executive Michael Hoy and including the former J&J executive Dr Denis Wade.

Biotron is inexpensive given the opportunity

We value Biotron at $0.28 base case and $0.51 optimistic case using a probability-weighted DCF valuation. Our target price of $0.40 sits at the midpoint of our valuation range, and reflects our optimism regarding BIT225 in both HCV and HIV. We see the initiation of a larger Phase II trial in HCV as a potential catalyst to reprice Biotron.

Biotron – Benefiting from the Hepatitis C gold rush

Figure 1 – Major developments for Biotron since 2001



SOURCE: BIOTRON, BELL POTTER SECURITIES

'These results are impressive. To have close to 90% of patients achieving a complete EVR after three months is extremely encouraging and demonstrates the clinical benefit of BIT225"

- Biotron CEO Dr Michelle Miller, speaking in December 2011 with results from BIT225's second successful proof-of-concept trial in Hepatitis C.

Introducing Biotron, ASX Code BIT

Who is Biotron? Biotron is a Sydney-based drug development company whose lead product is BIT225, a small molecule drug for the treatment of Hepatitis C and HIV infection. BIT225 generated favourable Phase I/II proof-of-concept data in Hepatitis C in two trials in 2009 and 2011, and a Phase I/II trial is currently ongoing to demonstrate that the same drug can treat HIV infection. Biotron is targeting the large global population of patients co-infected with both viruses. Behind BIT225 Biotron has a large library of ion-channel blocking drugs that the company believes can be useful in treating other viral infections such as influenza and dengue.

What is Hepatitis C? Hepatitis is inflammation of the liver, and Hepatitis C Virus (HCV) is one of five viruses (Hepatitises A to E) known to target liver cells and thereby cause hepatitis. HCV is passed from person to person by contact with infected blood, these days mainly through illicit injection drug use[1], and there is no prophylactic vaccine[2]. Most HCV infections are chronic[3], with serious and costly health consequences for patients in terms of the risk of hepatitis, cirrhosis of the liver, and liver cancer. Since the late 1980s when the virus was first discovered[4] HCV has evolved into a large area of unmet medical need.

An estimated 6-7 million people in advanced industrial countries have chronic HCV

- We estimate there are 6-7 million people in advanced industrial countries who are chronically infected with HCV, representing around 5% of a global patient population of 125 million;
- The current 'standard of care', a combination of two drugs called interferon and ribavirin, is considered by most observers to be inadequate, but this still drives a US$3bn global drug market dominated by Roche and Merck & Co.
- There is currently strong competition between various large companies looking to develop new drug regimens that could reasonably expand the market to >US$10bn pa.

What is HIV? AIDS, that is, Acquired Immune Deficiency Syndrome, is a disease in which the body's immune system is progressively shut down by infection with HIV, the Human Immunodeficiency Virus. HIV works by targeting certain of the body's white blood cells, which it gradually kills off until the infected person's immune system can no longer mount a response to other microbial infections. The patient eventually dies from 'opportunistic infection' by another microbe. As with HCV, there is no HIV vaccine. The market for HIV drugs is large and growing:

The current HIV drug market is worth US$15bn pa

- An estimated 34 million adults around the world were HIV positive at the end of 2010, with 2.7 million adults newly infected that year. Global prevalence in adults aged 15-49 was estimated at 0.8%[5].
- The global HIV drug market expanded 13% pa in local currency terms between 2005 and 2010, to reach US$15bn in size. As a result anti-HIV agents have become the world's tenth largest drug class.
- There remains strong demand for new classes of drug that can attack the virus in different ways, and preferably clear the virus out of its hiding places in the body.

[1] Around half of all Americans who have been infected with HCV under the age of 60 report a history of injection drug use. See Ann Intern Med. 2006 May 16;144(10):705-14.

[2] In March 2012 the Basel-based Okairos AG (www.okairos.com) announced that it was starting a 350-subject Phase I/II trial for a preventative vaccine for HCV. Okairos, which was spun out of Merck & Co in 2007, has technology centred on the use of adenoviral vectors to stimulate T cell responses to antigens of interest. Financial backing for Okairos has come from the Boehringer Ingelheim Venture Fund, Novartis Venture Funds, and the American VC house Versant Ventures. For a summary of the current state of HCV vaccine development see Expert Rev Vaccines. 2011 May;10(5):659-72.

[3] Unlike HIV, HCV is one of those viruses that some people's immune systems can actually defeat and clear from their systems. Not the majority, however. Around ten years ago in the US an estimated ~ 4 million people had been infected with Hepatitis C, of which 22% had cleared the virus with the remainder chronically infected (see Armstrong et. al., Ann Intern Med. 2006 May 16;144(10):705-14, which used NHANES data for the 1999-2002 period to show that 1.6% of the total US population had anti-HCV antibodies and 1.3% had chronic infection). Micallef et. al., conducting a meta-analysis of 31 studies related to spontaneous clearance of HCV in acute cases, found a mean clearance rate of 26%.See J Viral Hepat. 2006 Jan;13(1):34-41.

[4] Previously Hepatitis C was called 'Non-A, Non-B Hepatitis'. See Science. 1989 Apr 21;244(4902):359-62. For many years the American biotech company Chiron, now part of Novartis, basically controlled the HCV genome through key patents, the virus having been discovered at Chiron in 1987 by Dr Michael Houghton and others. Houghton is now working on a prophylactic Hepatitis C vaccine at the University of Alberta (see Immunol Rev. 2011 Jan;239(1):99-108).

[5] Source: UNAIDS.

What is BIT225? BIT225 is a small molecule that targets the p7 protein of HCV and the VPU protein of HIV. The drug originates from work done in the late 1990s demonstrating that amiloride derivatives could treat HIV infection by acting on VPU-formed ion channels in infected cells. BIT225, first unveiled in 2005 after a three-year rational drug design programme based on the amiloride derivatives, has been found to be effective in pre-clinical work in both HIV and HCV, which is promising because generally HCV drugs don't work in HIV and vice versa.

What's the clinical evidence for BIT225? In December 2011 Biotron's investigators reported results from a randomised, placebo-controlled Phase Ib/IIa proof-of-concept trial of BIT225 in 24 treatment naïve genotype 1 HCV patients. After four weeks of dosing 87% of trial subjects receiving BIT225 registered a complete EVR[6] at 12 weeks, predictive of therapeutic success[7], versus 63% for interferon and ribavirin alone. We think this indicates a powerful HCV drug with potential to show exceptional data with the standard 12 weeks of dosing that has been used with competitor drugs.

What's the plan for BIT225? Biotron is currently finalising its clinical program for 2012/13, and this is expected to include

- A HIV/HCV co-infected study, with dosing up to 28 days to commence mid-2012;
- A Phase II HCV trial with 12 weeks dosing to commence towards the end of 2012.

Biotron has 350 compounds in its library

What's in Biotron's pipeline? Biotron has a library of around 350 small molecules targeting p7/VPU from which it believes it can develop backup compounds to BIT225 that have superior preclinical efficacy in either HCV or HIV (although not both together). The company is also at the preclinical development stage on compounds that can treat dengue virus and influenza infections.

What's coming up? We look for the following news flow items to help move the stock towards our $0.40 share price target:

- Completion of Phase 1b/2a in HIV – 2Q2012;
- Results from 48 week follow-up period for HCV Phase 1b/2a trial – 2Q12;
- New formulations in order to provide more patient-friendly tablets, followed by 3-month tox studies on those formulations – 3Q2012;
- Initiation of Phase II trial in HIV/HCV co-infected patients – 3Q2012;
- Initiation of new Phase II trial in HCV for 12-week treatment window – 4Q2012;
- Presentations at this year Hepdart meeting[8] and, potentially, next year's CROI[9];
- Pre-clinical work on potential backup HCV and HIV drug candidates from Biotron's library;
- Pre-clinical work on synergies of BIT225 with other HCV drugs, both marketed and in development;
- Pre-clinical development of pipeline drugs focused on dengue and other indications.
- Potential licensing deal for BIT225.

[6] See Appendix II for an explanation of cEVR.

[7] See Intervirology. 2009;52(5):247-51. Epub 2009 Jul 14.

[8] A leading meeting for Hepatitis researchers, held every December.

[9] The Conference on Retroviruses and Opportunistic Infections, a leading HIV meeting held every March (see www.retroconference.org).

Seven reasons to look at Biotron

1 **BIT225 has performed well against Hepatitis C**. In December 2011 Biotron reported the results of a second Phase I/II trial in which the drug performed well as an add-on to conventional interferon/ribavirin therapy, generating, 12 weeks after initial dosing, a cure in 87% of patients versus 63% for placebo. This was after only four weeks of BIT225 treatment, an encouraging result which bodes well for future trials involving 12-week dosing.

2 **Hepatitis C is generating some strong commercial interest.** Chronic Hepatitis C infection is an area of large unmet medical need, with 2-3 million patients in the US alone that, until recently, had only interferon and ribavirin as treatment options in spite of this drug regimen's drawbacks. The FDA approvals of Vertex's Incivek and Merck & Co.'s Victrelis in 2011 have begun a revolution in HCV treatment in which direct-acting antivirals markedly improve cure rates with lower side effects. With other pharma companies looking to access the new, larger marketplace, which is expected to grow from US$3bn to US$10bn globally, the race is on to put together the best drug regimen. In recent days this has seen Gilead Sciences pay a massive US$11bn to acquire Pharmasset while Bristol-Myers Squibb paid US$2.5bn to acquire Inhibitex. In this sort of environment, we see strong licensing interest emerging for BIT225.

3 **Biotron's drug attacks HCV by a novel mechanism of action**. In 2004 Biotron was able to demonstrate that blockage of the p7 protein of Hepatitis C represented a viable treatment strategy. With most HCV drugs in clinical development being either NS3/4 protease inhibitors or NS5 polymerase inhibitors we expect that BIT225 will appeal to prospective licensees by successfully attacking a target that has attracted little attention to date.

BIT225 may be able to treat both HIV and HCV infection

4 **BIT225 can treat both HIV and HCV**. With up to 30% of HIV patients co-infected with HCV, there is likely to be strong commercial demand for any drugs that can treat both infections. We expect an ongoing Phase II clinical trial in HIV patients will demonstrate the clinical effectiveness of BIT225 in HIV.

5 **Biotron has a good CEO and board**. Since joining Biotron in 2002 CEO Dr Michelle Miller has brought discipline to the technology development process. She has also put in place the numerous building blocks to develop BIT225 and take it into the clinic and has done it while carefully conserving shareholders' funds[10]. We think Michelle has the skills to take Biotron to the next level of attracting licensing interest into the company and building the pipeline. Backing Michelle is a strong board chaired by the former Fairfax executive Michael Hoy and including the former J&J executive Dr Denis Wade.

6 **Biotron can create a pipeline from its valuable Virion platform technology**. BIT225 grew out of a body of scientific knowledge which Biotron inherited related to viral ion channel proteins. This platform technology, which Biotron has called 'Virion', has enabled the company to show that the SARS and dengue viruses have druggable ion channel proteins, as has the influenza virus. We think this platform will allow the company to create multiple new drugs once the HCV and HIV programmes gain some commercial traction.

7 **Biotron is inexpensive given our valuation.** Based on the potential of BIT225 in HIV and HCV alone, we value the company at $0.28 base case and $0.51 optimistic case using a probability-weighted DCF valuation. Our 12-month share price target price of $0.40 per share is at the midpoint of our valuation range and reflects our optimism regarding BIT225 in both HCV and HIV.

[10] Biotron's historical underlying expenditure has been only A$80,000 per month when costs associated with clinical trials etc are excluded. Biotron has only raised A$33m since IPO in 2001.

Valuing Biotron – target price 40 cents

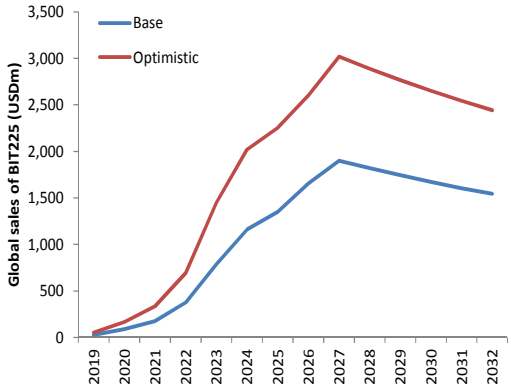
Base case $0.28, optimistic case $0.51. We value Biotron at $0.28 per share base case and $0.51 per share optimistic case using a probability-weighted DCF valuation of BIT225, diluted for a future A$20m equity raising that would fund further clinical development of the product. Our target price of $0.40 per share sits at around the midpoint of our DCF range.

Figure 2 - Our valuation of Biotron

	Base case	Optimistic case
BIT225 ($m)	83.6	176.2
Cash as at 12/2011 ($m)	9.1	9.1
Cash from options and cash to be raised ($m)	21.2	21.2
Total diluted value ($m)	113.9	206.6
Total diluted shares	405.7	405.7
Value per diluted share	$0.28	$0.51
Midpoint	$0.395	
Share price now	$0.145	
Upside to midpoint	172%	

SOURCE: BELL POTTER SECURITIES ESTIMATES

Figure 3 - Assumed sales profile for BIT225



SOURCE BELL POTTER SECURITIES ESTIMATES

We model BIT225 as a future blockbuster

In valuing Biotron we assume:

- A licensing deal within the next two years for BIT225 in both HIV and HCV with total upfronts and milestones of US$250m (base case) to US$400m (optimistic case);
- Global product approval by 2019-2020 for both HIV and HCV;
- A 32% chance of clinical success in HCV[11] and 20% in HIV[12];
- A tiered royalty on sales of 12-20%;
- Product exclusivity out to 2032;
- Peak sales around 2027 of US$1.9bn (base case) to US$3.0bn (optimistic case), after which sales decline due to reduced patient numbers in both HIV and HCV, driven by higher cure rates in HCV and the emergence of the Functional Cure in HIV;
- 80% price cuts after end of exclusivity and ~4% pa sales decline thereafter.

We then

- calculated the NPV of the resulting cash flow at a 16% discount rate and adjusted for a 30% tax rate;
- Converted our modelled revenues and costs, which we generated in US dollars, back to Australian dollars at an AUD/USD exchange rate at ~1.04;
- Diluted our valuation through a A$20m equity raising to fund further clinical work.

Biotron is well funded: As at December 2011 Biotron had ~$9m cash, but had burned only A$175,000 per month through 2011. We therefore see Biotron as well funded for the next stage of BIT225's development. That said, we see potential for Biotron to move forward on its development pathway for BIT225 with extra cash resources and we have therefore assumed a A$20m capital raising ahead of any licensing deal the company may contemplate.

[11] We assume BIT225's recent success in genotype 1 patients with interferon and ribavirin boosts the probability of success for later Phase II trials to around 60%. For historic drug development success rates see Clin Pharmacol Ther 87: 272- 277.

[12] We think this is conservative. A 2003 study (Health Aff (Millwood). 2006 Mar-Apr;25(2):420-8) estimated the success rate for anti-HIV drugs at a very high 36%.

Inside the Hepatitis C gold rush

Large pharma companies are currently paying big money for drugs like Biotron's

Biotron's lead compound is a Hepatitis C drug called BIT225. This drug, which was initially developed as an HIV therapy[13], has performed well in two Hepatitis C (HCV) proof-of-concept clinical trials, for which results were reported in 2009 and 2011. We argue that the 2011 results in particular position BIT225 for either a lucrative partnering deal, or the acquisition of Biotron by a larger company, given the strong demand that has emerged in recent months for new HCV drugs, and the unique qualities of Biotron's drug.

There's a 'gold rush' currently underway for new HCV drugs. This unmet medical need has driven increased interest in HCV by Big Pharma in recent years, interest that has accelerated markedly since late 2011 with the announcement of four extraordinary deals in the HCV space:

- Roche announced in October 2011 that it was buying Anadys Pharmaceuticals of San Diego for US$230m in scrip. This gave Roche ownership of Setrobuvir (ANA598), an HCV drug that that just reported interim data from a Phase IIb trial;
- Gilead Sciences[14], a specialty pharma company focused on HIV and HCV, announced in November 2011 that it was buying the Princeton-based Pharmasset for US$11bn of its scrip. That's right - 11 *billion* for a clinical-stage company whose lead compound, PSI-7977, had only recently reported full Phase IIb. This deal made people sit up and take notice because most of the US$11bn was borrowed.
- Bristol-Myers Squib announced in January 2012 that it was buying the Georgia-based Inhibitex for US$2.5bn for INX-189, a drug that only had Phase Ib data in HCV the difficult-to-treat genotype 1 of the virus (which accounts for 70-80% of US cases[15]) and was in Phase II for genotype 2 and 3.
- Novartis announced in February 2012 that it was licensing EDP-239 from the privately-held Enanta Pharmaceuticals of Watertown, Ma, for US$34m upfront and US$406m in milestones, which was an extraordinary price for a molecule at pre-clinical.

Interestingly, all these deals were for HCV polymerase inhibitors. As we note below, various companies are basically jostling for position to get a good representative of this kind of drug to be the linchpin of their new anti-HCV drug combinations. We argue that after the initial fight for polymerase inhibitors the search will begin for new drug classes, which potentially can include Biotron's new class of p7 inhibitor.

We see six main reasons for the high price-tags on promising new HCV drugs:

1 The large patient population, which we estimate to be around 7 million people in advanced industrial countries;

2 The already large market for interferon and ribavirin, in spite of their drawbacks;

3 The introduction of the first HCV protease inhibitors last year;

4 The number of large companies positioning to compete in the HCV space;

5 The current rise of interferon-free treatment regimens for HCV;

6 The likelihood of large global patient populations in the foreseeable future, due to the dynamics of HCV's spread.

HCV has been attractive to Big Pharma for many years

[13] For background on the history of BIT225 since the mid-1990s, see Appendix IV of this note.

[14] Nasdaq: GILD, Foster City, Ca., www.gilead.com. Gilead ranked No. 23 on *Pharmaceutical Executive*'s 2010 list of the world's 50 largest pharma companies. As at 16 April it was capitalised at US$34.7bn on Nasdaq.

[15] Gastroenterology. 2006 Aug;131(2):478-84. There are around 11 genotypes of HCV in all. Alongside genotype 1, genotypes 2, 3 and 6 are also relevant to US doctors treating HCV.

Figure 4 - Recent deals in the anti-HCV drug space

Developer	Licensee	Upfront (US$m)	Total deal value (US$m)	Equity component (US$m)	Date	Type of drug	Stage completed at time of license
Pharmasset (then privately held) [16]	Roche	0	168	4	Oct-04	Nucleoside inhibitor	Pre-clinical
Achillion (Nasdaq: ACHN)	Gilead	5	110	5	Nov-04	Protease inhibitor	Pre-clinical
Medivir (STO: MVIR-B)	J&J	9	91		Nov-04	Protease inhibitor	Pre-clinical
Anadys (Nasdaq: ANDS)[17]	Novartis	20	570		Jun-05	Toll-Like Receptor Agonist	Phase I
Idenix (Nasdaq: IDIX)	Novartis	25	525		Mar-06	Nucleoside inhibitor	Phase I
PTC Therapeutics (privately held)[18]	Schering Plough[19]	10	200		Mar-06	IRES Inhibitor	Pre-clinical
Human Genome Sciences (Nasdaq: HGSI)	Novartis	45	552		Jun-06	Fusion protein of human albumin and interferon α-2b[20]	Phase II
Vertex (Nasdaq: VRTX)	Janssen (J&J)	165	545		Jun-06	Protease inhibitor	Phase II
Genelabs (Nasdaq: GNLB)[21]	Novartis	13	188		Sep-06	Polymerase inhibitor	Pre-clinical
Intermune (Nasdaq: ITMN)	Roche	60	530		Oct-06	Protease inhibitor[22]	Pre-clinical
Biota (ASX: BTA)	Boehringer Ingelheim	0	103		Nov-06	Polymerase inhibitor[23]	Pre-clinical
LG Life Sciences (KSE: 068870)	Gilead	20	232		Oct-07	Caspase inhibitor[24]	Phase I
Santaris Pharma (privately held) [25]	GSK	3	703	5	Dec-07	Anti-RNA[26]	Pre-clinical
Tacere Therapeutics (privately held) [27]	Pfizer	0	145		Jan-08	RNA interference	Pre-clinical
Medivir (STO: MVIR-B)	J&J	8	97		May-08	Polymerase inhibitor	Pre-clinical
Metabasis Therapeutics (Nasdaq: MBRX)[28]	Roche	10	203		Aug-08	Prodrug to target liver	Pre-clinical
Zymogenetics (Nasdaq: ZGEN)[29]	Bristol-Myers Squibb	85	1087	20	Jan-09	Pegylated interferon lambda	Phase I
Regulus Therapeutics (privately held) [30]	GSK	0	150		Feb-10	microRNA-122 antagonist	Pre-clinical
Alios BioPharma (privately held) [31]	Vertex	60	715		Jun-11	Nucleoside inhibitor	Pre-clinical
Enanta Pharmaceuticals (privately held) [32]	Novartis	34	406		Feb-12	Polymerase inhibitor	Pre-clinical

SOURCE: COMPANY WEB SITES

A lot of people have Hepatitis C

We estimate 1.8% of the world's population has chronic HCV infection

We estimate ~1.8% of the world's population is chronically infected with HCV. No one really knows how many people have chronic HCV worldwide. Using various sources we estimate that there are around 125 million people who are chronically infected, which is 1.8% of the world's total population.

We estimate 6-7 million patients live in advanced industrial countries, representing 5% of the total patient population. On our numbers around 0.6% of the population in countries with a GDP per capita > US$20,000 have chronic HCV infection.

[16] Taken public in 2007 and then bought by Gilead in 2011 for US$11bn.

[17] Bought by Roche in October 2011 for US$230m.

[18] South Plainfield, NJ, www.ptcbio.com. This company is in Phase III with ataluren, for the treatment of muscular dystrophy and cystic fibrosis.

[19] Now owned by Merck & Co. after the 2009 merger.

[20] This drug, trademarked ZALBIN, received a Complete Response Letter from the FDA in October 2010. HGS and Novartis decided not to develop ZALBIN further.

[21] Bought by GSK in late 2008 for US$57m.

[22] This drug, danoprevir, was sold to Roche for US$175m in October 2010.

[23] This programme was terminated with the rights returned to Biota in April 2010. Biota continues to work on HCV nucleoside and non-nucleoside analogues of HCV. See www.biota.com.au.

[24] A Phase II trial of the caspase inhibitor GS 9450 was halted in April 2010 due to 'reports of significant laboratory abnormalities and adverse events in a number of clinical study participants'.

[25] Hørsholm, Denmark, www.santaris.com.

[26] GSK decided not to exercise its exclusive option to license an miR-122 antagonist candidate in February 2010.

[27] San Jose, Ca, www.tacerebio.com.

[28] Acquired by Ligand Pharmaceuticals (Nasdaq: LGND) in early 2010. The product licensed to Roche, RG7348, is still ongoing and earned Ligand a US$6.5m milestone payment in April 2010.

[29] Bought by BMS for US$885m in late 2010. The interferon lambda programme generated favourable Phase IIb data in April 2011

[30] San Diego, Ca, www.regulusrx.com.

[31] South San Francisco, Ca, www.aliosbiopharma.com.

[32] Watertown, Ma, www.enanta.com. This company has multiple HCV drugs in clinical development.

- The US has at least 2.6 million patients, many of them the result of infections prior to widespread screening of the blood supply began in 1992. 2.6 million represents around 0.8% of the total US population, but could underestimate true prevalence by around 50%[33];
- On our numbers the EU has chronic HCV prevalence of 0.4%[34], but that still leaves us with around 1.8 million patients, including 0.5 million from Romania[35], the highest prevalence country. France, Poland, Spain and Italy also have large patient populations.
- On our numbers Japan, whose prevalence rate is around one-fifth higher than the US, has 1.4 million patients, while Korea at around 10% less prevalence than in the US, has 0.4 million patients[36];

At least 22 million people have chronic HCV infection in China

We estimate ~38 million patients live in the BRIC countries, with China (1.6% prevalence) and Brazil (1.4%) having particularly high prevalence. On our numbers 22 million chronic HCV patients live in China[37].

We estimate another ~9 million patients live in middle income economies with improving healthcare systems, most notably Turkey (0.6 million), Malaysia (0.5 million), South Africa (0.4 million) and Mexico (0.4 million[38]).

Why only 125 million? Most countries don't keep track of Hepatitis C in the same way as HIV because the disease is, potentially, curable, although as we note below many patients fail on treatment. A figure commonly used by people reporting on prevalence is that there are 170 million people with HCV globally. This figure is based on data gathered by varying methods and reported by the World Health Organisation in 1999[39]. Our lower estimate reflects three main factors:

- *The arrival on the market of pegylated interferons in the early 2000s*. For around ten years now chronic HCV infection has been treated primarily using a pegylated version one of the 'interferon' drugs[40], plus another anti-viral drug called ribavirin. By improving treatment outcomes compared to regular interferons[41], more patients will have experienced clinical cure over the last decade;
- *A slowing in the rate of new infections*. Programmes to prevent the spread of HCV, such as needle exchange programmes have lowered the estimated rate of new infections in the US by 60% between 1999 and 2009[42].
- *A higher death rate for HCV-positive people*. One 15-year US population study found that people with chronic HCV had all-cause mortality 2.4 times higher than HCV-negative people[43], with liver disease accounting for only around third of the deaths. Basically people with Hepatitis C infections have poorer health overall.

125 million still reflects a large unmet medical need. We think that 125 million people, of whom at least 6 million live in countries with well-funded healthcare systems, still

[33] 2.6 million adults would represent 1.1% disease prevalence for adults. A 2011 analysis suggested that 'at least 5.2 million' HCV-positive people was a more appropriate estimate, with the NHANES surveys under-sampling homeless and incarcerated persons, where HCV is more prevalence. This would be 2.2% adult prevalence. See Liver Int. 2011 Sep;31(8):1090-101. Epub 2011 Mar 16.

[34] One recent estimate has suggested a typical European prevalence rate is more like 1.1-1.3%. See BMC Public Health. 2009 Jan 22;9:34.

[35] A result of negligent medical practices such as using non-sterile syringes and transfusions with untested blood in the 1980s. Gheorghe et. al. estimated adult prevalence in Romania in the 2006-2008 period at 3.2%. See J Gastrointestin Liver Dis. 2010 Dec;19(4):373-9.

[36] Around 1% of the Korean population has a Hepatitis C infection. See Intervirology. 2006;49(1-2):70-5.

[37] A commonly used prevalence figure is 3.2%, which would translate to~43 million people today. The 3.2% figure was derived from a 1992-1995 epidemiological survey (see Liu et. al., 'Epidemiology of hepatitis C virus', Infectious Disease Information 2007, 20:261-264). It gets used in WHO Fact Sheet No 164, June 2011.

[38] We estimate Mexican prevalence at 0.4% of the population. One recent study has suggested 1-2.5% is more reasonable. See J Infect. 2008 Apr;56(4):281-90. Epub 2008 Mar 17.

[39] Source: World Health Organisation, Weekly Epidemiological Record No. 49, 10/12/1999.

[40] The interferons are proteins made and released by cells in response to the presence of pathogens. Some of them have strong anti-viral properties, with the interferon-alphas being effective in HCV infection. A drug is pegylated when it is conjugated to polyethylene glycol in order to extend its half-life. Pegylation was the basic strategy that created the drug delivery major Enzon (Bridgewater, NJ, Nasdaq: ENZN, www.enzon.com). That company helped create Pegintron for Schering Plough and continues to collect royalties on its net sales by Merck & Co. We estimate these at 5%.

[41] In one trial peginterferon alfa-2b plus ribavirin enjoyed a 42% SVR in genotype 1 patients versus 33% for interferon alfa-2b plus ribavirin. See Lancet. 2001 Sep 22;358(9286):958-65.

[42] Source: CDC. A pooling of UK evidence has demonstrated that needle exchange programme and methadone treatment can cut the spread of HCV in injecting drug user populations. See Addiction. 2011 Nov;106(11):1978-88. Epub 2011 Aug 24.

[43] See Clin Infect Dis. 2011 Jul 15;53(2):150-7. Epub 2011 Jun 10.

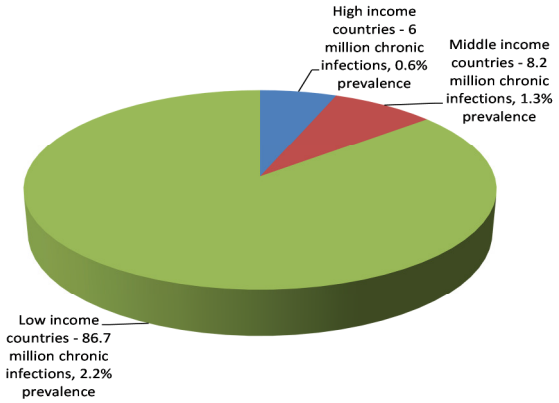
represents an extraordinary market opportunity. As we note below, that patient population has already created a US$3bn market for interferon and ribavirin, and we think the market can expand to US$10bn as new drugs, potentially including Biotron's come on the market over the next decade.

Figure 5 - Around 6-7 million chronically infected Hepatitis C patients live in rich countries

Country	% of population chronically infected	Patient numbers (million)
United States	0.8%	2.65
Japan	1.1%	1.37
Korea, South	0.8%	0.39
France	0.5%	0.34
Poland	0.7%	0.25
Saudi Arabia	0.8%	0.22
Spain	0.3%	0.15
Italy	0.2%	0.14
Greece	0.7%	0.08
Belgium	0.4%	0.04

SOURCE: BELL POTTER SECURITIES

Figure 6 - Around 1.8% of the world's population is chronically infected with HCV



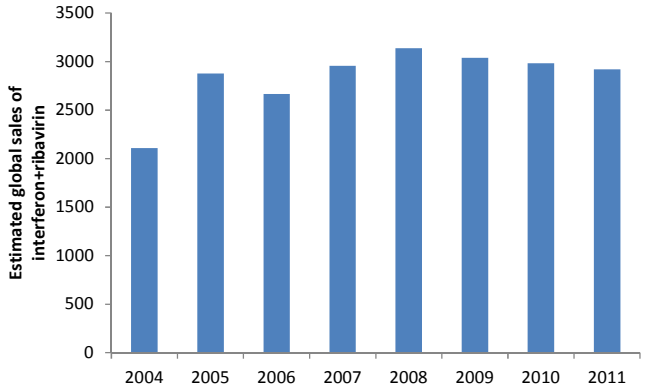
SOURCE: BELL POTTER SECURITIES

Interferon and ribavirin are a US$3bn market

Interferon and ribavirin have created the market

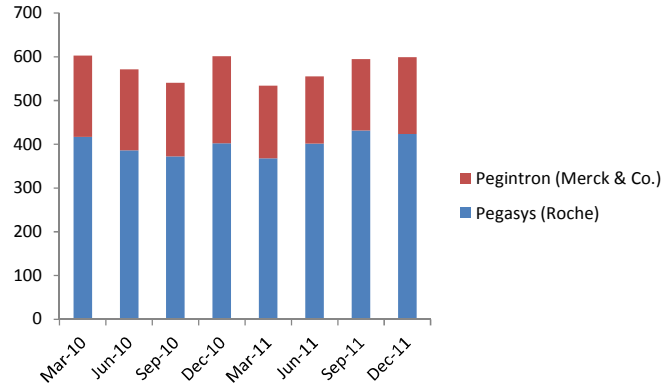
A US$3bn a year market, dominated by two companies. The US$3bn market for interferon and ribavirin is a dependable source of revenue for just two companies, Roche and Merck & Co.

Figure 7 – Interferon and ribavirin are a ~US$3bn global market



SOURCE: : MERCK/SCHERING-PLOUGH, ROCHE, BELL POTTER SECURITIES

Figure 8 – The introduction of the protease inhibitors has turned around declining interferon sales



SOURCE: MERCK & CO., ROCHE

- *Roche has the leading franchise in the area* with Pegasys, which is pegylated interferon alpha-2a[44], and Copegus, which is its ribavirin product. Roche has around 70% of the market primarily because of more favourable pricing and a pre-filled pen delivery option. Pegasys alone is Roche's fifth largest selling drug with around US$1.6bn in global sales in 2011.
- *Merck & Co. inherited its No 2 franchise* with the 2009 acquisition of Schering-Plough. It sells Pegintron, which is pegylated interferon alpha-2b[45], and Rebetol-brand ribavirin[46].

[44] See www.pegasys.com. Roche gained FDA approval for the use of standard interferon alpha 2a in 1996 while the pegylated product gained approval in 2002.

[45] See www.pegintron.com. The drug delivery company Flamel Technologies (Lyon, France, Nasdaq: FLML, www.flamel.com), whose Medusa technology uses poly-aminoacid nanoparticles as protein carriers to extend the half-life of drugs, has reformulated interferon alpha-2b using this technology and demonstrated, in a Phase IIa trial, better efficacy in terms of viral load than the standard-of-care in genotype 1 patients. Source: See Flamel press release, 25/10/2007.

Interferon and ribavirin have poor efficacy

The interferon/ribavirin standard of care is inadequate. This US$3bn market may be dependable but it exists largely for want of anything better:

- *The drugs come with a multitude of side effects*, most notably flu-like symptoms, mental problems[47] and lowered white blood cell count[48], with adverse events typically causing around 40% of patients to have their doses lowered and 6% of patients discontinuing treatment[49] - most of these side effect are understood to come from the interferon[50];
- *They are not-so-hot in terms of efficacy*. For example, the most favourable clinical data suggests that only around half of patients infected with the genotype 1 of the virus, which as we noted above is most US patients, will be cured by 48 weeks of interferon/ribavirin, 'cure' being SVR24, that is, a 'Sustained Virological Response' so that virus is undetectable at 24 weeks after cessation of therapy[51].
- *They don't act directly on the virus*. Interferon doesn't attack HCV directly but mediates an innate immune response to the virus[52], while ribavirin seems to potentiate interferon but by a still-unknown mechanism of action[53] and doesn't work well on its own[54].
- *Interferon is injected*, which may be a negative in terms of patient compliance.[55]

A large established market in the absence of an adequate therapy has driven Big Pharma's search for new HCV drugs for some years now, and as the table above headlined 'Recent deals in the anti-HCV drug space' will have indicated, the pharma companies have been offering generous partnerships to drug developers with compounds that potentially could take HCV therapy into the next generation. What has now raised the stakes has been the clinical and commercial success since last year of the first of these drugs, the protease inhibitors.

The HCV protease inhibitors have begun to enlarge the market

In May 2011 the FDA approved, after only a short waiting period, two breakthrough drugs for the treatment of HCV infection - Victrelis[56], from Merck & Co[57], and Incivek[58], from the American biotech company Vertex[59]. These were the first new drug approvals for Hepatitis C in 20 years[60]. Both drugs are inhibitors of HCV protease, the enzyme which the virus uses to assemble itself. Victrelis and Incivek are game-changing in HCV because they represent a significant improvement over the existing standard of care and have begun the process of enlarging the HCV drug market.

[46] Schering-Plough gained FDA approval for the interferon/ribavirin combination in 1998. It had licensed the intellectual property for the combination from the California-based ICN Pharmaceuticals, a precursor company to Valeant Pharmaceuticals. Previously Schering had gained FDA approval for the use of interferon-alpha-2b in treating Hepatitis C in 1991. Schering gained FDA approval of Pegintron, the first pegylated interferon, in 2001.

[47] See Antivir Ther. 2010;15(4):599-606. The investigators in a Phase III trial for Merck & Co's Victrelis noted that 'Two suicides…were judged to have possibly been related to peginterferon' - see Poordad et. al., N Engl J Med. 2011 Mar 31;364(13):1195-206).

[48] See Hepatology. 2002 Nov;36(5):1273-9.

[49] Derived from Lancet. 2001 Sep 22;358(9286):958-65 and N Engl J Med. 2002 Sep 26;347(13):975-82. Note, it may be possible to lower doses simply by using therapeutic filtration devices to remove circulating HCV. A San Diego-based company called Aethlon Medical (OTCBB: AEMD, www.aethlonmedical.com) has demonstrated this possibility in recent clinical work – see the company's 1/2/2012 press release headlined *'Aethlon Medical reports Immediate and Rapid Virologic Responses in Hepatitis C patients receiving Hemopurifier treatment protocol'*.

[50] See J Hepatol. 1996 Sep;25(3):283-91.

[51] In other words, you know 18 months after the start of therapy that it has worked. Fried et. al., studying pegylated interferon plus ribavirin in HCV patients, found a 46% sustained virologic response rate at 24 weeks after cessation of therapy for genotype 1 patients. See N Engl J Med. 2002 Sep 26;347(13):975-82. Schalm et. al. (Gastroenterology. 1999 Aug;117(2):408-13) found only 33% SVR24 for genotype 1. Of the two types of genotype 1, that is, genotype 1a and genotype 1b, Legrand-Abravanel found an SVR24 of 39% for 1b and only 30.6% for 1a (see J Med Virol. 2010 Sep;82(9):1627).

[52] See Nature. 2005 Aug 18;436(7053):967-72. Interferon stimulates a variety of different genes to produce antiviral compounds and to boost the host immune response against the virus. There are approximately 500 genes that are switched on by interferon, not all of them fully understood (See J Interferon Cytokine Res. 2011 Jan;31(1):1-4).

[53] See Hepatology. 2011 Jan;53(1):32-41.

[54] See Cochrane Database Syst Rev. 2009 Oct 7;(4):CD005527.

[55] Ribavirin is orally available, but it gets missed more often that Interferon – one US study found that 7% of patients missed at least one injection of interferon in the last 4 weeks and 21% reported missing at least one dose of ribavirin in the last 7 days. See Aliment Pharmacol Ther. 2008 Aug 1;28(3):289-93.

[56] Generic name boceprevir, see www.victrelis.com.

[57] A compound acquired when Merck merged with Schering-Plough in 2009.

[58] Generic name telaprevir, see www.incivek.com. Telaprevir is marketed in Europe by the J&J unit Jansen as Incivo while Mitsubishi Tanabe markets the drug in Japan as Telavic. Telaprevir gained European and Japanese approval in September 2011. Telaprevir is marketed in the US by Vertex.

[59] Nasdaq: VRTX, Cambridge, Ma, www.vrtx.com. As at 16 April 2012 Vertex was capitalised on Nasdaq at US$7.5bn. The company's early days, before it started work on what became Incivek, is the subject of Berry Werth's book *The Billion Dollar Molecule: One Company's Quest for the Perfect Drug* (New York: Simon & Schuster, 1995).

[60] The last one being Schering-Plough's approval for interferon alpha 2b in 1991.

The better-targeted protease inhibitors point to a higher cure rate, achieved more quickly. By contrast with interferon/ribavirin, the protease inhibitors perform much better. In Victrelis' SPRINT-2 trial the addition of the Merck & Co. drug to interferon/ribavirin was able to raise the SVR24 in treatment-naïve genotype 1 patients from 38% to 66%[61]. In a similar setting Incivek performed even better, raising SVR24 in the drug's ADVANCE trial from 44% to 75%[62]. Moreover in each case treatment response is swifter. The recommended treatment duration for interferon and ribavirin is only 24 weeks if the patient has undetectable virus after 12 weeks of Incivek. This means that treatment times compared to interferon/ribavirin alone can be cut in half[63]. For Victrelis the comparable figures are 28 weeks after undetectable virus at 8 weeks[64].

The protease inhibitors are the first of the Direct Acting Antiviral agents. The higher level of effectiveness of the new drugs has a lot to do with their specificity. Unlike interferon and ribavirin, the protease inhibitors are 'Direct Acting Antiviral' agents (DAAs) that act on HCV's NS3/4A protein. The developers of Victrelis and Incivek benefited from the large increases in knowledge in the 1990s and 2000s related to the biological functions, biochemistry, and three-dimensional structures of the main HCV proteins.

Vertex is the bellwether for the future of new generation HCV treatments. The commercial success of Incivek provides confirmation for us of strong demand for new-generation HCV drugs, with potential benefits for Biotron once further clinical data emerges:

- *Incivek is a premium drug*, with the US price tag of ~US$49,000 for a 12-week course[65], comparing favourable with the standard US$30,000 for 48 weeks of interferon and ribavirin[66], but also being justified in part by the much better patient outcomes[67]. This bodes well for pricing of other next-generation drugs[68].

Incivek will be one of the fastest blockbusters in history

- *Incivek will be one of the fastest blockbusters in history.* With the market preferring this drug's more favourable cure rate, swifter treatment duration and lower side effect profile when compared with Victrelis[69], Incivek has been so popular it has been one of the strongest drug launches in history. It generated a massive US$420m in net product revenue for Vertex in the three months to September 2011, its first full quarter on the market, and US$457m in the December 2011 quarter. The drug is widely expected to be one of the few in history to enjoy blockbuster sales in its first year[70].
- *Vertex is a ~US$7.5bn company today* thanks to Incivek. Part of this capitalisation is due to a pipeline of opportunities in cystic fibrosis, epilepsy and influenza. However we also think the market is capitalising a promising future for Incivek, with peak sales >US$5bn generally expected[71] in the light of the large global market opportunity. We note below that large market expectations can justify the sort of capitalisations enjoyed by Vertex today and the take-out value of Pharmasset late last year.

[61] See Poordad et. al., op. cit.

[62] See Jacobson et. al., N Engl J Med. 2011 Jun 23;364(25):2405-16.

[63] Source: Incivek Prescribing Information, Table 1.

[64] Source: Victrelis Prescribing Information, Table 1.

[65] See *'Vertex, Merck face little payer pushback with newly marketed HCV drugs*' by Christine Livoti, Financial Times, 2/9/2011.

[66] See Virology Journal 2012, 9:57. Unpegylated interferon plus ribavirin is around US$10,000 cheaper.

[67] Source: Medivir Capital Markets Day presentation, 15/11/2011, slide 44.

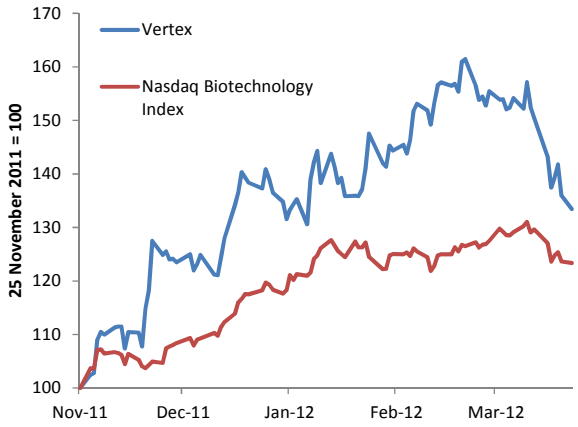
[68] Victrelis is cheaper than Incivek, at just US$13,000 for 12 weeks, but that's still a premium to interferon/ribavirin. Stanford researchers studying Victrelis found that drug to be cost effective (ie cost per QALY < US$100,000) with interferon and ribavirin across all patient genotypes (see Ann Intern Med. 2012 Feb 21;156(4):279-90.). In March 2012 Victrelis gained a favourable healthcare economics assessment from the National Institute of Clinical Excellence in the UK. NICE's report, headlined *'Final appraisal determination: Boceprevir for the treatment of genotype 1 chronic hepatitis C'*, is available at www.nice.org.uk.

[69] In SPRINT-2, 21% of Victrelis-treated patients suffered anemia that required a dose reduction, compared to 13% of the controls.

[70] Only Celebrex and Vioxx, the COX-2 inhibitor anti-inflammatory drugs (in 1999/2000), and the cholesterol-lowering drug Lipitor (in 1997/1998), have previously achieved this.

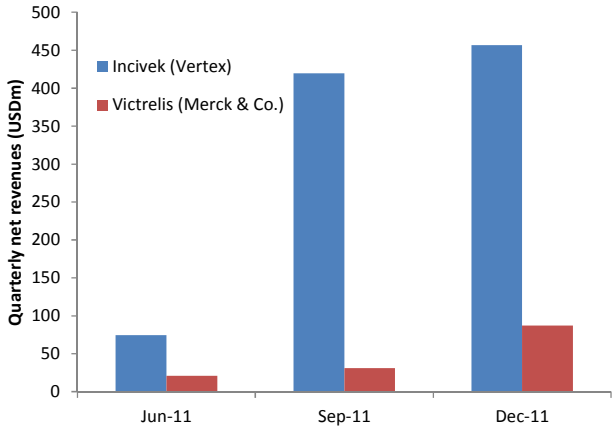
[71] See, for example, *FDA approves mega-blockbuster Vertex hep C drug Incivek* by John Carroll, Fierce Biotech, 23/5/2011.

Figure 9 – The market has welcomed Incivek's early sales success although it is concerned about its sustainability



SOURCE: NASDAQ

Figure 10 – Vertex finally has its Billion Dollar Molecule



SOURCE: VERTEX, MERCK & CO.

The new protease inhibitors are not without their issues, namely, potential for resistance, side effects, pill burden and cost:

- The protease inhibitors can't be used on their own for the treatment of HCV, since this would quickly engender drug resistance[72]. Other drugs such as interferon/ribavirin, or HCV polymerase inhibitors, or, indeed, BIT225, are needed to limit this.
- In the ADVANCE and SPRINT-2 trials the dropout rates for adverse events and for patient choice were a massive 33% and 19% respectively[73]. Partly driving these dropout decisions were the incidence of anaemia (both drugs), rash (Incivek), and dysgeusia (that is, altered sense of taste - Victrelis). More recently, in February 2012 the FDA ordered label changes for statin drugs related to the risk of muscle injury when HCV protease inhibitors are co-administered with statins. Given all these issues we understand that a lot of clinicians are talking about 'warehousing' their patients until the next generation of better tolerated drugs are available.

Patients on Incivek need to take six pills a day

- Both Incivek and Victrelis come with a big pill burden (6 a day and 12 a day respectively[74]), which may present compliance issues;

There are multiple large companies going after HCV

As scientific understanding of HCV grew in the 1990s and 2000s, various companies much larger than Vertex were able to initiate HCV drug development programmes, mostly DAAs targeted at

- NS3 and NS4a, which as we noted above are HCV protease proteins; or
- NS5a and NS5b, which are HCV polymerases, used by HCV to copy its RNA, and can be blocked with either nucleoside or non-nucleoside inhibitors similar to those used in HIV[75].

These programmes are now becoming valuable for their developers since:

- Incivek and Victrelis have the drawbacks we noted above, in spite of their large current sales, so the demand for newer and better HCV drugs remains;
- Many of the new drug candidates are generating competitive clinical data in genotype 1 patients when combined with interferon/ribavirin.

[72] This is due to HCV's high genetic heterogeneity and its rapid replication (see Gastroenterology. 2010 Feb;138(2):447-62. Epub 2009 Dec 16). Viruses like this become drug resistance unless hit more than one way at once.

[73] Calculated from Jacobson et al. and Poordad et. al., op. cit.

[74] Source, prescribing information.

[75] Nucleosides are the individual pieces of RNA in the virus. Nucleoside analogs, by being different from the real nucleotide sequences in HCV, disrupt copying of viral polymerase. Non-nucleoside inhibitors stop this copying by binding to viral polymerase.

Drug resistant HCV will be an issue going forward

- HCV is likely to be an area in which the virus gradually becomes resistant to the drugs[76].

Basically everyone with a new HCV drug is racing to be the first to have an all-oral DAA combo approved, although for the time being synergy with interferon/ribavirin is important. Gilead expects to be first to the market in 2014/2015 with a GS-7977-based combo, but there's a long road ahead for that company, as unfavourable data from February 2012, which we discuss further below, has demonstrated. This means that demand remains vigorous for earlier-stage drugs that will give a particular treatment regimen competitive advantage in terms of high cure rates, shorter treatment times and lower side effects. We see Biotron as well placed to benefit from this demand.

Bristol-Myers Squibb is trialling daclatasvir, an NS5a polymerase inhibitor, and INX-189, an NS5b inhibitor. BMS's main HCV drug in development until recently has been daclatasvir. INX-189 was the main reason that BMS acquired Inhibitex for US$2.5bn[77].

- Interim Phase IIb data from the COMMAND-1 study, presented in November 2011[78], saw daclatasvir plus interferon/ribavirin generate an 'extended Rapid Virologic Response' or eRVR[79] - in 75-78% of treatment naïve genotype-1 patients versus 43% in the control group. BMS has recently taken daclatasvir into Phase III trials with interferon/ribavirin. The company is also working on combinations of daclatasvir with TMC435, an NS3 protease inhibitor from J&J[80], and daclatasvir with the abovementioned Pharmasset drug PSI-7977[81].
- Inhibitex initiated a Phase II trial of INX-189 in genotype 2 and 3 patients with interferon and ribavirin in September 2011. For genotype 1 patients Inhibitex reported in November 2011 that once-daily dosing for seven days of 100 mg INX-189 with ribavirin but without interferon brought about a median 3.79 log reduction in viral load. INX-189 was granted Fast Track designation in February 2011.

Gilead/Pharmasset is trialling GS-7977, a nucleotide polymerase inhibitor, as well as numerous other drugs.

- GS-7977 is the new name for the old PSI-7977 drug from Pharmasset. In September 2011 Pharmasset reported very encouraging Phase IIb data from its PROTON study, where PSI-7977 was combined for 12 weeks with interferon/ribavirin in genotype 1 patients. The SVR12 – that is, a 'Sustained Virological Response' so that virus is undetectable at 12 weeks post cessation of therapy – was 91%[82].
- Gilead is also in Phase II with Tegobuvir, a non-nucleoside NS5B inhibitor; GS-9256, an NS3 protease inhibitor, GS-9451, another NS3 protease inhibitor, and GS-5885, an NS5A inhibitor.

Vertex is in Phase II with its Next Big Thing in HCV

Vertex is trialling VX-222, a non-nucleoside inhibitor of NS5b. Interim Phase IIb data from the ZENITH study, reported in July 2011, showed VX-222, in combination with Incivek, interferon and ribavirin, generated undetectable virus after 12 or 24 weeks of treatment in 90% of patients[83].

[76] See Hepatology. 2009 Apr;49(4):1069-82. Incivek resistance has already been identified. See Hepatology. 2011 Sep 2;54(3):781-8. Epub 2011 Aug 2.

[77] Inhibitex also brings FV-100, a nucleoside analogue to herpes zoster (the virus which causes shingles); Aurexis, a monoclonal antibody to a protein expressed by *S. Aureus*; and an *S. Aureus* vaccine which has been partnered with Pfizer.

[78] At the American Association for the Study of Liver Diseases (AASLD) 2011 Liver Meeting in San Francisco. AASLD is the premier US meeting for scientists working on Hepatitis C. See BMS's press release of 8/11/2011.

[79] That is, undetectable virus at 4 and 12 weeks after the commencement of treatment. See Appendix II for an explanation of eRVR's significance.

[80] BMS and the J&J unit Janssen/Tibotec agreed in December 2011 to start a Phase II of this combination in 2012.

[81] Collaboration announced January 2011.

[82] Note, all patients stayed on interferon and ribavirin for 24 weeks. Source: Pharmasset press release from 6/9/2011 headlined *'Pharmasset Announces 91% SVR12 From the PROTON Trial in Subjects With Hepatitis C Genotype 1*'.

[83] In this trial people who responded well to the drugs were eligible to stop at week 12, while others had to go to week 24. Source: Vertex press release of 26/7/2011 headlined '*Interim Data from Phase 2 Study of Combination Regimen Including VX-222 and INCIVEK Suggest Potential to Treat Genotype 1 Hepatitis C in as few as 12 Weeks and No More Than 24 Weeks'*. Vertex also has ALS-2200 (a nucleotide analogue programme) and ALS2158 (a nucleoside analogue programme) in Phase I.

Boehringer Ingelheim is trialling BI-201335, a protease inhibitor. Data from the SILEN-C3 study, presented in November 2011, showed BI-201335 plus interferon/ribavirin generating an SVR of 82% if they experienced an eRVR with the drug[84].

Novartis is trialling alisporivir, a cyclophilin inhibitor. Cyclophilin is a cellular protein that HCV uses in viral replication, so while alisporivir isn't a direct acting agent it does have promise in terms of avoiding viral resistance. In March 2011 Novartis reported that Alisporivir plus interferon/ribavirin generated a 76% SVR24 in a Phase II study[85].

Roche is trialling Mericitabine and Setrobuvir, both NS5B polymerase inhibitors[86]:

- Mericitabine, which Roche sourced from Pharmasset under a 2004 partnering deal, generated a 76% SVR12 in a Phase II trial combination with interferon/ribavirin where those patients had an eRVR[87]. Under a May 2011 strategic agreement with Merck & Co. a Phase II trial has started to evaluate Mericitabine's effectiveness with Victrelis as well as interferon/ribavirin.
- Setrobuvir plus interferon/ribavirin generated, in an interim Phase IIb analysis, a 78% 'complete Early Virological Response' or cEVR[88], versus 56% for interferon/ribavirin alone[89].

Abbott has obtained very high SVRs from its HCV drugs

Abbott Laboratories is trialling ABT-450 (a protease inhibitor), ABT-333 (a polymerase inhibitor) and ABT-072 (another polymerase inhibitor). These drugs were taken into Phase II trials in 2010. In April 2011 Abbott reported a cEVR of 92% in one of the studies, which combined ABT450 with Abbott's HIV protease inhibitor drug Norvir, generic name ritonavir[90]. In April 2012 Abbott reported that the combination of ABT-450/ABT-333 and ribavirin had generated an SVR12 of 93-95% in genotype 1, while ABT-450/ABT-072/ribavirin produced a 91% SVR24 in genotype 1[91].

Figure 11 - Some big companies are going after the new HCV marketplace

Company	Position in latest Pharm Exec 50[92]	2011 global sales (USDbn)	Current market cap (USDbn)[93]	Main HCV products
Novartis	2	58.6	132.8	Alisporivir
Merck & Co.	4	48.0	115.5	Victrelis, MK-5172
Roche	5	48.0	151.2	Mercitabine, Setrobuvir
J&J	8	65.0	175.6	TMC435
Abbott Laboratories	10	38.9	94.1	ABT-450, ABT-333, ABT-072
Bristol-Myers Squibb	11	21.2	55.6	Daclatasvir
Boehringer Ingelheim[94]	16	14.1		BI-201335
Gilead Sciences	22	8.1	34.7	PSI-7977

SOURCE: PHARMACEUTICAL EXECUTIVE, COMPANY DATA

[84] Presentation at AASLD 2011 – see the Boehringer Ingelheim press release dated 8/11/2011. Note, it's not clear from the presentation material whether the SVR was an SVR12 or SVR24.

[85] Alisporivir was in-licensed from the privately held Swiss drug company Debiopharm in February 2010. For the Genotype 1 Phase II data see the Novartis press release of 31/3/2011.

[86] Roche is also in Phase I on RG7432, a nucleoside polymerase inhibitor, and from Anadys inherited ANA773, a TLR agonist which has also gained favourable Phase I data.

[87] The JUMP-C trial, for which results were reported the April 2011 annual meeting of the European Association for the Study of the Liver.

[88] That is, undetectable virus at week 12 (but not at week 4). See Appendix II for an explanation of cRVR.

[89] Source: Anadys press release dated 13/10/2011 and headlined *'Anadys Announces Positive 12-Week Data for Setrobuvir in Phase 2b Hepatitis C Study'*.

[90] See the Abbott press release dated 4/4/2011 and headlined *'Abbott and Enanta Present Positive 12-Week Results and 3-Day Resistance Data from Phase 2 Study of ABT-450/r for Treatment of Hepatitis C'*.

[91] See the Abbott press releases dated 4/4/2012 and headlined *'Abbott to Present Positive Phase 2 Results from Multiple Interferon-Free Studies of Combination Regimens for the Treatment of Hepatitis C'*.

[92] The standard list of the 50 largest pharma companies in the world, published annually by Pharmaceutical Executive magazine.

[93] As at 16 April on NYSE and elsewhere.

[94] Note, privately held, sales number represents estimate.

Interferon-free treatment that will truly enlarge the market is coming

We believe HCV can be a US$10bn market with interferon-free therapies

Victrelis and Incivek have demonstrated that there are better therapeutic alternatives for HCV that are orally available, however these drugs are currently only approved for use with interferon/ribavirin. Consequently a big theme in HCV drug development over the next few years will be the development of all-oral, interferon-free treatment regimens. We expect that the interferon-free regimens will provide a serious expansion in global market size out to US$10-15bn due to further progress on cure rates, lower rates of adverse events, and ease of delivery. Given that BIT225 is orally available we see it benefiting from the interferon-free trend.

Bristol-Myers Squibb has demonstrated that an interferon-free drug combo can overcome HCV drug resistance. In January 2012 the New England Journal of Medicine published data showing that a combination of the BMS's abovementioned daclatasvir drug and another BMS-developed NS3 protease inhibitor called asunaprevir could cure some patients (4/11 = 36%) who have been interferon/ribavirin 'null responders', that is, who had failed previous treatment. This work was the first HCV clinical trial to demonstrate an SVR48 without the use of interferon[95].

Gilead/Pharmasset has demonstrated that an interferon-free drug combo can cure genotypes 2 and 3. Part of the reason why Gilead was motivated to pay US$11bn for Pharmasset was the data which the company had generated on a combination of PSI-7977 and ribavirin alone.

- In the ELECTRON Phase II study in genotype 2 and 3 patients, this combination dosed for 12 weeks, produced a 100% SVR 12 week after treatment. PSI-7977 is now in Phase III without interferon for genotypes 2 and 3
- A genotype 1 pivotal for GS-7977 will start in 2012. However GS-7977 is not without its problems – in February 2012 Gilead announced that a cohort of genotype 1 patients on GS-7977 plus ribavirin who had previously failed on interferon/ribavirin relapsed within four weeks of completing the twelve weeks of GS-7977/ribavirin treatment. What this suggested was that more drugs will have to be added to this combination for this kind of patient[96].

Various companies want their drugs to be the basis of an interferon-free standard of care:

- **Vertex with Incivek.** The abovementioned ZENITH study of VX-222 currently includes treatment arms looking at the combination of that drug plus Incivek and ribavirin but without interferon. End-of-treatment data is expected in early 2012.
- **Boehringer Ingelheim with BI-201335.** Interim Phase IIb data from the SOUND-C2 study, presented in November 2011, showed that BI-201335 plus another Boehringer Ingelheim drug, a polymerase inhibitor called BI-207127, and ribavirin could generate an SVR12 of 59% after 16 weeks of treatment[97].

Multiple companies are working on interferon-free HCV therapies

- **Novartis with alisporivir**. Interim Phase II data from Novartis' VITAL-1 study showed alisporivir plus ribavirin without interferon achieving undetectable virus by week 6 in 49% of genotype 2 and 3 patients[98].
- **Roche with danoprevir**. Roche bought Danoprevir, an NS3/4A protease inhibitor, from the specialty pharma company Intermune[99] in October 2010 for US$175m. The drug is now in Phase I in combination with ritonavir and ribavirin.

[95] See N Engl J Med. 2012 Jan 19;366(3):216-24.

[96] Source: Gilead press release from 17/2/2012 headlined '*Gilead Announces Data for Genotype 1 Null Responder Hepatitis C Patients Enrolled in ELECTRON Study*'.

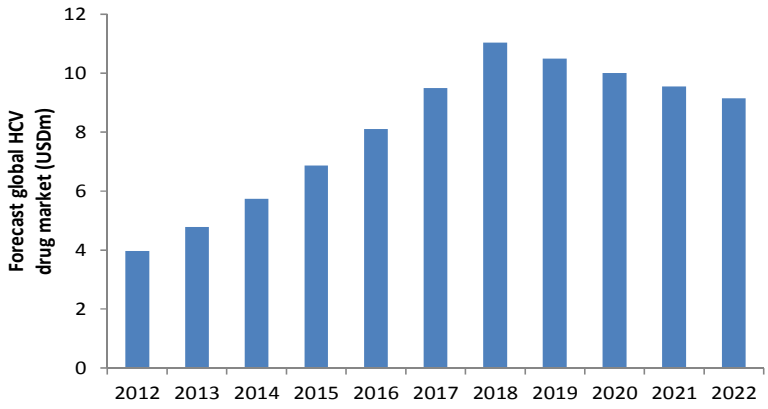
[97] Source: Boehringer Ingelheim press release dated 7/11/2011. This data was also presented at AASLD 2011.

[98] Data presented at AASLD 2011. Source: Novartis press release dated 5/11/2011 and headlined '*Novartis DEB025 data showed viral clearance as early as six weeks and potential for interferon-free therapy in hepatitis C patients*'.

- **Merck & Co. with MK-5172**. MK-5172, an NS3/4a protease inhibitor, is now in Phase II with interferon/ribavirin but Merck expects it can be part of an interferon-free regimen for HCV[100].

In our view the high-priced Anadys, Pharmasset, Inhibitex and Enanta deals we noted above basically represent the scramble by the buyers to gain HCV polymerase inhibitors that will anchor their new anti-HCV drug combinations. We argue that after the initial fight for polymerase inhibitors the search will begin for new drug classes, which potentially can include Biotron's new class of p7 inhibitor.

Figure 12 - We assume that the global HCV drug market can grow to US$11bn by 2018



SOURCE: BELL POTTER SECURITIES

With interferon-free regimens it wouldn't be hard for a US$3-4bn market to become a US$11bn market with new generation HCV therapies. We see three drivers of this expansion:

We expect the new drugs will result in more patients being treated

- *More patients for the newer drugs* – The new generation HCV drug regimes could potentially double patient numbers from present levels in advanced healthcare systems, given the higher cure rates. This alone would create a US$6bn market;
- *Higher pricing for the newer drugs* – As we have seen with Incivek, the better healthcare economics of the newer drugs will allow better pricing than prevails for interferon and ribavirin – in Incivek's case it is >60%. Allow 30% price expansion makes a US$6bn market a US$7.8bn market;
- *More patients for the older drugs* – As demand for interferon drops in major markets, we expect that lower prices may allow increased usage by emerging healthcare systems, such as, for example, Egypt with its ~8 million people chronically infected. Consequently we expect interferon and ribavirin to remain a US$3bn market into the foreseeable future. This would make the entire market worth ~US$11bn.

Economics suggests big returns for the healthcare system from the new drugs even at higher prices and drug usage. We modelled a situation in which US managed health enrollees in the early-to-mid-2000s[101] switched from interferon/ribavirin therapy to interferon-free therapy at three times the price but with a 90% cure rate that markedly lowered subsequent hospital and ambulatory care costs[102]. A healthcare inflation rate of

[99] Brisbane, Ca, Nasdaq: ITMN, www.intermune.com. InterMune's lead product is Pirfenidone, a drug for the treatment of idiopathic pulmonary fibrosis which is approved in Europe and is in Phase III in the US. Danoprevir was discovered through a collaboration between 2002 and 2007 with the drug discovery company Array Biopharma (Boulder, Co., Nasdaq: ARRY, www.arraybiopharma.com), which will ultimately receive royalties from danoprevir sales.

[100] See Merck press release from 10/11/2011 headlined *'Merck highlights pipeline progress and showcases novel innovations at R&D and business briefing'*.

[101] Original numbers for 2002-2006 period and measuring 21,662 patients obtained from J Clin Gastroenterol. 2011 Feb;45(2):e17-24

[102] We assumed that that insurers saved 80% of the extra costs incurred over HCV-negative enrollees as a result of higher cure rates.

6% pa, a discount rate of 11% and a 20-year treatment window suggested that the discounted cost of treating HCV patients with interferon/ribavirin was around US$273,000. The switch to interferon-free lowered this discounted cost by 45% to US$151,000. In other words an HCV market three times bigger more than pays for itself over the long-term.

The potential for market expansion makes sense of the Pharmasset and Inhibitex deals. While some commentators have questioned the size of the Pharmasset and Inhibitex transactions[103], a >US$10bn market for interferon-free HCV therapies can justify such a transaction. We argue that the price tags are reasonable. In order to get a seven-year pre-tax payback on an US$11bn investment, an HCV drug or suite of drugs would only have to earn roughly US$2.5bn pa in revenue, since gross margins are likely to be high (ie 80%) and distribution costs low (ie US$400-500m globally) in an environment where the sales force would target only gastroenterologists. We expect that the HCV drug market will peak at around US$11bn in 2018 and then decline in line with lower HCV prevalence.

The Hepatitis C problem will be with us for a while yet

Earlier in this note we put forward a lower estimate of global HCV patient numbers than the 170 million figure often quoted, thanks to progressively lower rates of incidence over time and higher-than-population-average death for people with HCV infection. In spite of this we argue that a large patient pool will remain in most countries for many years to come, even with newer, highly effective drugs coming through:

- *Many patients do not know they are infected.* US researchers evaluating NHANES data[104] found that around half of all people found to be HCV-positive by the surveyors did not previously know that they were infected[105]. Patients ignorant of their disease can't seek treatment but can spread it to others.
- *Even if patients know they are infected, not many are being treated.* One 2009 study has demonstrated that less than 3% of the estimated US patient population are being treated with antiviral therapy, and that treatment rates declined by around a third between 2002 and 2007. Partly this relates to lack of diagnosis but in many cases it relates to lack of follow-up[106].
- *New infections still outweigh liver-related deaths*. Around 12,000-15,000 Americans die each year from chronic liver diseases associated with HCV[107] but around 15,000-20,000 are newly infected[108]. Driving this growth is young people, with those aged 20-29 registering the highest incidence of acute Hepatitis C in 2009[109] and incidence apparently growing for those aged 15-34 over the period 2003-2008[110].
- *Injecting drug users provide a hard-to-reach viral 'reservoir'*. While the blood supply in most countries can be considered HCV-safe due to screening methodologies put in place 20 years ago, HCV continues to be transmitted through dirty needle sharing by injecting drug users. One recent analysis of the data on HCV epidemiology has suggested that around 10 million injecting drug users worldwide may be infected with HCV, with prevalence rates of 60-80% across a wide range of countries[111]. Data from

In the interferon/ribavirin era US treatment rates were declining

[103] See, for example, *Gilead bets $11 billion on hepatitis in Pharmasset* deal by Lewis Krauskopf and Anand Basu, Reuters, 21/11/2011, where one analyst described the Pharmasset acquisition as 'high risk' for Gilead.

[104] The National Health and Nutrition Examination Survey, an initiative of the CDC that has been keeping survey statistics on health and nutrition since the early 1970s.

[105] Others have suggested ignorance rates as high as 75% - See AASLD, *HBV & HCV: America's Hidden Epidemics*, September 2010.

[106] In 2007 an estimated 83,000 people were receiving antiviral therapy for Hepatitis C. That represent only about 3% of the estimated patient population of 2-3 million we noted above. See Hepatology. 2009 Dec;50(6):1750-5.

[107] Source: CDC Viral Hepatitis Surveillance data. By 2007 deaths from Hepatitis C had superseded deaths from HIV in the United States. See Ann Intern Med. 2012 Feb 21;156(4):271-8.

[108] Source: CDC estimate. The recent fall has largely been due to clean needle-exchange programmes.

[109] 0.7 cases per 100,000 population in 2009 – source: CDC surveillance data.

[110] See Boktor et. al., poster at the International Conference on Emerging Infectious Diseases entitled *'Increasing rates of Hepatitis C past or present infection reports among adolescents and young adults in Pennsylvania'*, March 2012.

[111] See Nelson et. al., Lancet. 2011 Aug 13;378(9791):571-83. Epub 2011 Jul 27.

around a decade ago in the US found that around half of all people found to have been infected with HCV reported a history of injection drug use[112]. Globally, ~90% of new Hepatitis C infections are attributed to injection drug use[113]. Regrettably, the rate of regular injecting drug use in the population seems to be stable in the US rather than declining[114].

- *Prison populations have high HCV prevalence*. In the US anywhere between 12% and 31% of prisoners are HCV-positive[115], which, with 1.6 million people in the state and federal prison systems in 2010 (representing 0.5% of the total US population) represents a second large viral reservoir due to historic growth in numbers of people incarcerated, and under-testing for the virus[116]. One recent Australian study has found a risk of HCV infection in prison of 34 per 100 person years[117].

HCV has been a Baby Boomer disease

- *There are still large numbers of 'pre-1989' HCV-positive people***.** In 2008 peak prevalence for Hepatitis C in the US was observed among persons 40 to 49 years of age[118], where 3.5% of people had been exposed to the virus versus 1.3% for the population as a whole. That represented around 1.5 million people, most of these people will have been infected with HCV because of blood transfusions prior to the 1990s rather than lifestyle factors. As this cohort ages diagnosis rates will likely increase through increased interactions with the healthcare system.
- *There is emerging evidence of HCV being sexually transmitted*. Even though sexual activity is not thought to 'efficiently' transfer HCV, that hasn't stopped HCV being sexually transmitted[119]. One of the largest and most complete cohorts of HIV patients in the world is tracked by the Swiss HIV Cohort Study. That study's investigators have found an 18-fold increase in HCV incidence in HIV-positive homosexual men between 1998 and 2011 unrelated to injection drug use[120].
- *Many lower-income countries may not know the extent of their HCV problem*. A good example is provided by Egypt, a country of 83.7 million people whose 2008 Demographic and Health Survey estimated that 9.8% of the population aged 15-59 was chronically infected[121], the largest prevalence in the world. One recent study has suggested that there are 500,000 new infections annually[122], but the government thinks the figure is more like 100,000[123]. Other low-income countries with high HCV prevalence such as Vietnam, Indonesia, Pakistan[124], Bangladesh, Thailand and the Philippines, which we estimate between them have 18 million people chronically infected with HCV, may represent an international viral reservoir than can continue to 'export' HCV to more advanced countries.

[112] See Armstrong et. al., op. cit.

[113] See Clin Infect Dis. 2009 Aug 15;49(4):561-73.

[114] Consider that around 0.1% of the US population over 12 are regular heroin users. This 0.1% estimate did not change between 2002 and 2010 - see Table 7.3 of the 2010 National Survey on Drug Use and Health from the Substance Abuse and Mental Health Services Administration. In 2009 0.1% represented around 260,000 people in the US. That number could easily fuel the estimated 16,000 new infections the CDC estimates occurred in 2009.

[115] Hepatology. 2008 Nov;48(5):1387-95.

[116] In 2010 the US prison population was steady, but had risen 1.7% pa between 2000 and 2009 (source: Bureau of Justice statistics). Most prisons test inmates for HCV, but many target only at-risk groups (ie known injecting drug users) rather than all prisoners (source: Bureau of Justice statistics report from 2004 headlined *'Hepatitis Testing and Treatment in State Prisons'*).

[117] See Eur J Epidemiol. 2010 Feb;25(2):143-8.

[118] See CDC, NCHS Data Brief No 27, March 2010, which reports NHANES data.

[119] See, for example, Curr Infect Dis Rep. 2010 Mar;12(2):118-25.

[120] Wandeler G et al. *Hepatitis C incidence in the Swiss HIV Cohort Study: a changing epidemic*. CROI Abstract 743. 2012.

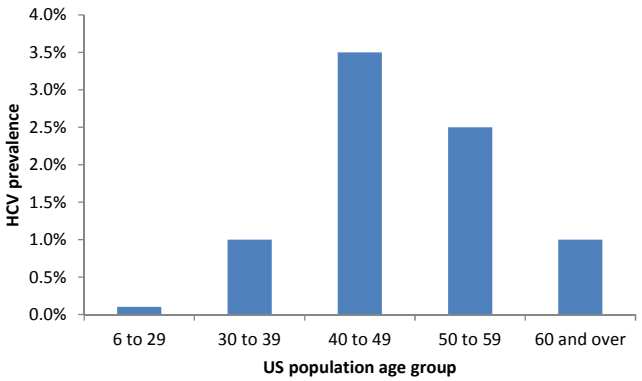
[121] Source: Egypt Demographic and Health Survey 2008, Table 18.6. Egypt's HCV problem has its origin in the contamination of reusable needles and syringes from the 1950s to the 1980s. See Lancet. 2000 Mar 11;355(9207):887-91.

[122] See Proc Natl Acad Sci U S A. 2010 Aug 17;107(33):14757-62. Epub 2010 Aug 9. We note the 1991 observation by the American musician LaTour that "People Are Still Having Sex".

[123] Source: '*Study warns of Hepatitis C epidemic in Egypt*' by Tarek Amin, Egypt Independent, 9/8/2010.

[124] One recent estimate has suggested that around 3% of Pakistani adults have been infected with HCV (see Int J Infect Dis. 2009 Jan;13(1):9-19. Epub 2008 Oct 2). Pakistan still has a problem with syringe reuse in hospitals. See 'Reusing syringes spreading Hepatitis C', The Express Tribune, 16/3/2012.

Figure 13 - The highest rate of HCV prevalence in the US is in the 40-49 age group in 2008



SOURCE: CDC, NHANES DATA ANALYSIS

Figure 14 - Various low-income countries have very high HCV prevalence

Country	% of population chronically infected	Patient numbers (million)
Egypt	9.8%	8.2
Vietnam	3.3%	3.0
Indonesia	1.1%	2.8
DR Congo	3.5%	2.6
Pakistan	1.3%	2.5
Bangladesh	1.3%	2.1
Thailand	3.0%	2.0
Philippines	1.9%	2.0

SOURCE: BELL POTTER SECURITIES

The costs of Hepatitis C are high. Not everyone chronically infected with HCV (ie HCV RNA in their blood after six months following initial infection) are sick in bed. Indeed, many people carry HCV in their bodies asymptomatically for years[125]. However:

- 60-70% experience chronic hepatitis[126], with symptoms such as jaundice[127] and fatigue.
- An estimated 10-20% of chronically infected people will ultimately develop cirrhosis of the liver[128], with a median time from infection to cirrhosis estimated to be 30 years[129]. Cirrhosis of the liver ultimately ends in liver failure. Around 40% of liver transplants are performed in patients who have chronic HCV[130]
- 1-5% will be victims of liver cancer[131], where median survival time will probably be two-three years[132]

One nationwide cohort study found the five-year death rate for chronic HCV was 14%[133].

Cirrhosis and liver cancer make chronic hepatitis C a costly disease

HCV patients cost the healthcare system 2-3 times more than other patients

- Costs increase about four-fold between the disease's initial and late phase[134].
- The incremental cost of HCV infection in the US is around US$23,400, of which US$6,500 is ambulatory care, US$1,800 is hospital care and US$6,900 is drugs. In effect HCV-infected people are 2-3 times more expensive to the healthcare system than the general population[135].
- Treating liver cancer can costs US$62,000 in the first year while the first year cost of a liver transplant can be US$267,000[136].

[125] On CDC estimates only around 16% of infections result in acute clinical cases of hepatitis.

[126] See, for example, N Engl J Med. 1992 Dec 31;327(27):1899-905, where 62% of a cohort of HCV-infected patients followed for 9 to 48 months develop chronic hepatitis.

[127] A condition characterised by yellow skin and associated with too much bile in the blood, due to the inability of the liver to clear the bile.

[128] Kanwal et al., tracking a large cohort of US veterans over the 1996-2006 period, registered cirrhosis prevalence of 18.5%. See Gastroenterology. 2011 Apr;140(4):1182-1188.e1. Epub 2010 Dec 22.

[129] See Lancet. 1997 Mar 22;349(9055):825-32.

[130] See Int J Med Sci 2006; 3:79-83.

[131] Sangiovanni et. al. (Hepatology. 2006 Jun;43(6):1303-10), tracking a population of people with compensated cirrhosis (a heavily scarred liver but one that still performs most functions) over 17 years, found 32% progressing to liver cancer, at a rate of 3.9% pa. Kanwal et. al. (op. cit.) registered a ten-year liver cancer experience of 1.3%. Note, the majority of liver cancer is associated with alcohol-related cirrhosis. A Taiwanese-led research team recently developed a model to predict liver cancer risk associated with Hepatitis C (source: China Post news story from 20/2/2012 headlined *'Researchers create new model to predict risk of hepatitis C cancer'*)

[132] See Ann Surg. 2009 Dec;250(6):908-13.

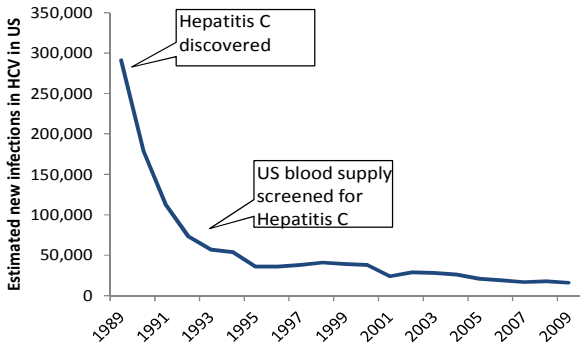
[133] J Hepatol. 2010 Jul;53(1):36-42. Epub 2010 Mar 29.

[134] See Can J Gastroenterol. 2010 Dec;24(12):717-26.

[135] Clin Ther. 2011 Sep;33(9):1268-80. Epub 2011 Aug 12.

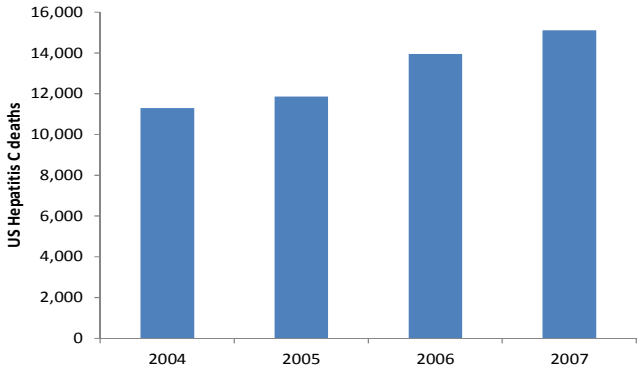
[136] Source: Milliman (www.milliman.com), *Consequences of Hepatitis C (HCV): Costs of a Baby Boomer Epidemic of Liver Disease, 2009*. This report was commissioned by Vertex Pharmaceuticals.

Figure 15 - There are still 15,000-20,000 new HCV infections recorded in America each year



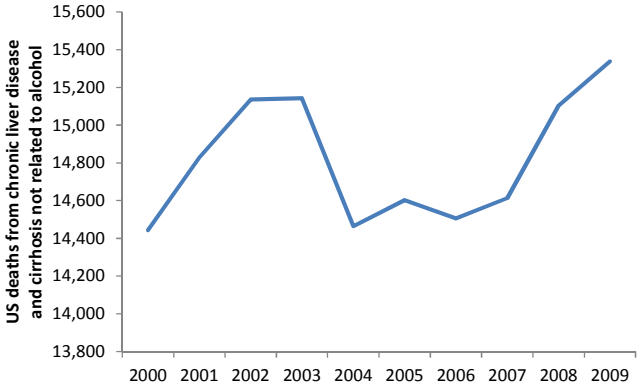
SOURCE: CDC

Figure 16 – US deaths where Hepatitis C is an underlying or contributing cause are on the rise[137]



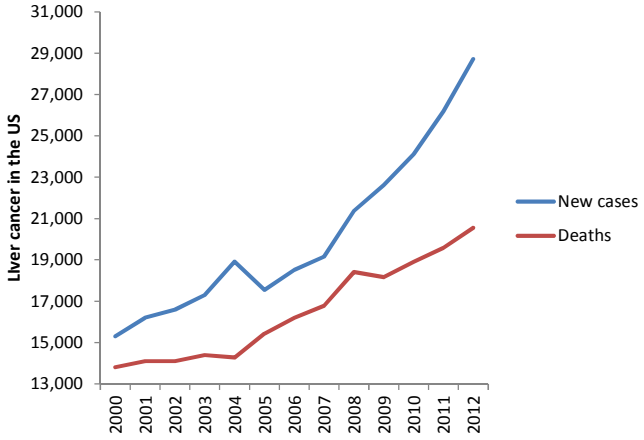
SOURCE: CDC VIRAL HEPATITIS SURVEILLANCE DATA

Figure 17 – US deaths from chronic liver disease not related to alcohol are rising



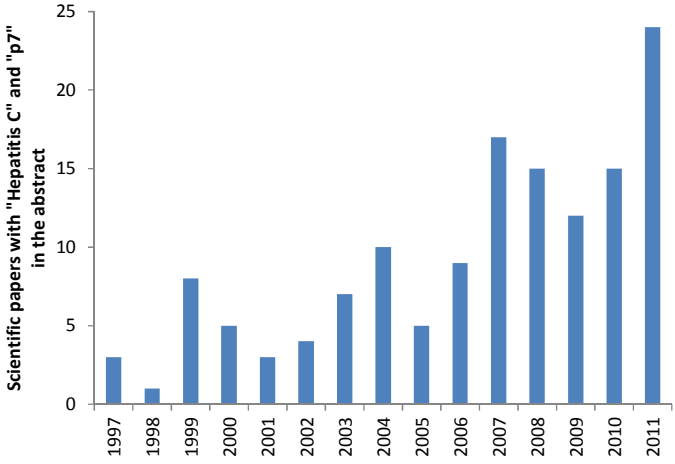
SOURCE: : CDC NATIONAL VITAL STATISTICS REPORTS

Figure 18 – Liver cancer is also claiming more lives in the US



SOURCE: AMERICAN CANCER SOCIETY, CANCER FACTS AND FIGURES REPORTS

Figure 19 - Scientific interest in the p7 protein of HCV, which BIT225 targets, has been growing



SOURCE: PUBMED

[137] For many deaths there is more than one cause. Wise et. al. (Public Health Rep. 2010 May-Jun; 125(3): 414–422), surveying US HCV-related deaths from 1999 to 2004, found that 18% also had alcohol abuse and 11% had HIV as a cause of death.

Why the Pharma companies are going to want BIT225

Favourable pre-clinical evidence, 2006-2008. In September 2006 Biotron announced that it was getting *in vitro* hits in surrogate virus models with various compounds including BIT225[138]. In February 2007 Biotron announced that BIT225 was able to inhibit virus-induced cell death in infected cells *in vitro*. In August 2007 the company reported that BIT225 was synergistic with interferon and ribavirin, increasing the level of inhibition of viral replication from 70% to 100% when BIT225 was added to the other two drugs. And in September 2008 the company announced that BIT225 was also synergistic with some of the new generation NS5b polymerase inhibitors[139].

BIT225 generated its first clinical data in HCV in 2009

A strong Phase Ib/IIa performance, October 2009[140]. In October 2009 Biotron reported highly encouraging data from an 18-patient randomised, placebo-controlled[141] Phase Ib/IIa clinical trial of BIT225 in HCV patients, in which patients were dosed with either 35 or 200 mg of BIT225 twice daily or placebo for 7 consecutive days after which viral load was measured out to 21 days[142]. The proof-of-concept trial, which was conducted in Sydney, recruited all-comers and therefore had multiple genotypes, and both treatment naïve patients and treatment non-responders[143]. The drug generated encouraging results:

- There was a modest (ie maximum 0.5 log[144]) but 'highly significant compared to placebo controls' reduction in viral load from baseline at Day 0 through to the end of the study at Day 21 at 200 mg twice daily[145];
- At this dose BIT225 reduced blood virus levels in three of the six subjects dosed;
- The drug proved active against genotype 1 (10 of the 18 patients were this genotype);
- The only side effect appeared to be nausea in the first week for some patients

This suggested the potential for serious viral load reductions for a longer dosing period.

A strong Phase Ib/IIa performance with interferon and ribavirin, December 2011[146]. In December 2011 Biotron's investigators reported results from a second randomised, placebo-controlled Phase Ib/IIa proof-of-concept trial, this one of 24 patients. In this trial BIT225 was combined with interferon and ribavirin and the investigators recruited only treatment naïve genotype 1 patients, randomised to receive placebo, 200 mg twice daily or 400 mg twice daily for 28 consecutive days, after which the patients reverted to just interferon and ribavirin for another 44 weeks to complete the standard 48 weeks of interferon/ribavirin therapy. While SVR data is not available at this time, once again the results were encouraging:

- 87% of trial subjects receiving BIT225 registered a complete EVR[147] at 12 weeks, predictive of therapeutic success[148], versus 63% for interferon and ribavirin alone - this

[138] The viruses BVDV (Bovine Virus Diarrhoea Virus) and GBV-B (GB virus-B), are closely related to HCV and grow readily in cell culture. This allows them to be used as surrogate virus models for HCV, since at present there is no adequate viral culture system for HCV. That said, various scientists around the world are working on this problem. See, for example, Wakita et. al., Nat Med. 2005 Jul;11(7):791-6. Epub 2005 Jun 12.

[139] In WO/2009/018609 Biotron discloses (in Example 15) that BIT225 is highly synergistic with the nucleoside analogue drug 2'-C-methyladenosine (see J Med Chem. 2007 Aug 9;50(16):3891-6. Epub 2007 Jul 18.), which in 2007 was being developed by the American biotech company Metabasis and was later the subject of a licensing deal with Roche.

[140] This trial, which commenced in August 2008, followed on from a successful 48-subject single-dose Phase I clinical trial in uninfected volunteers conducted in 2007.

[141] Placebo was lactose mixed with 25 ml OraSweetSF.

[142] Biotron had initially intended to dose for 14 days but had difficulties in patient recruitment so after ethics approval the dose window was reduced to 7 days.

[143] Patients currently undergoing treatment were excluded.

[144] Changes in hepatitis C viral load are measured in 'log reductions' where 1 log is a drop from baseline of 10 times, a 2 log reduction is 100 times and so on. Generally a patient who achieves less than a 2-log reduction on interferon-ribavirin by week 12 is considered a 'null responder'.

[145] 35 mg twice daily proved ineffective, suggesting the potential for a dose response, with better viral load reductions above 200 mg.

[146] This trial commenced in October 2010. The trial was conducted at Sirijaj Hospital in Bangkok. Results were presented at HEP DART 2011, a hepatitis drug development meeting in Koloa, Hawaii. For the results presentation see www.ihlpress.com/pdf%20files/hepdart11_presentations/33_Tanwandee.pdf

[147] See Appendix II for an explanation of cEVR.

[148] See Intervirology. 2009;52(5):247-51. Epub 2009 Jul 14.

shows that including BIT225 in the interferon/ribavirin mix translates into a relevant clinical benefit, that is, it reduces virus below level of detection in more patients than in those who only received interferon/ribavirin.

- At four weeks from baseline 400 mg patients had registered a ~1 log viral load reduction above interferon and ribavirin alone. This was quite an achievement because control arm patients had been good responders to interferon/ribavirin – the latter generated a 3.01 log reduction whereas 400 mg BIT225 did 4.08 logs. What the viral load reduction shows is that BIT225 has a real effect.
- The cEVR and 1 log viral reduction was achieved with only four weeks of dosing. With the charts on viral load steady dropping at every time point between baseline and 28 days it's reasonable to suggest that the standard dosing regimen of 12 weeks that has been used with other DAAs would generate a much better response for BIT225.

Future trials are being planned. Biotron is currently finalising its clinical program for 2012/13, and this is expected to include

- A HIV/HCV co-infected study with dosing up to 28 days to commence mid-2012;
- A HCV trial with 12 weeks dosing[149] to commence towards the end of 2012[150].

Why Pharma companies are going to be interested in BIT225

We see four main reasons why BIT225 can be licensed by a larger pharma company:

There is no clear winner in the race for new generation HCV drug regimens. The sheer size of the Pharmasset and Inhibitex transactions may have suggested to some that the race was more or less over for the first all-oral DAA combo. On the contrary, we are far from it, as the recent treatment relapses reported by Gilead in February 2012 for GS-7977 will have demonstrated. The need for new compounds to shore up a combination like GS-7977/ribavirin will mean that BIT225 is continuously on the pharma companies' radar.

Biotron has p7 as an HCV target to itself

Biotron has p7 to itself. BIT225 is the only drug in the world so far that seems to be able to go after HCV's p7 protein as a target. HCV p7 is known to form ion channels in cells that assist in viral budding and release[151], making it an attractive target for anti-HCV drug development (see Appendix IV), particularly since p7 seems to be conserved across all genotypes[152]. We see BIT225's dominant position in the p7 area as helping it to attract licensing interest from companies looking for novel targets with the potential to further lower the level of non-responders in the HCV marketplace.

BIT225 is easy to make, with relatively few steps in the manufacturing process[153]

Biotron has encouraging pre-clinical evidence on drug synergy. Biotron has previously inferred, from pre-clinical work, that BIT225 is synergistic with both

- the current standard of care (ie interferon combined with ribavirin); and
- some HCV polymerase inhibitor drugs[154].

We think this apparent multiple synergism, when combined with what we know from the Phase I/IIa clinical trials, suggests the likelihood for this drug to be highly effective against HCV in combination therapy.

[149] As per the leading new therapies in development for HCV.

[150] This could include testing in multiple genotypes rather than just type 1, and testing that explores not only BIT225 plus interferon/ribavirin but also BIT225 with only ribavirin.

[151] See, for example, PLoS Pathog. 2007 Jul;3(7):e103.

[152] See Eur Biophys J. 2010 Jun;39(7):1097-104. Epub 2009 Sep 2.

[153] Source: Biotron AGM presentation 14 October 2005. Biotron reported in July 2006 that a contract manufacturing programme for the drug was being conducted by Dr Reddy's Laboratories (Hyderabad, India, BSE:500124, www.drreddys.com - Reddy's is the second largest drug maker in India). Apparently, '*excellent results have been achieved in terms of product quality, and have demonstrated that BIT225 may be successfully scaled up from lab to commercial scale*'.

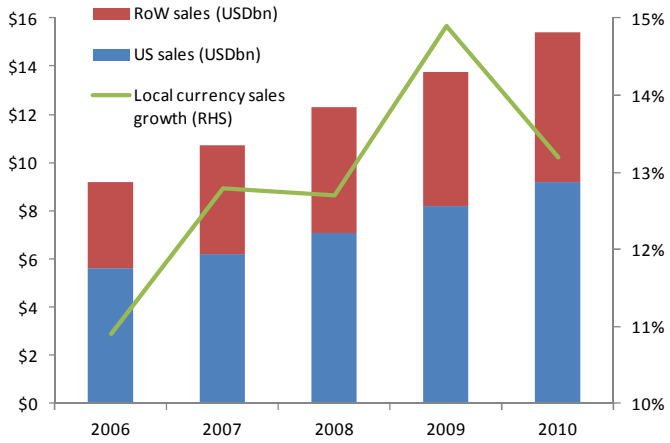
[154] See BIT's 9/9/2008 ASX release.

BIT225 and the new wave in HIV drug development

BIT225 may be part of a future Functional Cure for HIV

As well as showing promise in HCV, BIT225 also has strong potential as a new-generation HIV drug. The pre-clinical data is favourable and the drug is currently in a Phase Ib/IIa proof-of-concept trial in treatment-naïve HIV patients for which we expect data in mid-2012. We argue that the drug's apparent ability to deal with HIV in hitherto undruggable HIV 'reservoirs' positions the company for a strong commercial payoff in the coming new era of HIV drug development aimed at a Functional Cure.

Figure 20 - HIV antivirals is a US$15bn market globally



SOURCE: IMS HEALTH

Figure 21 - Twelve rich countries in particular have significant HIV-positive populations, including Australia

	People living with HIV	Adult (age 15-49) prevalence rate
United States	1,200,000	0.6%
France	150,000	0.4%
Italy	140,000	0.3%
Spain	130,000	0.4%
United Kingdom	85,000	0.2%
Canada	68,000	0.3%
Germany	67,000	0.1%
Portugal	42,000	0.6%
Poland	27,000	0.1%
Netherlands	22,000	0.2%
Australia	20,000	0.1%
Switzerland	18,000	0.4%
Total	1,969,000	0.4%

SOURCE: CIA WORLD FACTBOOK

HIV is currently a large drug market but with low levels of innovation

Anti-HIV drugs constitute a large First World market. While people often think of HIV as primarily a Third World health issue because of the high prevalence figures in Africa[155], around 6% of HIV-positive people live in rich countries[156] where disease prevalence is steadily rising:

The US HIV-positive population grows at three to four times general population growth

- The US HIV-positive population, which is around three-fifths of the total for high-income jurisdictions, has been growing 3-4% pa since 2000 versus population growth for the US as a whole of around 0.9%. There has been fairly steady HIV incidence figures[157], but lower AIDS death rates[158].
- Typically European HIV populations have tracked the US experience of 3-4% growth, with the notable exceptions of the UK and Germany. There has been a tripling of UK prevalence since the late 1990s, possibly due to immigration from Africa[159], and a near doubling of German prevalence.

[155] For example, in the US in 2006, HIV prevalence was 0.4% of the population (source: CDC, Morbidity and Mortality Weekly Report, 3/10/2008). By comparison South Africa's HIV prevalence rate in 2008 was 10.9% of the population aged over two (source: South African National HIV Prevalence, Incidence, Behaviour and Communication Survey, 2008)

[156] Ie GDP per capita > US$20,000. We estimate around 25% of the world's HIV-positive population live in middle-income countries (GDP per capita US$10,000-20,000) and 68% live in low income countries (GDP per capita below US$10,000).

[157] Driven largely by male homosexual contact (50%), 'high risk' heterosexual contact (30%), injection drug users (14%) and injection drug use by male homosexuals (5%). Around 2.3% of US men aged 18-44 are homosexual (source: Adv Data. 2005 Sep 15;(362):1-55) while around 0.1% of Americans over 12 are injection drug users (source: Substance Abuse and Mental Health Services Administration, The NSDUH Report, 29/10/2009).

[158] In the period 2006-2009 there were an average 50,000 new HIV cases, roughly steady and 10,000 AIDS deaths, with death rates declining (source: CDC surveillance stats)

[159] Around 35% of UK people receiving specialist care in the UK for HIV in 2010 were Black Africans. Source: National AIDS Trust.

- The US is around 60% of a global market worth US$15bn pa that has been growing at double digits in recent years and now represents the world's tenth largest drug class[160]. The US spends around US$7,700 in HIV drugs per patient, meaning that the rest of the world spends only US$200 per patient.

There's hardly any HIV drugs in late stage pipelines

In spite of the large First World market, late stage HIV drug innovation has slowed. Big Pharma is no longer investing strongly in new HIV drugs, in spite of the fact that Gilead[161], Bristol-Myers Squibb, Merck & Co., J&J, Abbott and GSK/Pfizer all have billion dollar franchises in the area. Indeed, we counted only three noteworthy programmes ongoing at the moment:

- The GSK/Pfizer unit Viiv Healthcare[162] is in Phase III with Dolutegravir, an HIV integrase inhibitor;
- Bristol-Myers Squibb has done some Phase II work on BMS-663068, an HIV-1 attachment inhibitor.
- Gilead is in Phase III with Elvitegravir, an integrase inhibitor and Cobicistat, a pharmacoenhancer (ie it boosts the effect of other drugs); and in Phase II with GS-7340, a nucleotide RTI[163].

There has also been very little partnering activity in the space in recent years.

Figure 22 - Leading anti-HIV drugs

Brand	Generic name	Company	Class	2011 sales (USDm)	Growth rate in 2011	US patent expiry
Atripla	efavirenz/emtricitabine/tenofovir	Gilead	NNRTI/NRTI	3,220	10.0%	2017
Truvada[164]	emtricitabine/tenofovir	Gilead	NRTI	2,880	8.0%	2017
Reyataz	atazanavir	Bristol-Myers Squibb	NRTI	1,569	6.1%	2017
Sustiva	efavirenz	Bristol-Myers Squibb	NNRTI	1,485	8.6%	2013
Isentress	raltegravir	Merck	Integrase inhibitor	1,359	24.7%	2022
Prezista	darunavir	J&J (Janssen)	Protease inhibitor	1,211	41.3%	2013
Kaletra	lopinavir/ritonavir	Abbott	Protease inhibitor	1,170	-6.8%	2016
Epzicom	abacavir/lamivudine	Viiv Healthcare	NRTI	989	15.3%	2016
Viread	tenofovir	Gilead	Protease inhibitor	738	0.8%	2018
Combivir	lamivudine/zidovudine	Viiv Healthcare	NRTI	517	-7.9%	2012
Total				15,137	10.9%	

SOURCE: COMPANY DATA

There is less HIV drug innovation these days because of the success of HAART. We think Pharma is no longer investing heavily in new HIV drugs because the existing drugs have turned HIV from a death sentence into a manageable chronic disease condition[165]**.** Around 1997 physicians started figuring out how to combine the various available drugs into effective 'drug cocktail' regimes collectively known as 'Highly Active Anti-Retroviral Therapy' (HAART), whose effect is to reduce HIV viral loads in the patient's body to undetectable levels and keep it there indefinitely. With HAART the virus never goes away, but there's not enough of it to lead to AIDS. In the last decade this medicine has matured to the point where:

[160] This partly makes up for intellectual property issues in emerging markets, where countries routinely tear up patents on HIV drugs in order to introduce generics so as to lower the cost of treatment. See, for example, *Brazil overrides Merck patent on HIV drug* by Andrew Jack and Richard Lapper, Financial Times, 4/5/2007.

[161] Gilead has the leading franchise in the area with Atripla and Truvada, and in August 2011 it gained FDA approval for Complera, which is efavirenz and tenofovir plus the J&J NNRTI drug rilpivirine (brand name Erudant).

[162] ViiV Healthcare (www.viivhealthcare.com) was created when GSK and Pfizer pooled their portfolios of approved HIV drugs into a new company, to be owned 85% by GSK. This decision was announced in April 2009 and Viiv was launched in November 2009. Dolutegravir was originally created by the Japanese drug company Shionogi.

[163] Quad, which is elvitegravir and cobicistat plus emtricitabine and tenofovir, reported favourable Phase III data in March 2012, showing non-inferiority to ritonavir-boosted atazanavir (ATV/r) plus Truvada. Quad's PDUFA date is 27 August. The combination will allow Gilead to compete with Merck & Co.'s integrase inhibitor Isentress.

[164] In 2010 the iPrEx study demonstrated that this drug combination could provide some 'pre-exposure prophylaxis' to HIV, reducing infection rates by 44% in homosexual men (See N Engl J Med. 2010 Dec 30;363(27):2587-99. Epub 2010 Nov 23). An FDA advisory committee will look at this indication on 10 May ahead of a 15 June PDUFA date.

[165] "Longevity is having a chronic disease and taking care of it" – Oliver Wendell Homes Sr (1809-1894), US physician and writer.

- projected median age at death for HIV-positive homosexual men in advanced industrial countries is now 75 years, although this is still around eight years below the median for men overall[166]
- only 3,300 Americans died in 2009 from AIDS, with mortality down 42% on 2000[167].

Figure 23 - Recent deals in the anti-HIV drug space

Developer	Licensee	Upfront (US$m)	Total deal value (US$m)	Equity component (US$m)	Date	Type of drug	Stage completed at time of license
Medivir (STO: MVIR-B)	Bristol-Myers Squibb	7.5	97		Sep-06	NNRTI[168]	Pre-clinical
Ambrilia[169]	Merck & Co.	17	215		Oct-06	Protease inhibitor[170]	Pre-clinical
Idenix (Nasdaq: IDIX)	GSK	34	450		Feb-09	NNRTI[171]	Phase II
Concert Pharma (Privately held)	GSK	18.3	>1000	16.7	Jun-09	Protease inhibitor[172]	Pre-clinical
Oncolys BioPharma (Privately held)	GSK/Viiv	0	286		Dec-10	NRTI	Phase II

SOURCE: COMPANY WEB SITES

In spite of the success of HAART, it hasn't dealt with the long-run effects of low level HIV infection. HIV researchers have started seriously grappling in recent years with the problem of HIV 'reservoirs' – cells where the virus 'hides' for long periods when the patient otherwise seems to be carrying negligible viral load[173]. HAART can't eliminate this off-the-grid latent or slowly replicating virus, which bounces back the moment the patient goes off therapy[174], and the viral reservoirs have long-run health implications for the patient:

2% of HIV-positive people end up with HIV-associated dementia

- The common issues of HIV-associated dementia and HIV-related peripheral neuropathy arise from HIV's use of neurons as reservoirs. One study found that 27% of HIV-positive patients with undetectable virus over a median four years had cognitive complaints, and 2% had HIV-associated dementia[175]. Another study found a 9% prevalence of peripheral neuropathy in HIV-positive patients over three years[176];
- Large population studies have found higher levels of renal failure, bone fracture, diabetes, cardiovascular disease and hypertension in patients on HAART as against HIV-negative controls, such that the HAART patients had health statuses ten years older than their actual age[177]. This is an increasingly serious issue when the median age of people living with HIV is rising[178]. HIV-induced activation of inflammation is a player in these poor outcomes[179], with the inflammation clearly raising the risk factors for cardiovascular disease in particular[180]. It may be latent virus in the gut that is causing the inflammation[181], but the jury is still out as to the cause. Basically too much inflammation is bad for you because it destroys tissues vital for organ health[182].

[166] See AIDS. 2012 Jan 28;26(3):335-43.

[167] Source: CDC National Vital Statistics reports.

[168] BMS terminated this programme in July 2007.

[169] This company filed for bankruptcy in 2011.

[170] Merck ceased work on this drug, called PPL-100, in mid-2008.

[171] Viiv Healthcare informed Idenix in February 2011 that this drug had been placed in a clinical hold by the FDA.

[172] This programme, for a drug called CTP-298, yielded a US$4m milestone from GSK in June 2011.

[173] The existence of viral reservoirs was first revealed in 1997 - see Proc Natl Acad Sci U S A. 1997 Nov 25;94(24):13193-7.

[174] For the ability of HIV to rebound even after 10 years of optimal therapy and extremely low reservoir levels see AIDS. 2010 Nov 27;24(18):2803-8.

[175] See AIDS. 2010 Jun 1;24(9):1243-50.

[176] See AIDS. 2011 Apr 24;25(7):919-28. The California drug developer NeurogesX (San Mateo, Ca, Nasdaq:NGSX, www.neurogesx.com) markets a capsaicin patch for the treatment of postherpetic neuralgia which gained regulatory approval in Europe and the US in 2009. The product, called Qutenza, in March 2012 received a Complete Response Letter from the FDA related to HIV-related neuropathy.

[177] See, for example, Clin Infect Dis. 2011 Dec;53(11):1120-6. Epub 2011 Oct 13.

[178] In 2009 33% of people living with HIV in the US were over 50. The comparable figure for 2007 was 29%. Source: CDC, HIV Surveillance Report 2010.

[179] See, for example, PLoS Med. 2008 Oct 21;5(10):e203.

[180] See AIDS. 2009 May 15;23(8):929-39.

[181] Through latently infected cells in gut-associated lymphoid tissue (GALT) damaging the gut wall, allowing microbial translocation. See Curr Opin HIV AIDS. 2010 Mar;5(2):189-93.

[182] See the entry headlined *'The Body's New Bad Guy'* in the University of Rochester Medical Centre's online health encyclopaedia (http://www.urmc.rochester.edu/encyclopedia).

- Other studies are finding that people on HAART have 'immunosenescence' – weakened immune system cells characteristic of the very old[183].

We think that research efforts to solve the known drawbacks of HAART are helping to kick off another round of innovation in HIV drug development, with Biotron set to play a part in the new wave with BIT225, centred on the goal of a Functional Cure.

A new HIV drug innovation wave is just getting started

The Berlin Patient opened a new era in HIV drug development

The Next Big Thing in HIV is the Functional Cure. Around three years ago HIV researchers started using that four letter word with 'c' in it – 'cure' – without embarrassment when talking about HIV. Specifically, what they are now envisaging is a Functional Cure, where there is no readily detectable virus in absence of therapy for prolonged periods[184]. The Functional Cure talk is largely because of the 'Berlin Patient', an HIV positive person who achieved this in late 2008. The Berlin Patient needed a bone marrow transplant in order to treat his Acute Myeloid Leukaemia (AML). Dr Gero Hütter of the Charité Hospital in Berlin sourced donor cells where the CD4+ cells had a mutated version of the CCR5 receptor that HIV uses to infect such cells. This mutation confers resistance to HIV-1 and is present in around 10% of Caucasians[185]. The CCR5 mutant cells, successfully transplanted to the Berlin Patient, not only treated the AML but resulted in rapid HIV clearance that was maintained[186]. Regrettably, this is probably not a way forward for eliminating HIV from the human race, not only because bone marrow transplants are expensive[187] but also because the donor cells would be difficult to source. What the Berlin Patient has done, however, is raise the credibility of other approaches.

Targeting viral reservoirs is the cost-effective way of pursuing the Functional Cure. There are four main ways in which researchers are pursuing the Functional Cure:

- *'Shock and kill'* – This approach involves the use of drugs that can activate the HIV reservoirs cells (shock), pushing the virus into the open where the immune system and existing drugs can deal with it (kill). A frequently talked about approach is to use histone deacetylase[188] (HDAC) inhibitors as the latency activator[189]. Two well-known HDAC inhibitors, Merck & Co's Zolinza[190] and Celgene's Istodax[191], are currently approved for the treatment of lymphoma. In March 2012 Dr David Margolis of UNC presented results of a small trial showing that Zolinza could markedly boost HIV RNA in resting T cells, indicating that latent HIV has been successfully reactivated in these cells[192].
- *Gene therapy* – This approach involves modifying a patient's CD4 cells so that they can resist HIV. A prominent example is the California-based biotech company Sangamo BioSciences[193], which uses a naturally occurring class of DNA transcription factors called zinc finger DNA-binding proteins (ZFPs) to modify the CCR5 receptor on a patient's CD4 cells. Sangamo's SB-728 product has generated interesting data in early stage clinical work[194].

[183] See J Antimicrob Chemother. 2009 Sep;64(3):579-88. Epub 2009 Jul 16.

[184] As opposed to a 'sterilising cure', where all HIV-infected cells in the body are eliminated.

[185] See Hum Mol Genet. 1998 Mar;7(3):399-406.

[186] This happy outcome was announced in November 2008 (see *'Rare Treatment Is Reported to Cure AIDS Patient'* by Donald G. McNeil, New York Times, 13/11/2008) and published in February 2009 (see N Engl J Med. 2009 Feb 12;360(7):692-8). The cure was confirmed in late 2010 (see Blood. 2011 Mar 10;117(10):2791-9. Epub 2010 Dec 8).

[187] In the United States they can cost around US$250,000 in hospital charges alone, with costs having risen 7% pa over the last decade. Source: HCUP data.

[188] Histone is the protein which sits at the core of the chromosomes. When DNA is bound to the histone it's difficult for the genes to be expressed. An acetyl group loosens the grip of histone, allowing this to happen. Histone deacetylase prevents this loosening, making it an effective 'gene silencer'.

[189] See Curr Opin HIV AIDS. 2011 Jan;6(1):25-9.

[190] Generic name vorinostat. See www.zolinza.com.

[191] Generic name romidepsin. See www.istodax.com. Celgene acquired the privately-held Gloucester Pharmaceuticals in 2010 for US$340m plus US$300m in regulatory milestones in order to control this drug.

[192] See *'AIDS Cure Quest Advances as Merck Cancer Drug Attacks Hidden HIV'* by Simeon Bennett, Bloomberg, 9/3/2012.

[193] Richmond, Ca, Nasdaq: SGMO, www.sangamo.com.

[194] See the Sangamao press release dated 8/3/2012 and headlined *'Sangamo Presents New Clinical Data at CROI 2012 Demonstrating Persistent Positive Effects of ZFN Therapeutic for "Functional Cure" of HIV/AIDS'*. See also the 18/9/2011 press release headlined 'Sangamo BioSciences Announces Presentation of Groundbreaking Clinical Data From ZFN Therapeutic for HIV/AIDS at ICAAC 2011'. At ICAAC Sangamo presented on one patient whose virus fell back to an undetectable level just before the end of the 12-week testing period for SB-728. This man has been dubbed 'the Trenton patient', after the New Jersey capital where he lives (see *New Hope for a Cure for HIV* by Andrew Pollack, New York Times, 28/11/2011).

- *Immunotherapy* – This approach involves vaccine-based approaches that allow the immune system to better targets HIV proteins[195]. The DNA vaccine player Inovio Pharmaceuticals[196] recently reported a strong T cell immune responses in a Phase I clinical study of its HIV vaccine[197] while another DNA vaccine from GeoVax[198] is in Phase IIa.
- *Reservoir targeting*. This involves drugs that can target reservoir cells occupied by HIV and kill those cells. Biotron believes it has one such drug in BIT225.

Of these four approaches, we argue that reservoir targeting is the most straightforward and potentially cost-effective.

- The shock and kill approach uses toxic drugs (ie chemotherapy agents) to activate latent virus. However if the activated virus is not then cleaned up properly the result could be negative for the patient. There's also the risk that they could activate other viruses that have been hidden in our DNA such as cytomegalovirus[199], and the possibility that they could cause oncogene activation and thereby result in cancer[200].
- Gene therapy and immunotherapy may be expensive;

Gilead and J&J are going after HIV reservoirs

- Reservoir targeting has potential because scientific knowledge of what cells act as reservoirs is increasing, and because development of reservoir targeting drugs is within the technical capability of the pharma companies with their high throughput screening methodologies. Interestingly, at the 5th International Workshop on HIV Persistence in December 2011[201], representatives from Gilead and J&J presented on their models of HIV latency and their compound screening work.

Why BIT225 will be part of the New Wave

We see several reasons why BIT225 can be a candidate for Big Pharma to work with as a Next Generation drug:

In terms of 'classic', HAART-oriented, HIV drug development, BIT225 has the Right Stuff. BIT225, which Biotron unveiled in September 2005 after a three-year rational drug design programme, is a good anti-HIV drug when looked at from the perspective of HAART, giving a future licensing partner comfort that the drug is safe and effective:

- *BIT225 represents a new drug class, being a 'VPU inhibitor'*. Viral Protein U (VPU), like HCV p7, is a protein that HIV uses in the assembly of new virus particles, and in the 'budding' of new viruses from the host cell. Lack of VPU in HIV has been demonstrated to cut viral budding by >80%[202]. Deletion of VPU significantly decreases HIV replication in human lymphoid tissue[203]. *In vitro,* BIT225 has been able to markedly cut viral budding in VPU-positive HIV strains[204]. Traditionally new drug classes have been looked on with favour given the tendency of HIV to develop resistance to existing drugs[205].

[195] See Immunotherapy (2012) 4(3), 245–248

[196] Blue Bell, Pa., Amex: INO, www.inovio.com.

[197] Source: Inovio press release dated 13/3/2012 and headlined *'Inovio Pharmaceuticals' PENNVAX-B HIV Vaccine Demonstrates Strong T-Cell Immune Responses in Therapeutic Vaccine Trial'*.

[198] Smyrna, Ga, OTCBB: GOVX, www.geovax.com.

[199] A herpes virus that generally causes only mild flu-like symptoms but can be dangerous in immunocompromised people.

[200] See AIDS. 2011 Apr 24;25(7):885-97.

[201] Held on the island of St Maarten in the Dutch Antilles – HIV researchers cure disease in style.

[202] See J Virol. 1990 Feb;64(2):621-9.

[203] See J Virol. 2004 November; 78(22): 12689–12693.

[204] See Khoury et. al., Antimicrob Agents Chemother. 2010 February; 54(2): 835–845.

[205] So long as the drug is patient-friendly (ie, orally available with low side effects), and not overpriced. Isentress (raltegravir), from Merck & Co., which became the first HIV integrase inhibitor upon FDA approval in late 2007, fitted all these qualities and is now a blockbuster, with revenue to Merck in 2011 of US$1.36bn. Selzentry (maraviroc), which gained FDA approval in mid-2007 as the first HIV 'entry inhibitor' drug, didn't fit the bill. The drug may have been first-in-class – it's an HIV 'entry inhibitor' drug - but it hasn't grown strongly due to the need for the patient to take specialised tests before being prescribed the drug. 2011 sales for Viiv Healthcare, which inherited the drug from Pfizer, were only US$176m.

- *BIT225 is active against drug-resistant strains of the virus*[206], at low doses.
- *BIT225 has good basic drug qualities.* The drug is around 68% orally 'bioavailable', meaning it can be taken in pill form and still get to where it needs to go in order to attack viruses. It has proved in animal studies to be stable, safe, and have a reasonable half-life (ie. it won't break down too quickly)[207].

BIT225 is synergistic with existing HIV drugs

- *BIT225 is synergistic with existing HIV drugs.* When tested in vitro alongside an NNRTI (the Bristol-Myers Squibb drug Sustiva), and two protease inhibitors (the Gilead drug Viread and the Abbott drug Lopinavir), BIT225 was found to be synergistic with two of the three existing HIV drugs (Sustiva and Lopinavir), improving the antiviral activity of each drug, and had an additive effect with the third drug[208].
- *The drug has good safety data.* A Phase I study in healthy volunteers for which data was reported in August 2007 gave BIT225 a clean bill of health, with potentially therapeutic blood levels of the drug achieved[209].

BIT225's activity in monocyte-derived macrophages suggests that it can play in the Functional Cure era of HIV drug development. HIV uses various cells for reservoir purposes, including hematopoietic cells[210], and cells within the gastrointestinal tract, genitourinary tract, and brain. However two classes of reservoir cells, called 'memory T-cells'[211] and 'monocyte-derived macrophages' (MDMs)[212], have particularly attracted researchers because these cells tend to live a long time, are widely distributed in the body and can harbour components HIV needs to replicate itself. Since 2005 Biotron has gathered evidence that BIT225 can attack HIV in MDMs:

- A 2004 paper in the journal *Antimicrobial Agents and Chemotherapy*[213] showed that BIT225's precursor compounds could inhibit HIV replication in MDMs;
- By 2006 Biotron had evidence that BIT225 was also effective against HIV in MDMs[214]. This work was published in *Antimicrobial Agents and Chemotherapy* in 2010[215].
- A 2010 paper from scientists at Rush University Medical Center in Chicago has established that VPU appears to play a role in helping infected cells evade an immune reaction that would otherwise eliminate these cells[216]. Obviously a VPU inhibitor drug like BIT225 could help with this issue.

BIT225 can kill both HIV and HCV

There are currently no marketed drugs targeting both viruses, so it's reasonable to suggest that such a drug could attract strong commercial interest.

- *Up to one-third of HIV patients are co-infected with HCV,* as various population studies have shown[217], due mainly to the provenance, in many instances, of both infections in

[206] Source: Khoury et. al., op. cit. Biotron announced this activity against drug resistant strains on 17 August 2005, just prior to formal announcement of BIT225's development. In this release the drug is described as Biotron's 'prime lead candidate compound'.

[207] Source: Biotron AGM presentation 14 October 2005.

[208] Source: Khoury et. al., op. cit. Biotron announced this synergism work to the market on 30 November 2005.

[209] Based on calculations extrapolated from preclinical in vitro antiviral efficacy studies. See Biotron's 16/8/2007 market release.

[210] Blood-forming cells.

[211] T-cells that have previously encountered an antigen of interest that can therefore mount a faster and stronger immune response than the first time the immune system responded to the antigen.

[212] Cells that can activate T-cells to attack an antigen the immune system has previously encountered. Monocytes are created in the bone marrow and then fan out to various tissues and organs where they morph into macrophages. These macrophages eat what they identify to be foreign substances and then place the peptides that indicate the characteristics of what they've just eaten - the antigen - on their surface. Also on the surface of macrophages are MHC Class II molecules. Those MHC Class II molecules process the antigen and present that antigen to a kind of T-Cell called the Helper T-Cell. Those Helper T-Cells, also called 'CD4+' cells, once activated, produce proteins that activate other cells such as the 'Killer T-Cells' that can in turn deal with the pathogen captured by the macrophages.

[213] See Ewart et. al., Antimicrob Agents Chemother. 2004 Jun;48(6):2325-30.

[214] See the company's 27/6/2006 presentation.

[215] Khoury et. al.,op. cit.

[216] See Cell Host Microbe. 2010 Nov 18;8(5):389-91.

[217] One multi-country study found a HIV/HCV coinfection prevalence in HIV patients of 16.1% (see HIV Med. 2004 May;5(3):174-9). In the US an analysis of a US Veterans Affairs database between 1991 and 2000 showed 29% of hospitalised HIV-infected patients also had HCV (see Clin Gastroenterol Hepatol. 2005 Feb;3(2):175-83), while the Women and Infants Transmission study found 29% of HIV-positive women in the study were co-infected (see Clin Infect Dis. 2005 Mar 15;40(6):859-67. Epub 2005 Feb 18.

injection-drug use. Co-infected patients are more difficult to treat than HCV-only patients since they tend to respond less well to interferon/ribavirin therapy[218], and HIV drugs have not been able to work against HCV. Consequently drugs that can treat HCV in co-infected patients can enjoy a huge commercial opportunity by lowering overall treatment costs.

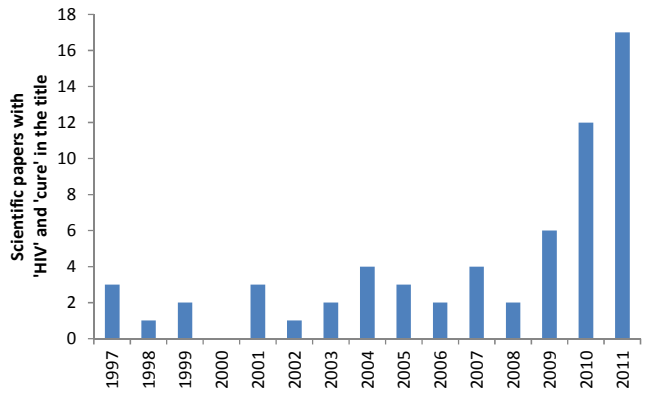
- *Incivek and Victrelis will be addressing the co-infection patient population*, with interim Phase II data released in March 2012 showing that Incivek could generate an HCV SVR12 in 74% of patients with a co-infection, versus only 45% for interferon/ribavirin. The comparable figures for Victrelis were 61% and 27%[219].
- *Biotron thinks it can go one better than Incivek and Victrelis* in that the same drug seems to be able to hit both viruses - in the case of HCV, via the p7 protein, and in the case of HIV, via the Vpu protein. Obviously these proteins have structural differences[220] but both are viroporins so there is potential for a drug that hits one target to hit the other as well[221]. If that proves to be the case for BIT225, the market upside is likely to be strong.

Biotron will report clinical data in HIV patients in 2012

An HIV proof-of-concept trial commenced in September 2011. In 2010 Biotron designed a small, 24 patient Phase Ib/IIa clinical trial in order to gain proof-of-concept in treatment-naive HIV patients and this trial was finally initiated in September 2011[222]. The trial, being conducted in Thailand (where treatment-naive patients are available) randomises patients to either placebo or 400 mg of BIT225, with 10 days of dosing and another 10 days of follow-up. Patients are relatively healthy (ie high T cell counts) but also high viral load, and the trial will measure the impact of the drug on viral load. The trial is expected to complete recruitment in the second quarter of 2012.

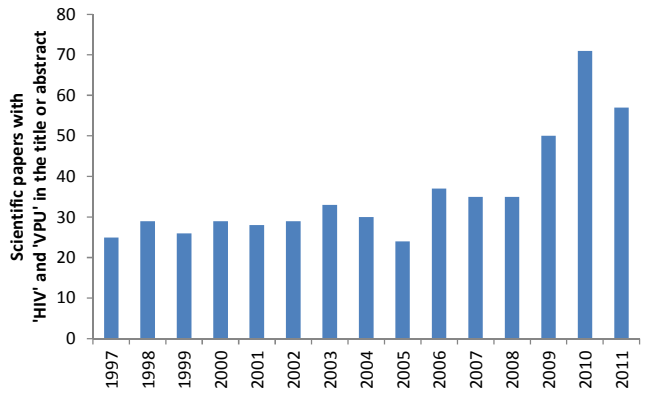
Future trials are planned. As we noted above, Biotron is working on the design of a HIV/HCV co-infection study for BIT225, with dosing out to 28 days rather than 20 days.

Figure 24 – Scientists started talking about an HIV cure in 2009



SOURCE: PUBMED

Figure 25 – Scientific interest in HIV's VPU protein is growing



SOURCE: PUBMED

[218] A comparison of monoinfected versus co-infected patients found a 56% SVR for monoinfection versus 27% for co-infection. See Antivir Ther. 2008;13(8):1047-55.

[219] Data presented at CROI 2012 in Seattle. Victrelis has another disadvantage compared to Incivek in co-infected patients – in February 2012 Merck & Co. reported that the drug can interfere with the HIV drugs boosted by ritonavir.

[220] See Biochim Biophys Acta. 2011 Feb;1808(2):554-60. Epub 2010 Aug 18.

[221] *In silico* work has suggested that it is possible to design multiple drugs suitable for targeting both viruses simultaneously. See See BMC Bioinformatics. 2011; 12: 294.

[222] It had previously been deferred due to funding constraints.

Commercial leadership

We have a high regard for the leadership team at Biotron, which has positioned the company for strong financial upside on a low outlay of only A$23m to date.

We have a high regard for Biotron CEO Dr Michelle Miller

A value-for-money CEO. Biotron's CEO, **Dr Michelle Miller**, gained her PhD studying the molecular genetics of cancer, and then worked in Big Pharma developing gene therapy products for J&J. More importantly in terms of Biotron's commercial prospects, Michelle spent the late 1990s and early 2000s heavily involved in the management of early stage biotech ventures through her role as Investment Manager at Start-up Australia, a Sydney-based venture capital company. Since joining Biotron in 2002 Michelle has brought discipline to the technology development process, overseeing the company's transformation from an ANU-associated technology incubator into a focused drug developer. She has also put in place the numerous building blocks to develop BIT225, and has been tenacious in terms of pushing the drug into the clinic. Also, she has done all this while burning less than $200,000 per month in capital, which has represented excellent value for money. We think Michelle has the skills to take Biotron to the next level of attracting licensing interest into the company and building the pipeline.

A quality board. Backing management is a strong board that includes Michelle Miller as well as:

- Chairman **Michael Hoy**, best known as deputy chief executive of John Fairfax in the Conrad Black era of the early 1990s. Hoy brings three decades worth of corporate experience in Australia, the UK, the US and Asia;
- **Bruce Hundertmark**, an ex News Corp executive, but who also came to Biotron with a background of start-up ventures, mainly in the IT space;
- **Dr Denis Wade,** a pharmacologist who formerly helped spearhead J&J's research effort in Australia and who more recently has served on the board of HeartWare, a successful developer of LVADs for the treatment of heart failure[223];
- **Rob Thomas,** an investment banker who was instrumental in building County NatWest in Australia in the 1990s, and is also a current HeartWare director;
- **Dr Susan Pond**, a former head of J&J's Australian research arm who is an authority on the functions and mechanisms of the liver and therefore brings strong expertise in Hepatitis C therapy.

[223] Nasdaq: HTWR; Framingham, Ma; www.heartware.com. HeartWare is also traded on the ASX (code HIN), where it originally did its IPO in 2005. We initiated coverage on HeartWare on 11/11/2010 in a note headlined *The quest for the world's smallest LVAD.* HeartWare's HVAD device is considerably lighter and smaller than the competitor HeartMate II product and, unlike HeartMate II, is implantable within the pericardial space next to the heart. HVAD gained European approval in 2009 and has performed well in a Bridge to Transplant trial in the US, for which data was released in November 2010.

The risks

Biotechnology is risky

The stocks of biotechnology companies without revenue streams from product sales or ongoing service revenue should always be regarded as speculative in character. Since most biotechnology companies in Australia fit this description, the speculative moniker also applies to the entire sector. The fact that biotechnology's intellectual property base lies in science not generally regarded as accessible to the layman adds further to the riskiness with which biotechnology ought to be regarded. Investors are advised to be cognisant of this risk before buying any Australian biotech stock including BIT.

BIT is not without risk

We see six major risks specifically related to BIT as a company and a stock:

1 **Clinical risk** – There is the risk that BIT HCV and HIV clinical trials could fail to reach their endpoints;

2 **Sentiment risk** – Biotech-oriented investors tend to prefer drug development stocks where the lead candidate is in Phase III rather than Phase II, where BIT is currently situated;

BIT has burned under A$200,000 per month since 2004

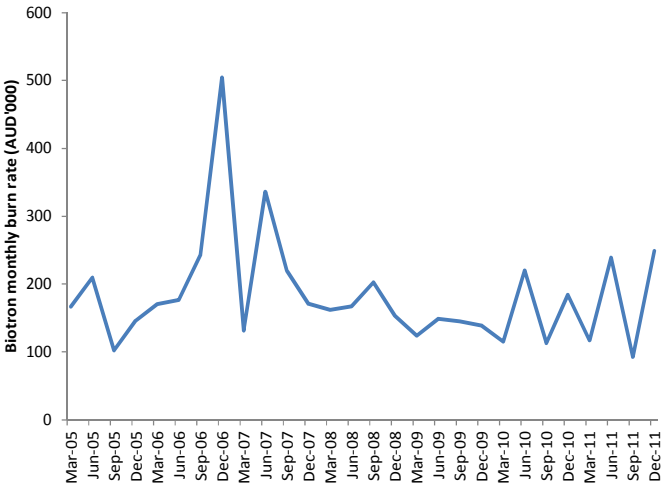
3 **Timing risk** – There is the risk that BIT could take much longer to get its drugs to market than the timing we have postulated in this note;

4 **Partnering risk** – There is the risk that BIT's prospective partners may strike too hard a bargain for BIT shareholders to enjoy a strong return;

5 **IP risk** – There is the risk that BIT could find itself locked in dispute over patent infringement should its science be found to lean too heavily on unrelated or unlicensed predecessor science;

6 **Burn rate** - At 31/12/2011 BIT had $9.1m cash after burning around $184,000 per month since late 2004, including $175,000 per month in 2011. The company has raised ~$33m, in equity capital and options in an IPO and seven subsequent rounds. It may have to make further capital raisings to fund its burn rate in the future.

Figure 26 – Biotron's burn rate since 2004 has been modest



SOURCE: BIT

Appendix I – Biotron's capital structure

Figure 27 - BIT's current capital structure

Shares (ASX Code BIT)	228,296,944	Price (c)	14.5
Unlisted options	5,000,000	Undiluted cap ($m)	33.1
Total diluted shares	233,296,944	F.D. cap ($m)	33.8

OPTIONS	Number	Exercise price	Expiry date	Cash
	2,000,000	$0.22	30-Oct-15	440,000
	3,000,000	$0.25	30-Oct-15	750,000
Total	5,000,000	$0.24	30-Oct-15	1,190,000

SOURCE: BIT.

BIT's average equity raising price has been 19 cents

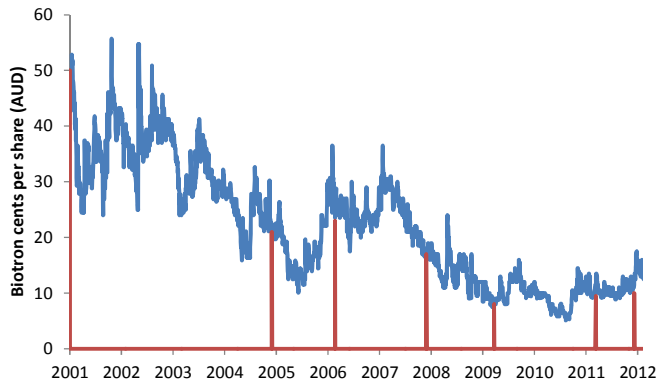
Figure 28 - BIT's equity capital raising history

Date	Shares (million)	% of current shares on issue	Price	Amount raised ($m)	Note
Jan-01	24.0	10.5%	$0.50	12.0	IPO
Dec-04	5.7	2.5%	$0.21	1.2	Share Purchase Plan
Mar-06	19.9	8.7%	$0.23	4.6	2 for 7 rights
Dec-07	14.7	6.4%	$0.17	2.5	Placement / Share Purchase Plan
Apr-09	10.1	4.4%	$0.08	0.8	Placement / Share Purchase Plan
Dec-09				2.3	Jumbo options issue[224]
Apr-11	18.0	7.9%	$0.095	1.7	Placement / Share Purchase Plan
Dec-11	79.9	35.0%	$0.100	8.0	Exercise of listed options
Total	172.3	75.5%	$0.192	33.1	

SOURCE: BIT

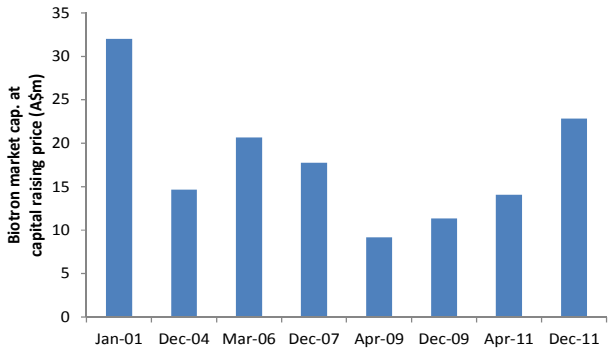
Major shareholders. Currently we understand there are no substantial shareholders in the company.

Figure 29 – Biotron has undertaken eight major capital raisings since 2001



SOURCE: BIOTRON

Figure 30 – The value of Biotron as a company has been increasing since 2009



SOURCE: BIOTRON

[224] In December 2009 BIT raised $2.3m through a 1 for 1 issue of listed options at 2 cents per option. This issue was partly underwritten by Bell Potter Securities. The new options were exercisable at 10 cents but were 'jumbo options', in that if exercised before 31/3/2010, each option would yield another option exercisable at 20 cents by 30/3/2012, while if not exercised before 31/3/2010, the options would expire on 30/12/2011. Around 6% of the original options were exercised before March 2010, raising another $0.64m.

Appendix II – How Hepatitis C drugs are evaluated

Hepatitis C infection can be cured. With existing drug regimens a percentage of patients will experience a Hepatitis C cure, meaning that the virus becomes undetectable in the patient's blood below a certain level, for example, 50 IU/ml[225] and stays that way for at least three months and, more preferably, six months. In the field this outcome is called a 'response'.

There are four response measurements involved in a typical Hepatitis C drug trial, each measuring the cure rate at various time points from baseline.

- *Rapid Virological Response (RVR)* - This is the percentage of patients who have undetectable virus at week 4;
- *Extended Rapid Virological Response (eRVR)* - The percentage of patients who have undetectable virus at both week 4 and at week 12;
- *Early Virological Response (EVR)* – The percentage of patients who have undetectable virus by week 12 *(complete EVR or cEVR)*, or alternately the percentage of patients whose viral load dropped by more than two logs (ie 100 times) from baseline to week 12 *(partial EVR or pEVR)*;
- *Sustained Virological Response (SVR)* – Undetectable virus at certain time points after the cessation of treatment. An SVR12 is undetectable virus 12 weeks after the end of treatment while an SVR24 is undetectable virus 24 weeks after the end of treatment. SVR24 is what is generally regarded as a true viral cure since patients generally don't relapse after this point.

Each of the earlier response measures tends to be predictive of SVR. For example:

Undetectable virus at week 4 is a good sign

- Rapid Virological Response is considered the most important predictor of SVR across genotypes[226]. In one large study only 15% of genotype 1 patients enjoyed an RVR with interferon and rivavirin, but the SVR for those that had an RVR was 52% versus only 18% for those that didn't[227];
- In a study of Incivek, patients who had an eRVR with that drug plus interferon and ribavirin enjoyed an SVR24 of 88-92% whereas the overall SVR24 was only 72% overall[228]
- A 2003 study of interferon and ribavirin has suggested that a failure to reach partial EVR is generally indicative of failure to achieve response to any further therapy[229].

The new drugs are opening up an era of 'response guided therapy' where treatment times can be shortened depending on rapid response. In the abovementioned Incivek trial the 88% SVR24 was obtained in eRVR patients who then went on 48 weeks of interferon and ribavirin after the initial 12 weeks of Incivek. The 92% SVR24 was from eRVR patients who only went on 24 weeks of interferon and ribavirin. This suggested that eRVR could markedly cut the rate at which patients stayed on the traditional drugs.

[225] Where 100,000 'International Units' is the amount of virus in one ml of a standard sample of virus-infected blood. This standard was set by the WHO in 1999 (see Vox Sang. 1999;76(3):149-58.). While 50 IU/ml is standard (this is what Biotron used for its second Phase IIa study) other studies have had lower levels of detection. For example, an Incivek's pivotal trial (see Fried et. al., op. cit.) used version 2.0 of a COBAS TaqMan HCV RNA assay (from Roche), where the lower limit of quantification was 25 IU/ml and lower limit of detection was 10 IU/ml.

[226] See J Hepatol. 2011 Jul;55(1):69-75. Epub 2010 Nov 23.

[227] See Aliment Pharmacol Ther. 2012 Jan;35(1):105-15. Epub 2011 Nov 7.

[228] See N Engl J Med. 2011 Sep 15;365(11):1014-24.

[229] See Hepatology. 2003 Sep;38(3):645-52.

Appendix III - Intellectual property

The intellectual property related to BIT225 is covered by five published patent applications, the first four of which were created by the ANU but transferred to Biotron in December 2006.

Method for Determining Ion Channel Activity of a Substance, WO/98/13514[230] (Priority date 27/9/1996; Invented by Peter Gage, Graeme Cox and Gary Ewart)

This patent application covers assays devised by the Gage laboratory to determine the level of VPU inhibition by compounds. The work involved was basic to the development of BIT225.

A Method of Modulating Ion Channel Functional Activity, WO/00/21538[231] (Priority date 12/10/1998; Invented by Peter Gage, Graeme Cox and Gary Ewart).

This patent covers the use of the Gage team's amiloride analogues, DMA[232] (BIT008) and HMA (BIT009) in antagonizing VPU and thereby cutting HIV viral budding.

Antiviral Acylguanidine Compounds and Methods, WO/2004/112687 (Priority date 26/6/2003; Invented by Peter Gage, Anita Premkumar[233], Gary Ewart, Lauren Wilson[234] and Wayne Best[235])

This patent application, the first to be filed by Biotron rather than the ANU, covers the first of the anti-HIV compounds that the Biotron-associated scientists invented in 2003 and 2004. It also covers the use of Biotron's compounds in combating other viruses, notably Hepatitis C, SARS and other coronaviruses, and dengue.

Biotron has patent protection over BIT225 to at least 2026

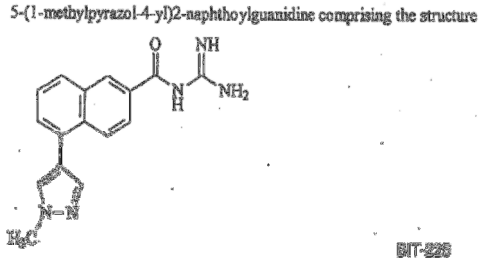
Antiviral Compounds and Methods, WO/2006/135978 (Priority date 24/6/2005; Invented by Gary Ewart and Wayne Best)

This patent covers the second batch of anti-HIV compounds in Biotron's library, including BIT225. Given that patent life is 20 years from filing date (ie a year after priority date), this gives Biotron patent protection for BIT225 until at least 2026[236].

Hepatitis C Antiviral Compositions and Methods, WO/2009/018609 (Priority date 3/8/2007; Invented by Gary Ewart, Carolyn Luscombe and Michelle Miller).

This patent covers the use of the BIT compounds, including BIT225, in combination Hepatitis C therapy.

Figure 31 – Structure of the BIT225 molecule



SOURCE: WO/2009/018609

[230] This patent was granted in the US as No. 6,355,413 in March 2002.

[231] This patent was granted in Europe as EP 1 019 526 in May 2006 and in the US as No. 7,179,803 in February 2007.

[232] Short for dimethyl amiloride.

[233] The ANU staff were included due to their input in identifying ion channel properties of the various viruses covered in these applications, not from their input into designing and testing the compounds which are covered in these applications.

[234] Ewart and Wilson were Biotron employees at the time, working out of premises in Canberra.

[235] Wayne Best is MD of the Perth-based chemistry services firm EpiChem, which is now part of PharmAust, ASX Code PAA. Best was a key player in the rational drug design programme that led to BIT225.

[236] We say 'at least' because of the provision of many jurisdictions for patent extension based on the time spent in clinical development. We think Biotron will have exclusivity to 2032.

Appendix IV – The science behind Biotron

Scientists associated with Biotron were the first to demonstrate that HIV VPU was druggable

Initial work on the drug as an HIV inhibitor. BIT225 has its origins in work done in the late 1990s by the late Professor Peter Gage (1937-2005[237]) and some colleagues at the Australian National University (ANU) in Canberra. Gage et. al. demonstrated that VPU formed gates called 'ion channels' in the membrane of infected cells. They also showed that these channels, by allowing sodium to pass into and out of the cell, facilitated the viral budding process. The Gage lab invented a process of detecting VPU's ion channel activity in cells, but more importantly, the team proved that VPU was potentially druggable[238]. Using existing derivatives of a cardiovascular drug called amiloride[239], which is a sodium channel blocker, the team established two important points:

- That their compounds could block VPU's ion channel activity, and thereby cut viral budding by up to 90%[240]. This work was published in the *European Biophysics Journal* in its March 2002 edition.
- That the compounds could lower virus replication in the human form of a type of white blood cell called the macrophage, which is one of the main viral reservoirs in HIV-positive patients. This work was published in *Antimicrobial Agents and Chemotherapy* in June 2004.

Proof that Biotron can potentially drug Hepatitis C. Scientists working with Biotron demonstrated in 2003 that BIT009 was a potential Hepatitis C treatment via the p7 protein. This work was published in the European journal *FEBS Letters* in January 2004.

Drug development work since 2002. Biotron had initially expected to develop one of the above two amiloride analogues, and in particular one called hexamethylene amiloride, HMA or BIT009[241], as an anti-viral drug[242]. However from 2002 the company embarked upon a rational drug design program that by September 2005 had yielded BIT225, arguably a much better drug.[243]

There is potential for Biotron to develop other anti-viral drugs based on the 'Virion' concept. Beginning around 2003 the scientists associated with Biotron at ANU starting discovering and publishing on a new class of viral proteins called 'viroporins', which are hydrophobic proteins with ion channel activity and have proved to be good drug targets.

- Shortly after the 2002/2003 SARS epidemic Biotron found that the E protein of the SARS virus was druggable, and this was followed by successful discovery work on the M protein of Dengue virus[244].
- In March 2006 Biotron announced one of its compounds had shown good activity against the H5N1 strain of influenza. Not only did the company have a potential anti-influenza candidate, but it was able to quickly create an assay to do high-throughput

[237] See *Proceedings of the Australian Physiological Society* (2006) 37:29-30 for Gage's obituary notice.

[238] The primary reason why the early Gage lab work was important had to do with VPU's similarity to M2, an influenza protein. Amantadine, which in 1976 became the first anti-viral drug to gain FDA approval for treating influenza infection, works by hitting M2, which is an ion channel-forming protein. In effect Gage and his colleagues had re-discovered a way to therapeutically attack viruses. The amantadine/M2 phenomenon had established that the blockade of a virus-generated ion channel could prove a valid drug treatment. And then the Gage team established that HIV also generated ion channels. At the same time they had demonstrated that the VPU channels were sodium-permeable, which hinted at the possibility that a sodium channel blocking drug could become an anti-HIV drug, one that at the very least slowed down the rate of viral budding and therefore augmented the work of other anti-HIV drugs.

[239] Amiloride is a diuretic drug that has been used since the 1960s to treat hypertension and congestive heart failure.

[240] In 2008 scientists at New York's Aaron Diamond AIDS Research Center announced the discovery of the tetherins, antiviral proteins that inhibit the release of retrovirus particles (see Nature. 2008 Jan 24;451(7177):425-30. Epub 2008 Jan 16) and which are antagonised by VPU. It has now been established that BIT225 doesn't stop VPU from antagonising tetherin but seems to specifically target the viroporin function of VPU (see PLoS One. 2011;6(11):e27660. Epub 2011 Nov 14).

[241] Biotron's codename for the drug.

[242] The trouble with this approach was that the compounds that Gage et. al. used were somewhat deficient when it came to drug-like properties. That is, their half-life inside the body was too short; they weren't all that bioavailable; and so on. Also, these other compounds were not novel so Biotron would not have any ownership over them.

[243] By 2004 this programme, initially based on the amiloride derivatives, had yielded a proprietary drug library of around 200 compounds. During 2004 and 2005 this library was winnowed down to the best six compounds through various *in vivo* and *in vitro* tests that sought to maximise desired drug properties while maintaining anti-HIV efficacy. BIT225 was selected as the best of the best late in 2005.

[244] Biotron has an active, albeit early drug development programme in dengue, in collaboration with the Universities of Wollongong and Canberra under an ARC Linkage Grant. We understand that the programme, ongoing since 2007/08, is making good progress towards generating anti-dengue drugs.

screening to look for further drug candidates. We think this programme represents a significant extra 'blue sky' element given the H1N1 pandemic of 2009.

We think there is potential for a pipeline of anti-viral drugs to be built once BIT225 has been moved forward in HIV and HCV.

The 1996 *Journal of Virology* paper

In this paper[245] Ewart et. al. pointed to the potential of HIV to form ion channels in the cells that it infects, via VPU.

VPU can form ion channels. Ewart et. al. proved this by conducting an electrophysiological experiment[246]. Taking a plastic cup that was divided into two chambers with a tiny hole in the middle, they painted a 'lipid bilayer' across the hole[247], and added solutions of potassium and sodium to the two chambers. They then measured electrical activity across the wall between the two chambers before and after the addition of purified VPU protein into one of the chambers. Before the addition of VPU there was no electrical conductance. Afterwards there was such conductance.

Biotron's development of BIT225 has been backed by some peer-reviewed papers

VPU's ion channels are sodium-permeable. Ewart et. al. demonstrated this by expressing VPU into *E. coli* cells and using a 'cross-feeding assay'. Cross-feeding assays are designed to detect the presence of a particular substance in one cell line by placing, in the same test tube, a second cell line that feeds off whatever is produced by the first cell line. Ewart et. al. hypothesised that if VPU formed sodium channels, then *E.-coli*-expressing VPU would leak the amino acid proline but not another amino acid called methionine[248]. When they placed *E. coli* cells expressing VPU into the same minimal media (that is, media lacking any added proline) as cells that could not synthesise their own proline, the latter cells were able to grow, indicating that the proline they were getting was leaking from the former cells. A second experiment, with starved cells that could not synthesise their own methionine, saw those cells unable to grow in the presence of the VPU-expressing cells. Because the protein responsible for proline transport in *E. coli* cells is energised by the sodium 'gradient' normally maintained across the plasma membrane[249], and the protein responsible for methionine transport is not sodium dependant, Ewart et. al. concluded that VPU formed sodium channels in the *E. coli* cells[250]. The cross-feeding assay work provided the basis for Biotron's WO/98/13514 patent application.

The 2002 *European Biophysics Journal* paper

In this paper[251] Ewart et. al. demonstrated that two amiloride derivatives – HMA and DMA – are able to inhibit VPU ion channel activity, and that HMA was able to inhibit viral budding. This work provided the basis for Biotron's WO/00/21538 patent application.

HMA and DMA inhibit VPU activity. Ewart et. al. set up the same two-chamber electrophysiology experiment as that conducted for the *Journal of Virology* paper, only this time added HMA and DMA to the mix. HMA was the best inhibitor of VPU ion channel activity, with average conductance dropping from 14.1 picoSiemens[252] to 0.9 picoSiemens (a 94% drop). For DMA the figure was a drop from 16.1 picoSiemens to 0.5 picoSiemens

[245] Ewart et. al., J Virol. 1996 Oct;70(10):7108-15. Visit http://jvi.asm.org/cgi/reprint/70/10/7108.pdf for a full reprint.

[246] Electrophysiology is the study of the electrical properties of biological cells and tissues.

[247] Lipids are a class of compounds that include fats and waxes. The cell membrane is a lipid bilayer.

[248] Since synthesis of proline required sodium to stay within the cell, and methionine did not.

[249] That is, more sodium on one side of the cell wall than the other.

[250] Others researchers have since shown in 'patch clamping' experiments – where electrodes are placed on opposite sides of cell walls - that VPU can form ion channels in the plasma membrane of eukaryotic cells, that is, the cells of multi-cellular organisms. It is well known that VPU is membrane located (mainly in two structures called the 'endoplasmic reticulum' and the 'Golgi apparatus') in HIV infected mammalian cells. So with the Ewart et. al. work, it would now seem very likely that VPU is able to form ion channels in the cells of humans infected with HIV.

[251] Ewart et. al., Eur Biophys J. 2002 Mar;31(1):26-35

[252] The siemens is the SI unit of electric conductance.

(97%). By contrast amiloride didn't depress ion channel activity at all, and neither did the anti-viral drug amantadine.

HMA cut Gag protein production. Ewart et. al. then expressed VPU and the 'Gag' protein of HIV inside HeLa cells[253] and found that the amount of Gag protein in the 'supernatant' (that is, released from within the cells to the outside culture medium in the form of virus like particles) dropped by more than 90% when HMA was added.

The 2004 *Antimicrobial Agents and Chemotherapy* paper

In this paper[254] Ewart et. al. demonstrated that HMA and DMA could inhibit HIV replication in human monocyte-derived macrophages (MDMs).

Ewart et. al. took some MDMs from healthy donors and infected them in the test tube with HIV. The supernatant was then tested for the presence of p24, the protein which makes up HIV's 'capsid' that is, protein coat, over a 28 day period. In the test tubes in which no DMA or HMA were subsequently added, p24 counts rose inexorably over that time, reflecting the normal process of virus replication and release. By contrast the drug-treated test tubes exhibited marked inhibition of virus release, as measured by p24. Ewart et. al. then tested for HIV DNA and RNA inside cells and found that drug treatment tended to reduce this as well, but not to the same extent as p24 release. This suggested that the drug's main effect was on viral budding.

BIT225 was designed as an anti-HIV compound but was found to be useful against HCV in some serendipitous science

The 2004 FEBS Letters[255] paper

In this paper[256] Premkumar et. al. demonstrated that the p7 protein of HCV was ion channel forming and that the ion channels could be blocked using HMA. Premkumar et. al. set up the same two-chamber electrophysiology experiment as that conducted for the *Journal of Virology* paper, only this experiment used p7 rather than VPU. They were able to demonstrate the presence of viral ion channels and then inhibition of the ion channels using HMA.

2010 papers

Biotron scientists published three interesting papers in the course of 2010:

Another *Antimicrobial Agents and Chemotherapy* paper, February 2010. In this paper[257] Biotron scientists build on the 2004 *Antimicrobial Agents and Chemotherapy* paper by showing that BIT225 can inhibit HIV replication in human MDMs, with replication levels down by up to 99% and inhibition of virus transferring to uninfected T-cells.

Biotron is benefiting from increased scientific understanding of VPU

The *Analytical and Bioanalytical Chemistry* paper, April 2010. In this paper[258] some scientists in the Biomembrane Structure Unit of Oxford's Department of Biochemistry, collaborating with Biotron, show what is required of potential drug candidates that bind to VPU.

The *Antiviral Research* paper, May 2010. In this paper[259] Biotron scientists demonstrate that BIT225 is an effective inhibitor of BVDV, which is bovine viral diarrhoea virus, a surrogate model for HCV. BIT worked successfully against BVDV both as a monotherapy and in combination with interferon and ribavirin, as well as nucleoside analogue drugs.

[253] HeLa is an 'immortal' cell line often used in cancer research, as the original cells were derived from a cervical cancer patient.

[254] Ewart et. al., Antimicrob Agents Chemother. 2004 Jun;48(6):2325-30. Visit http://aac.asm.org/cgi/reprint/48/6/2325 for a full reprint of this paper.

[255] FEBS is the Federation of European Biochemical Societies and *FEBS Letters* is one of its journals (www.febsletters.org).

[256] Premkumar et. al., FEBS Lett. 2004 Jan 16;557(1-3):99-103.

[257] See Khoury et. al., Antimicrob Agents Chemother. 2010 Feb;54(2):835-45. Epub 2009 Dec 7.

[258] See Patargias et. al., Anal Bioanal Chem. 2010 Apr;396(7):2559-63. Epub 2010 Feb 18.

[259] See Luscombe et. al., Antiviral Res. 2010 May;86(2):144-53. Epub 2010 Feb 13.

Appendix V – HCV and HIV companies

Figure 32 - Biotron comparables

Company	Location	Code	Market cap (USDm)[260]	Web site
Idenix Pharmaceuticals	Cambridge, Ma	Nasdaq: IDIX	795	www.idenix.com
Dynavax	Berkeley, Ca	Nasdaq: DVAX	728	www.dynavax.com
Ardea Biosciences	San Diego, Ca	Nasdaq: RDEA	726	www.ardeabio.com
Achillion Pharmaceuticals	New Haven, Ct	Nasdaq: ACHN	619	www.achillion.com
Transgene	Illkirch-Graffenstaden, France	Euronext Paris: TNG	421	www.transgene.com
SciClone Pharmaceuticals	Foster City, Ca	Nasdaq: SCLN	375	www.sciclone.com
Progenics Pharmaceuticals	Tarrytown, NY	Nasdaq: PGNX	323	www.progenics.com
Medivir	Huddinge, Sweden	OMX: MVIR	307	www.medivir.se
Sangamo Biosciences	Richmond, Ca	Nasdaq: SGMO	226	www.sangamo.com
BioCryst Pharmaceuticals	Durham, NC	Nasdaq: BCRX	190	www.biocryst.com
Astex Pharmaceuticals	Dublin, Ca	Nasdaq: ASTX	158	www.astx.com
Inovio Pharmaceuticals	Blue Bell, Pa.	AMEX: INO	80	www.inovio.com
XTL Biopharmaceuticals	Herzliya Pituach, Israel	OTCBB: XTLBY	53	www.xtlbio.com
BioLineRx	Jerusalem, Israel	Nasdaq: BLRX	47	www.biolinerx.com
Medgenics	Misgav, Israel	AMEX: MDGN	45	www.medgenics.com
Peregrine Pharmaceuticals	Tustin, Ca	Nasdaq: PPHM	44	www.peregrineinc.com
Median			267	

SOURCE: BELL POTTER SECURITIES

Achillion Pharmaceuticals. This company is in Phase II for ACH-1625, an HCV NS3 protease inhibitor, while ACH-2684, another NS3 inhibitor, and ACH-2928, a NS5A inhibitor, are in Phase I. ACH-1625, a once-daily product, has performed well with interferon and ribavirin in a Phase II trial, with a 40 mg dose generating an 80% RVR and 100% cEVR in 35 genotype 1 patients in an interim analysis reported in January 2012. Also in January 2012 the product was granted Fast Track designation.

Ardea Biosciences. This company is focused on small molecule drug discovery, with programmes in gout, cancer and HIV. The company's Lesinurad drug for the treatment of gout has performed well in Phase II, is now in Phase III, and will compete with a limited range of treatment options on approval. Ardea is in Phase I with an anti-cancer MEK inhibitor[261] drug called BAY 86-9766, which was partnered to Bayer in 2009. That drug is being studied as a potential adjunct to the Bayer/Onyx renal cancer drug Nexavar. Ardea's RDEA806 NNRTI drug for the treatment of HIV infection brought about viral load reductions at day 8 in a Phase II monotherapy trial.

Astex Pharmaceuticals. This company's first marketed product is Dacogen, for the treatment of myelodysplastic syndrome with various other drugs at Phase II and earlier, mainly focused on oncology. In April 2012 the company unveiled AT26893, which binds a novel target on HCV NS3 protease.

BioCryst Pharmaceuticals. This company is based on technology that can design drugs to block disease-causing enzymes. The company's technology was used to create peramivir, a viral neuraminidase inhibitor for the treatment of influenza that is approved in Japan and Korea. A gout drug and a leukaemia/lymphoma drug is in Phase II. BCX5191, an HCV polymerase inhibitor, has generated favourable pre-clinical data.

[260] As at 16 April 2012 close on Nasdaq and elsewhere.

[261] Short for mitogen-activated ERK kinase, MEK is a key protein kinase in the RAS/RAF/MEK/ERK pathway, which signals for cancer cell proliferation and survival.

BioLineRx. This drug development company is in Phase II/III with a schizophrenia drug called BL0-1020 and is going into a CE Mark registration trial with BL-1040, a drug that converts from liquid to gel on contact with cardiac tissue, providing mechanical support for that tissue after a heart attack. The company is in preclinical with BL-8020, which inhibits HCV-induced autophagy, and BL-8030, which is an HCV protease inhibitor. Both these drugs have been in-licensed in early 2012[262].

Dynavax. This vaccine developer has been built on short synthetic sequences of DNA that target the Toll-like Receptors either for adjuvanting[263] or immune regulation (ie damping down an immune response). It has major partnering deals with GSK (for autoimmune and inflammatory disorders), with AstraZeneca (for asthma and COPD) and with Novartis (for influenza). Dynavax's HEPLISAV Hepatitis B vaccine is in Phase III. For Hepatitis C the company reported Phase Ib data in January 2010 showing that once-weekly dosing of its SD-101 product for four weeks could generate a strong anti-viral immune response as well as engineer a >1 log reduction in viral load[264].

Idenix Pharmaceuticals. This company developed Tyzeka, a Hepatitis B drug for which Novartis gained FDA approval in 2006[265]. Idenix is in Phase II with IDX184, a once-daily nucleoside HCV polymerase inhibitor. Interim Phase IIb data reported in January 2012 showed a 100 mg dose generating a 73% RVR in genotype 1[266].

Inovio Pharmaceuticals. This company's SynCon technology enables better DNA vaccine delivery using electroporation. The company is in Phase II with two cancer vaccines and an HCV vaccine. Merck & Co has partnered with Inovio on V934/V935, potentially useful in various solid tumours. The ChronVac-C HCV vaccine, being worked on by the Swedish company ChronTech Pharma[267] is a codon-optimised[268] version of HCV's NS3/4a protein. Interim results from a Phase I/II study showed five-of-six genotype 1 patients enjoyed SVR24 when administered the vaccine followed by interferon and ribavirin. There was also a strong T-cell response against the virus[269]. Interim results from a Phase I study in HIV-positive patients showed that Inovio's PENNVAX-B HIV vaccine achieved strong T cell immune responses[270]. PENNVAX-B has the potential to be used for both treatment and prevention of HIV.

Medgenics. This company is commercialising technology called Biopump, in which a gene of interest is introduced into a sliver of a patient's dermal tissue, causing the tissue to produce the protein of interest, after which the tissue is implanted subcutaneously. Medgenics is using this technology to make a Biopump called INFRADURE that can produce interferon alpha for the treatment of Hepatitis C. Medgenics intends to commence a clinical trial of INFRADURE in 2012.

Medivir. This company's lead product is TMC435, an HCV NS3/4a protease inhibitor that is in Phase III in partnership with the J&J unit Janssen. In November 2011 Medivir presented data from TMC435's PILLAR Phase IIb study showing that the drug, in combination with interferon and ribavirin in genotype 1 patients, generated an SVR24 of

[262] The main creators of these drugs are Professor Philippe Halfon of Genoscience (see www.3dgenoscience.com) and Professor Raymond Schinazi of Emory University (see www.rfspharma.com). The latter has been a founder of Pharmasset and Idenix, among other companies.

[263] Using CpG motifs - see Expert Rev Vaccines. 2007 Oct;6(5):747-59.

[264] Source: Dynavax press release from 26/1/2010 headlined '*Dynavax reports positive Phase 1b data for SD-101 in chronic Hepatitis C infection*'.

[265] In a March 2003 partnering deal Novartis bought 51% of Idenix for US$255m, as well as paid $75m to license the rights to two Idenix hepatitis B drugs, one of which was Tyzeka. GSK22468761, an NNRTI for the treatment of HIV infection, was partnered to GSK in 2009 and is currently in development by Viiv Healthcare. That drug was placed on clinical hold by the FDA in February 2011.

[266] This allowed a partial clinical hold on the trial to be removed by the FDA.

[267] Huddinge, Sweden (southern suburbs of Stockholm), OMX: CTEC, www.chrontech.se.

[268] Codon optimisation is a DNA vaccine development process whereby codons are changed in the vaccine antigen in order to increase the expression of that antigen in target cells. Codon optimisation technology is a key feature of the DNA vaccines being developed by Coridon, a venture partly owned by Allied Healthcare (Brisbane, Australia, ASX: AHZ, www.alliedhealthcaregroup.com). For a primer on DNA vaccines see our 29 November 2011 research note on Allied Healthcare headlined '*Upside in DNA vaccines and soft tissue repair*'.

[269] Source: Inovio press release from 14/3/2011 headlined 'Inovio Pharmaceuticals' partner Chrontech initiates Phase II clinical trial of Hepatitis C Virus DNA vaccine using Inovio's electroporation delivery technology'

[270] See the company's press release of 13 March 2012 headlined '*Inovio Pharmaceuticals' PENNVAX-B HIV Vaccine Demonstrates Strong T-Cell Immune Responses in Therapeutic Vaccine Trial*'.

75-82% versus 65% for the controls[271]. As we noted above, TMC435 is also being worked on by Bristol-Myers Squibb as a combination drug for daclatasvir. Medivir also has other HCV, HIV, Herpes and dengue drugs in early stage development.

Peregrine Pharmaceuticals. This company is in Phase II with Bavituximab, a cancer antibody being trialled in non-small cell lung cancer and pancreatic cancer, and Cotara, another antibody which has been trialled in a brain cancer called glioblastoma multiforme. Favourable data has been reported on these programmes in 2011. Bavituximab, because it targets phosphatidylserine, a cellular membrane component that is often exposed on the surface of virally-infected cells[272], is also being trialled in HCV. A Phase II trial completed enrolment in September 2011.

Progenics Pharmaceuticals. This company completed a Phase III of RELISTOR, which is oral methylnaltrexone, for the treatment of opioid-induced constipation in September 2010 and its NDA was accepted by the FDA in August 2011. PRO-140m, a monoclonal antibody that functions as an HIV entry inhibitor by binding to CCR5, has completed Phase II.

Sangamo BioSciences. This company is developing SB-728, a 'zinc finger DNA-binding protein nuclease drug' that would treat HIV infection by disrupting the CCR5 receptor. This drug is in Phase I/II clinical trials.

SciClone Pharmaceuticals. This specialty pharma company is mainly focused on China, where it derived the majority of its US$134m in 2011 revenue. Its lead product is Zadaxin, which is a synthetic version of thymosin alpha 1, a product of the thymus gland which is part of the body's immune response. Zadaxin is frequently used to treat Hepatitis C in China and around 30 other, mainly emerging countries.

Transgene. This company has been built on viral vector technology in which a virus, such as recombinant vaccinia virus, expresses both the antigen of interest as well as an immunostimulatory molecule such as the cytokine Interleukin-2[273]. There are currently several products in Phase II - TG4010 for non small cell lung cancer (partnered with Novartis), JX594/TG6006 for liver and colorectal cancer (partnered with the privately-held American biotech Jennerex[274]), TG4001 for HPV, and TG4040 for HCV. Transgene announced in November 2011 that it had achieved 64% cEVR with the TG4040 product in a Phase II trial in genotype 1 patients, in combination with interferon and ribavirin[275].

XTL Biotherapeutics. This company's main product is recombinant human erythropoietin for the treatment of multiple myeloma. The company has also previously discovered several anti- HCV drugs, with the programme outsourced in 2008 to the privately-held San Francisco-based drug developer Presidio Pharmaceuticals. That company has completed Phase Ia work on PPI-668, an HCVB NS5a inhibitor.

[271] Source: Medivir press release of 7/11/2011 headlined '*Medivir's partner Tibotec announced that final SVR24 results from phase IIb PILLAR study of TMC435 will be presented at the AASLD meeting today*'.

[272] See Nat Med. 2008 December; 14(12): 1357–1362.

[273] A small vaccine developer called Virax (Melbourne, Australia, ASX:VHL, www.virax.com.au) uses a similar approach for its vaccine, which it calls Co-X-gene.

[274] In November 2011 the company announced strong survival data from JX594/TG6006 in liver cancer patients.

[275] See the Transgene press release of 7//11/2011 headlined *'Transgene's therapeutic HCV vaccine TG4040 combined with commonly used treatment achieves substantial viral suppression in randomized Phase II trial*'.

Appendix VI – Non-core projects

Biotron has evolved from technology incubator to focused drug developer

When Biotron was formed in 2000 it was a biotech 'incubation' company, designed to work on a number of very early stage projects then emerging from the ANU's John Curtin School of Medical Research. The VPU project was one of these projects, and it became the core project when Michelle Miller joined as CEO in 2002. There were three other projects:

- **C-Test** is designed to detect cancers at their early stages of development[276]. The thinking is that cancers have a different glycolipid expression pattern in blood sera to ordinary sera. Scientists in the laboratory of Professor Chris Parish[277] have developed techniques for extracting certain carbohydrates from the blood and then analysing the expression profile of the carbohydrates using proprietary algorithms. The technology has been trialled using blood sera from patients with various kinds of cancers.
- **GeneTrans** is a test that can help predict the effect of new drugs. The technology is based on MRP2, a so-called 'drug transport' protein whose function, as the name suggests, is to move drugs across the walls of cells. Scientists in Professor Philip Board's laboratory have created a cell line that expresses MRP2[278], and the rate at which these cells die when exposed to drug candidates can provide a good indication as to whether or not the drug is toxic to cells.
- **Muscion**, which emanates from Professor Angela Dulhunty's lab[279], is a project focused on small molecule drugs that target calcium channels called 'ryanodine receptors'[280]. The thinking is that these drugs, by releasing calcium inside heart cells, can induce heart muscle to contract. This could lead to a new-generation drug to treat heart failure.

Biotron has retained ownership of C-Test although that project is currently on hold while the company focuses on BIT225. As for the other two projects, under a December 2006 deal with ANU Biotron received $440,000 for relinquishing rights to the possible future intellectual property from the projects, but will receive a royalty from commercialisation should it occur. The development of GeneTrans and Muscion will not require any funding by Biotron.

[276] See *Method of identifying cancer markers and uses therefor in the diagnosis of cancer* (WO 02/087690, priority date 19 July 2000), and *A novel cancer marker and uses therefor in the diagnosis of cancer* (WO 03/014724, priority date 3 August 2001). The inventors in each case are Chris Parish and Dr Vivian Cabalda-Crane.

[277] Chris Parish was the principal inventor of PI-88, the carbohydrate-based cancer drug that the Brisbane-based Progen (ASX Code PGL) spent many years commercialising.

[278] See *Modified proteins, isolated novel peptides, and uses thereof* (WO 02/18438, priority date 31 August 2000), invented by Philip Board and PhD student Matt Harris.

[279] Professor Dulhunty is a major shareholder of Biotron with 6.7% of the ordinary shares on issue.

[280] See *Method of modulating the activity of calcium channels in cardiac cells and reagents therefor* (WO 02/092119, priority date 17 May 2001), invented by Angela Dulhunty and Dr Marco Casarotto.

Appendix VII – A Biotron glossary

Agonist - A drug designed to enhance the function of receptors, as opposed to antagonists, which are designed to block receptors.

AIDS – The Acquired Immune Deficiency Syndrome, a condition in which the immune system ceases to function effectively due to destruction of white blood cells by HIV.

Amiloride – A cardiovascular drug that is a sodium ion channel blocker. Biotron-associated scientists initially used amiloride analogues when searching for a VPU inhibitor drug. *See HMA below.*

Analogues – Chemical compounds that are based on a known substance but where various elements of the original compound have been changed. Scientists often create analogues of known compounds when looking for new drugs that have similar properties to the compound but are better as drugs.

Antibodies – Substances in the blood that can attach themselves to antigens, thereby neutralising them.

Antigen - The 'bad guy' substance that stimulates the immune system to respond to the perceived threat.

Assay – A test that allows the presence or absence of a substance in a test tube to be verified.

Baseline – The starting point for measurement in a scientific experiment or clinical trial.

Berlin Patient – An HIV positive person who achieved a Functional Cure in late 2008.

Bioavailability – The quantity of a drug that is able to make it to its target once inside the body. High bioavailability is an important component in a drug's prospects for commercial success. High oral bioavailability is even more desirable because then the drug can be administered in pill form. Some drugs have high bioavailability when injected intravenously but low bioavailability orally. BIT225 is considered to have good oral bioavailability.

Blockbuster – A drug that sells more than a US$1bn worth of product annually.

BIT009 – Biotron's initial proof-of-concept compound, based on HMA. BIT009 was superseded in 2005 by BIT225.

BIT225 – A rationally designed drug that Biotron has developed for the treatment of HCV and HIV infection.

CCR5 – A receptor on the surface of some immune system cells that HIV uses to enter the cell. Many 'entry inhibitor' drugs work by blocking CCR5 or its co-receptor, CXCR4.

CD4 cells - White blood cells that assist in the body's immune response through the creation of antibodies. HIV uses the CD4 structure on the cell surface, as well as the co-receptors CCR5 and CXCR4, to enter and infect cells.

Compound library – A collection of proprietary chemical compounds that a drug developer uses when looking for a drug to hit a particular target. Biotron has over 300 compounds in its library.

Coronavirus – A virus with a halo or crown-like appearance mainly known for infections of the upper respiratory tract. SARS is a coronavirus.

CXCR4 – A receptor on the surface of some immune system cells that HIV uses to enter the cell. Many 'entry inhibitor' drugs work by blocking CXCR4 or its co-receptor, CCR5.

Dengue virus – The virus that causes dengue fever, a disease characterized not only by fever but also rashes, headaches and muscle pain. Biotron has demonstrated that its compounds are capable of blocking the M protein in dengue virus.

DNA - Short for deoxyribonucleic acid, a complicated molecule that houses the body's operating instructions. It is made up of a long, long string of base pairs twisted around in a helical shape. Every living being has DNA, none as complicated as the human being's.

E coli – A bacterium typically used in laboratory experiments because of its ability to rapidly multiply.

Entry inhibitor – Anti-HIV drugs that prevent the entry of virus into cells, generally by blocking the cell surface receptors CXCR4 and CCR5.

Enzyme - A protein that helps speed up in biochemical reactions in the body. Enzymes generally have the suffix 'ase' in their name. Reverse transcriptase is an enzyme, as is protease.

E Protein - A protein in the SARS virus which Biotron's compounds seem to be able to block.

eRVR – See RVR.

RVR – Early Virological Response, in which an HCV treatment reduces virus to undetectable levels within 12 weeks.

FDA - The Food and Drug Administration, the American government body which regulates the pharmaceutical industry and from whom approval must be received before a drug can be marketed in the US.

Functional Cure – A situation in an HIV-positive person in which there is no readily detectable virus in absence of therapy for prolonged periods. The Berlin Patient proved that a Functional Cure was possible.

Fusion inhibitor – A drug that can prevent HIV from fusing with its target cell. Fuzeon is a fusion inhibitor.

Gag - Short for 'Group Antigens'. Gag is one of three major proteins encoded within the HIV genome and represents the core structure of the virus

Genotype – A distinct genetic subtype of an organism. There are six genotypes of the Hepatitis C Virus with genotype 1 having historically proved hard to treat. For US patients genotypes 2 and 3 are also relevant.

GMP – Short for Good Manufacturing Practice, GMP is the set of standards that have been laid down by regulators such as the FDA for the production of clinical-grade pharmaceuticals.

H5N1 – The strain of influenza virus commonly known as 'bird flu'. Biotron compounds have been shown to be active against this strain of virus.

H1N1 – The 'swine flu' strain which has generated a human pandemic in 2009.

HAART – Short for Highly Active Anti-Retroviral Therapy, HAART is the various 'drug cocktail' regimes that physicians use to treat HIV infection. HAART is generally one three or more antiretrovirals, one of which has to be a protease inhibitor, one an NNRTI and one an NRTI. Integrase and entry inhibitors are now being included in HAART as well. Biotron considers BIT225 to be a good candidate to fit into HAART.

Hepatitis C –A virus that infects liver cells. Biotron's compounds including BIT225 are capable of blocking the p7 protein in Hepatitis C.

HCV – Short for Hepatitis C.

High-throughput screening – Running multiple compounds from a compound library past a drug target in order to determine if any are able to hit the target.

HIV – The Human Immunodeficiency Virus, which ultimately causes AIDS. BIT225 is an anti-HIV drug.

HMA – Short for hexamethylene amiloride, HMA was Biotron's BIT009 proof-of-concept compound. HMA was superseded by BIT225 in 2005.

IND – Short for Investigational New Drug, an application filed with the FDA to conduct human trials of a new drug in the United States.

Inhibitor – An anti-viral drug that can inhibit a particular viral action, thereby slowing or stopping the rate of infection.

Ions – Atoms or group of atoms with an electrical charge.

Ion Channel - A 'tunnel' in a cell's membranes through which ions - mainly sodium, potassium, calcium, and chloride - travel in and out. Biotron's BIT225 drug inhibits HIV's VPU ion channel activity.

Integrase – HIV enzyme that integrates the viral genetic material into human chromosomes.

Interferon – One of suite of drugs currently used in the treatment of Hepatitis C infection, in conjunction with ribavirin.

***In vitro* –** Testing in the test tube.

***In vivo* –** Testing in live organisms including animal models and humans.

Macrophages – White blood cells involved in the immune system's response to infection. Macrophages are not found in the bloodstream but at locations where body organs interface with the environment or the bloodstream. They are often the 'reservoir' that allows HIV to hide in the body. BIT225 can hit HIV that is in danger of 'hiding' in macrophages.

Mechanism of action – The way in which a drug achieves its therapeutic effect. The mechanism of action of Biotron's BIT225 anti-HIV drug is to inhibit VPU.

Monoclonal antibodies - Antibodies cloned from a particular cell-making antibody that is highly specific for a particular antigen.

Monotherapy – A single-drug approach to the treatment of disease.

M Protein – A protein in the dengue virus which Biotron's compounds seem to be able to block.

Monocyte – The class of white blood cells that includes the macrophages. BIT225 appears to be able to hit HIV in monocyte-derived macophages.

Monotherapy – A treatment regimen in which only a single drug is used.

NNRTI – Short for Non-nucleoside reverse transcriptase inhibitors, drugs that interfere with a virus's reverse transcriptase by preventing that enzyme from binding to the nucleic acid that is going to be copied by the enzyme. The first such drug in HIV, Nevirapine, came on the market in 1996.

Non-responders – Patients that fail to enjoy a clinical response to a particular drug.

NRTI – See nucleoside reverse transcriptase inhibitor.

NS3 – HCV's protease protein.

NS5a – An HCV protein required for viral replication.

NS5b – HCV's polymerase protein.

Nucleoside reverse transcriptase inhibitor – A drug that interferes with a virus's reverse transcriptase through a process whereby a nucleoside analogue causes the copying process of stop short. AZT, the first drug specifically approved as an anti-HIV treatment (in 1987), is a nucleoside reverse transcriptase inhibitor.

Nucleoside – Nucleotides without the phosphate groups.

Nucleotides – Combination of sugar, phosphate and one of four 'bases' that make up DNA and RNA. Nucleotides are genetic 'letters' in what is a four-letter alphabet.

PDUFA date – The day by which the FDA seeks to review an NDA under the Prescription Drug User Fee Act, which allows the agency to charge drug makers for the review process.

Pharmacokinetics – The study of the time course of a drug's absorption, distribution, metabolism, and excretion from the body.

Phase I/IIa – An early-stage safety study (a Phase I study) but one conducted in patients rather than in healthy volunteers.

Phase IIb – A clinical trial to test the efficacy of a drug in a small number of patients.

Phase III – A. clinical trial to test the efficacy of a drug in a large number of patients.

Pegylation – Conjugation of polyethylene glycol to a drug to slow its release into the body. Often pegylated interferon is used to treat Hepatitis C infection.

Polymerase – An enzyme which viruses uses to copy their DNA or RNA. Many HCV drug candidates are polymerase inhibitors. As with NRTIs and NNRTIs in the HIV field, HCV polymerase inhibitors can be nucleoside or non-nucleoside.

Pre-clinical – The stage of a drug's development in which a candidate drug has been selected and it is being tested for its safety ahead of human trials.

Prodrug – A drug that is administered in an inactive form and then metabolised into an active drug. Prodrugs are useful in targeting therapies to the right place in the body.

Prophylactic vaccine – A vaccine used to prevent disease, rather than treat existing disease (which is a therapeutic vaccine).

Protease – An enzyme involved in completion of viral assembly. Protease cuts viral protein chains apart so they can be assembled into their final configuration.

Protease inhibitors – Drugs that inhibit viral replication by hitting the enzyme that completes assembly of the virus. The first anti-HIV protease inhibitor was Roche's Saquinavir, approved in 1995. The first anti-HCV protease inhibitors were Merck & Co.'s Victrelis and Vertex's Incivek, both approved in 2011.

Proteins – A class of fairly common molecules in the living things that includes antibodies and enzymes. Protein-based drugs have a high molecular weight compared to small molecules.

p7 – A protein in Hepatitis C which BIT225 seems to be able to block. HCV p7 is known to form ion channels in cells that assist in viral budding and release.

Refractory – A disease that does not respond to therapy very well.

Retrovirus - A virus whose method of replication is the reverse of the usual method used. Generally viruses have DNA cores and replicate via RNA. Retroviruses, by contrast, consist of only a single strand of RNA coated with protein and replicate via reverse transcriptase. The HIV viruses are retroviruses.

Reverse transcriptase – An enzyme used by retroviruses in their replication process, allowing viral RNA to be converted to DNA. The NRTI and NNRTI anti-HIV drugs work by impacting on reverse transcriptase.

Ribavirin – An anti-viral drug currently used in conjunction with one of the interferons to treat Hepatitis C infection.

RNA – The body's 'photocopier', in that it copies each individual strand of DNA in order to allow it to be made into proteins.

RVR – Rapid Virological Response, in which an HCV treatment reduces virus to undetectable levels within four weeks. An extended Rapid Virological Response (eRVR) is undetectable virus at both four weeks and twelve weeks.

SARS – Short for Severe Acute Respiratory Syndrome, a potentially fatal lung disorder resulting from infection with the SARS virus. SARS was first identified during its sole outbreak to date, in 2003. Biotron's compounds are capable of blocking the E protein in the SARS virus.

Small molecules – Drugs that have a low molecular weight, making them easier to penetrate cell membranes and the blood-brain barrier. All of Biotron's compounds are small molecules. Protein drugs are not small molecules.

Supernatant – Material floating on the surface of a liquid mixture.

SVR – Sustained Virological Response, which is undetectable virus at a certain point after end of treatment. For example, SVR24 is undetectable virus at 24 weeks after therapy ends.

Therapeutic Index – In pharmacology, the ratio of effective dose to minimum tolerated dose. The higher this number, the better. Biotron believes that BIT225 has a good Therapeutic Index.

Therapeutic vaccine – A vaccine used to treat an existing disease, rather than prevent that disease (which is a prophylactic vaccine).

Treatment-naive – A patient whom has yet to be treated with drugs for a particular disease.

Toll-Like Receptors (TLRs) - Molecules on the surface of immune system cells that recognise foreign substances in the body and participate in an immune response.

Toxicology – Tests to see if a drug is harmful in the body.

Virion – The name of Biotron's 'platform' technology, involving the blockage of viral ion channels in cells.

Viral budding – The process by which a newly created virus 'buds' off from an infected cell. BIT225 works to inhibit viral budding.

Viral load – The measure of the amount number of viruses that an infected individual is carrying.

Viral reservoirs – Cells in the body in which a virus such as HIV is able to 'hide' for long periods of time, out of the reach of drug therapy. BIT225 seems to be able to go after viral reservoirs.

Virologic response – The extent to which an anti-viral therapy lowers levels of virus in the bloodstream of patients.

Viroporins - Hydrophobic viral proteins with ion channel activity.

Virus – A strip of DNA or RNA surrounded by a protein coat that is capable of replication only within human or animal cells. HIV is a virus, as are Hepatitis C, dengue and SARS.

VPU – Short for 'Viral Protein U', a protein in HIV that forms ion channels in the membrane of the cell that the virus has infected, thereby facilitating viral budding. BIT225 is a VPU inhibitor.

Biotron

COMPANY DESCRIPTION

Biotron (BIT) is a Sydney-based early stage biotechnology company working on anti-viral drugs. The company's lead compound, BIT225, has shown promise in pre-clinical work in HIV and Hepatitis C (HCV) and two small proof-of-concept trials in Hepatitis C patients have shown efficacy with a dose response. The company's compounds tackle infection by new mechanisms of action. An HIV study is currently underway.

INVESTMENT STRATEGY

We see a payoff to shareholders arising from partnering deals for HIV and HCV as clinical data emerges from the trials. We expect a licensing deal will yield upfront and significant milestone payments as well as royalties.

VALUATION

We assume that Biotron has value for both HCV and HIV. Our $0.40 target price for Biotron is at the midpoint of our base case $0.28 / optimistic case $0.51 per share probability-weighted DCF valuation range. We see the initiation of a larger Phase II trial in HCV as a potential catalyst to reprice Biotron.

RISKS

We see the main risk in Biotron as being clinical risk – ie that products fail to perform in human trials. Another major risk facing the company is that prospective licensing partners may drive too hard a bargain for Biotron shareholders to enjoy a strong return. A third significant risk is burn rate. At 31/12/2011 Biotron had $9.1m cash after burning around $175,000 per month in 2011. The company has raised ~$33m, in equity capital and options in an IPO and seven subsequent rounds. It may have to make further capital raisings to fund its burn rate in the future.

Recommendation structure

Buy: Expect >15% total return on a 12 month view. For stocks regarded as 'Speculative' a return of >30% is expected.

Accumulate: Expect total return between 5% and 15% on a 12 month view. For stocks regarded as 'Speculative' a return of between 5% and 30% is expected.

Hold: Expect total return between -5% and 5% on a 12 month view

Reduce: Expect total return between -15% and -5% on a 12 month view

Sell: Expect <-15% total return on a 12 month view

Speculative Investments are either start-up enterprises with nil or only prospective operations or recently commenced operations with only forecast cash flows, or companies that have commenced operations or have been in operation for some time but have only forecast cash flows and/or a stressed balance sheet.

Such investments may carry an exceptionally high level of capital risk and volatility of returns.

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