

MARKET GUIDE 2001

SPECIAL ISSUE

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7 BIOTECHS SET TO RISE

No need to be

Phase II, phase III – how much can the average investor read into drug trial results, and how can we translate all that medical jargon into a bottom line?

Mark Pachacz puts forward a plain language diagnosis

FOR NEW COMPOUNDS TO MAKE IT TO market as therapeutic medicines, they need to pass through a three-stage clinical trial approval process. The all-important Phase II trials in the past have shown this is where the most value is generated within the drug development process as reflected in the company's share price.

Phase II results deliver for the first time the biological proof-of-concept results in humans, and whether the drug candidate has the realistic potential to become one of the world's next blockbuster drugs – or whether it will be shelved and filed away into oblivion. It is a telling exercise to look at the companies with drugs in Phase II trials. These can also tell investors when they can expect to see some results.

A drug development program really begins to take shape once a lead compound has been selected. Candidates are selected either by screening natural compound libraries, screening libraries of human proteins (such as the massive antibody libraries being generated), creating synthetic molecules through rational drug design (Relenza is a good example) or from bioengineering therapeutics, such as vaccines. The compounds are

tested to get preliminary efficacy and safety data before clinical trials.

Phase I trials assess the compounds for any adverse side effects in humans. Phase II trials establish medium-scale efficacy data on the drug candidate in up to 200 people with varied doses to determine the optimum dosing regime for the next phase. And Phase III trials confirm the positive efficacy data generated from the previous phase on a much larger scale – sometimes on as many as 3000 people, depending on the complexity of the disease.

One of the problems that early stage biotech companies face is generating good quality results from the Phase II trials. Not only do the compounds need to clearly display efficacy in treating a particular disease or disorder, but the trials need to be conducted according to standards accepted by regulatory bodies when the drugs go up for approval after Phase III. The standard biotech model is to deliver good quality Phase II results that will attract the attention of big pharmaceutical companies, and to partner the compound in what can be very expensive Phase III trials.

In a catch-22 situation, young biotech companies can lack the experience in running Phase II clinical trials, although the companies need the results to attract the interest of big pharmaceutical partners. Inadequately structured or conducted Phase II trials can contribute to failures further down the drug development pathway. Some companies, such as Genesis R&D, get around this problem by partnering earlier and concentrating on delivering lead drug candidates.

Companies with compounds in Phase

II trials are Bresagen, Prana Biotechnology, Amrad, Pi2, Genesis R&D (a New Zealand company but also listed locally), CSL and GroPep.

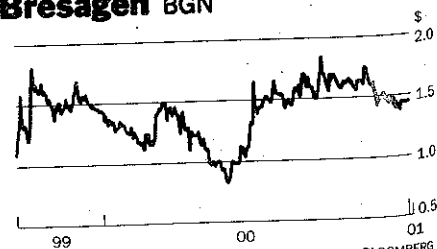
Bresagen

This company listed in 1999. It has a diversified portfolio of early and middle stage research projects and an existing biopharmaceutical business. The company is involved in the cutting edge of biotech research – cell therapy – and is producing growth hormones for horses with the possibility of entering the lucrative human growth hormone market. The company has two therapeutic proteins for the treatment of myeloid leukemia, breast cancer and asthma. The compound for treating leukemia – which may also be used to treat breast cancer – is about to enter Phase II clinical trials.

There are two types of white blood cells. Lymphoid cells, which generate antibodies and T-cells for the body's immune system, and myeloid cells, which produce macrophages to clear waste products in the blood, red blood cells to carry oxygen and platelets to enable blood clotting.

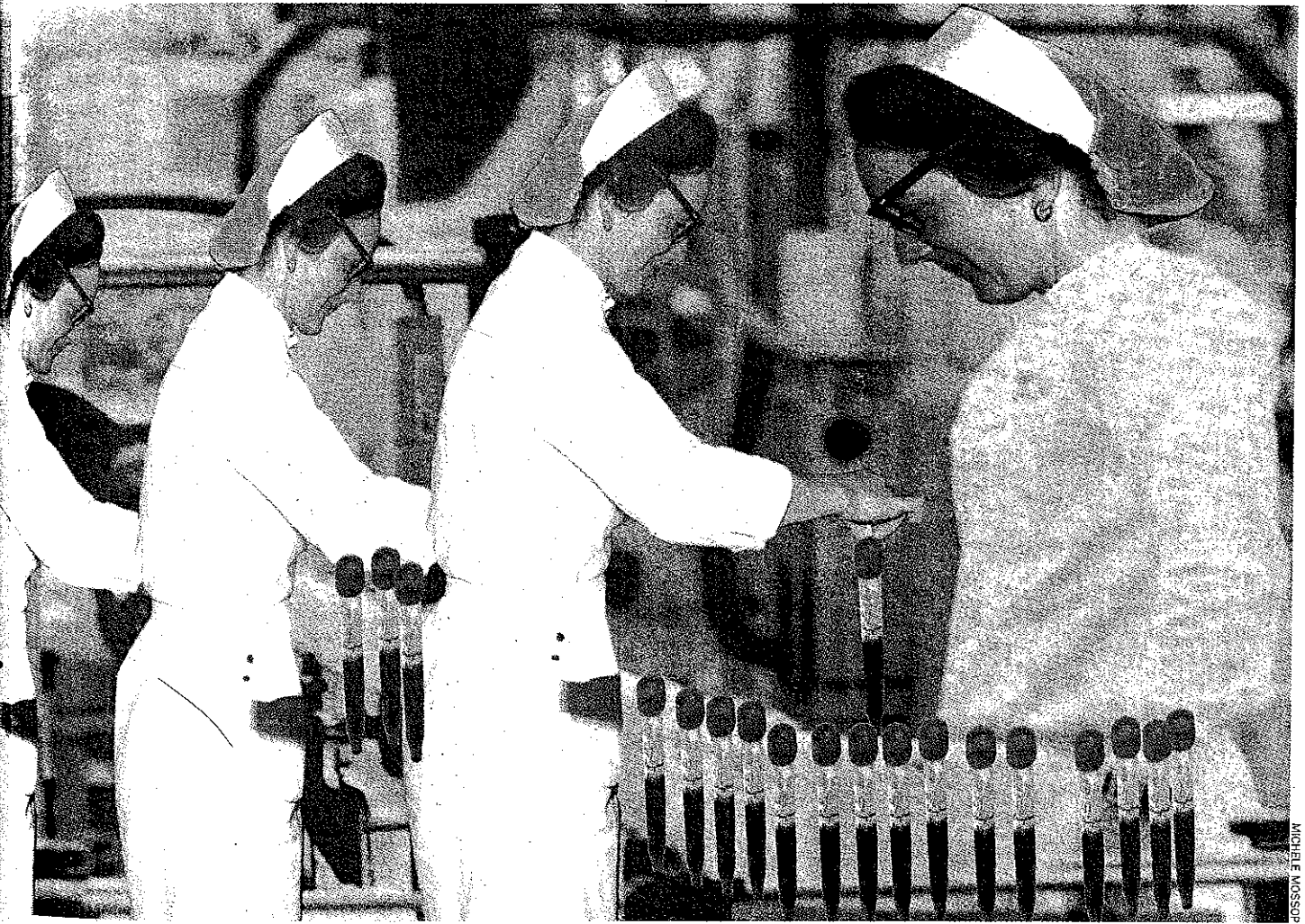
Myeloid leukemia is a breakdown of the white blood cell system in the body. The cancer is simply due to an uncon-

Bresagen BGN



Source: BLOOMBERG

phased



MICHELE MOSSOP

trolled over-replication of a myeloid lineage that is not very functional and takes over the blood stream. It is estimated that one in 10,000 people are affected by this disease. Existing treatment using chemotherapy can produce nasty side effects and the only long-term treatment for children with the disease is a bone marrow transplant, which is only 50 per cent effective. Most chil-

dren with the disease generally do not live longer than five years after the initial diagnosis. The compound was shown to have a very good safety profile in Phase I clinical trials. In September, under compassionate grounds, the compound was given to an eight-year-old boy in France with the disease. After two courses of Bresagen's therapy, the boy's white blood cell count

returned to normal, after being five-fold higher than that, and the boy was free of pain and back to playing sports again. Bresagen's managing director, John Smeaton, says this could be "one of the most promising things in biotechnology to come out of Australia". This was the first time the compound was shown to have a biological effect in a specific disease treatment.

The market for myeloid leukemia is estimated at \$550 million a year. Bresagen will likely partner the development of the drug with a large pharmaceutical corporation to run the expensive Phase III trials. Hospital approvals have been received for Phase II trials, which will begin in Adelaide, Melbourne and Sydney on about 20 adults. Results from the trials can be expected to be released towards the end of 2001. Bresagen's general manager, Meera Verma, says the Phase II results will be a important milestone for the program.

The compound in trials, named E21R, was discovered at the Hanson Centre for Cancer Research in Adelaide. Bresagen has exclusive rights to the commercial use of the protein and will pay royalties to the Hanson Centre in return. Patents for the research have been granted in the US, New Zealand, Australia and Singapore and are pending in Europe, Canada and Japan.

The project received external validation from the Federal Government by way of an Industry Research and Development Start Grant in 1997 for \$2.9 million to go towards funding of clinical trials.

Prana Biotechnology

Prana is seeking to develop and commercialise compounds for the treatment of Alzheimer's disease (see last month's *Shares*). Its lead compound, PBT-1, recently entered a Phase II trial in Melbourne and results are expected to be released towards the end of 2001.

Existing treatments for Alzheimer's disease are even less effective than for myeloid leukemia. The treatments are

expensive and, if anything, have only a mild effect on delaying the onset of the disease. With more than five million people suffering from the disease in the US alone, and with our aging population, the potential market for this therapeutic is estimated at \$5 billion a year.

The results to date for Prana's lead compound have been promising. PBT-1 has shown to be effective in animals in dissolving plaques and preventing the formation of hydrogen peroxide. It has shown to dissolve the plaques in post-mortem brain tissue samples from Alzheimer's sufferers. By the end of this year, investors will know whether PBT-1 is effective to any degree in improving cognitive function in patients afflicted with the disease.

Although Prana has follow-up compounds to PBT-1 that may be more effective, the importance of this clinical trial in establishing preliminary proof-of-concept in people will be a massive milestone for the company. Unlike Bresagen, which has a raft of diversified biotech interests, Prana's narrow focus may result in its share price experiencing some volatility towards year's end, in one direction or the other.

Riding in Prana's favor are two factors that need to be kept in mind - Prana's lead compound was previously prescribed as an antibiotic in the 1970s so its safety profile has been well established; and the bar for an Alzheimer's therapeutic is not set very high at present. Just a hint of evidence in slowing, stopping or reversing this disease will strongly increase the chances of this compound becoming a commercial reality once again.

Pi2

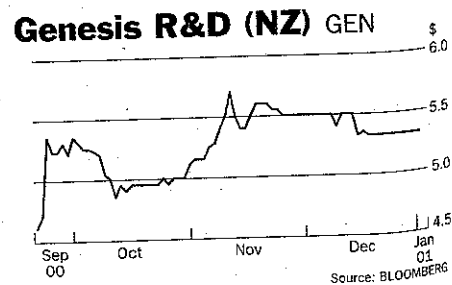
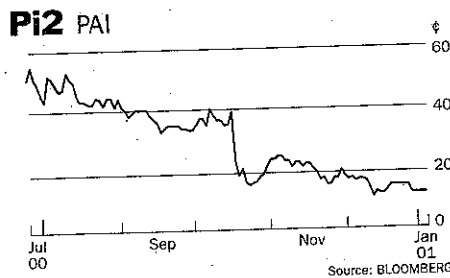
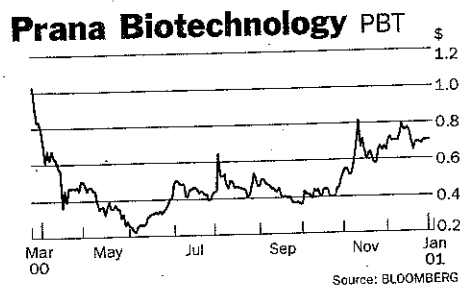
This is a good example of what can happen to a company's share price after disappointing Phase II trial results. Pi2 listed on the ASX in August at 50 cents to commercialise its lead compound, PAI-2. The company had licensed the compound from its major shareholder, Human Therapeutics, for the treatment of psoriasis and CVLU (chronic venous leg ulcers). In October, the company stated that PAI-2 had not been "statistically significant" in treating psoriasis during Phase II clinical trials. On that news, its share price fell by 43 per cent to 20 cents.

The poor efficacy of PAI-2 for the treatment of psoriasis is believed to be linked to poor penetration of the skin and the company's scientific advisory committee has recommended further research. The market for effective psoriasis treatments is estimated at \$US1.5 billion, although existing treatments are ineffective and can only be used for short periods before side effects escalate. As a result, sales of current treatments are in the order of \$US300 million a year.

Pi2 has completed a Phase II trial for the treatment of CVLUs. Leg ulceration occurs as a result of poor blood circulation. PAI-2 is a topical gel application and works by reducing tissue degradation by promoting tissue regrowth. The company will be looking to retrace some lost ground in its share price when results from this trial are released this month.

Genesis R&D Corporation (NZ)

Genesis made a dual listing in Australia and New Zealand in September. It is



another diversified biotechnology company with a platform stemming from genomics research. The company uses genomics to assist in the development of human therapeutics and innovative products in forestry and agriculture.

Genesis is generating a pipeline of products. It has two compounds in clinical trials, and also provides contract research services in the area of gene sequencing.

Where Genesis differs from most biotech companies is in its approach to partnering and out-licensing compounds to other groups. Its lead compound, PVAC, is in Phase II trials for the treatment of psoriasis. The standard model for most biotech companies is to achieve positive Phase II results and then partner the development of the compound with a large pharmaceutical company.

Genesis, however, looks to partner earlier – at the end of Phase I trials – to reduce its risk profile, generating earlier milestone and licensing fees. The company obviously sees its strength as being able to rapidly generate a pipeline of lead compounds from its genomics program.

The development of PVAC has been partnered with a large US biotech company, Corixa Corporation, and this compound has now been licensed to Medicis Pharmaceutical Corporation. Corixa and Genesis will share a royalty stream from any future sales of PVAC.

Psoriasis is a skin disorder that occurs when the top layer of the skin grows so quickly that it continuously falls off. It affects about 2 per cent of the population and ranges from mild to severe forms. It is believed to be an auto-immune disorder

Companies with drugs in Phase II clinical trials

Company	Price (\$) 4/1/01	Market cap (\$m)	Expected impact of Phase II results on share price	Results expected	Compound name	Disease indication	Estimated market size(\$US)	Development partner
Amrad	0.85	99	High	Mar. 2001	Emflermin	Nerve damage	\$1 billion	-
			High	End 2001	AM365	Chronic hepatitis	>\$1 billion	-
			High	End 2001	AM336	Intractable pain	\$400 million	-
Bresagen	1.40	60	Moderate	End 2001	E21R	Myeloid leukemia	500 million	-
CSL	39.95	5978	Low	Mid 2001		HPV	>\$2 billion	Merck (USA)
Genesis R&D	5.36	135	Low	Dec. 2000	PVAC	Psoriasis	\$3 billion	Corixa/Medicis
GroPep	3.33	126	Moderate	Aug. 2001	PV705	Diabetic neuropathy	\$1 billion	-
			Low	Nov. 2001	PV707	Skin graft treatment	\$50 million	-
			Moderate	July 2002	PV702	Venous ulcers	\$1 billion	-
PI2	0.125	5	Moderate	Feb. 2001	PAI-2	Venous ulcers	\$1 billion	-
Prana Biotech	0.76	12	High	End 2001	PBT-1	Alzheimer's disease	\$5 billion	-

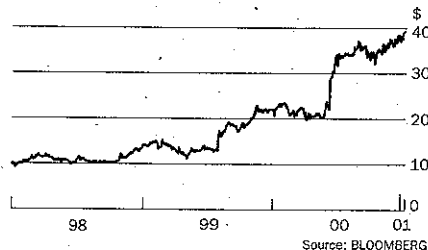
that works in multiple pathways, which makes the disease difficult to treat. The immune system releases cytokines that causes skin growth to go into overdrive, as if trying to heal a wound that isn't there.

PVAC is a novel vaccine that works by reprogramming the immune system. Early Phase II trials have produced some of the most effective clinical results seen to date for the treatment of psoriasis, with more than half the patients demonstrating a 75 per cent reduced severity of the disease over a 52-week period, and with no significant side effects.

CSL

In 1999, CSL initiated Phase II trials for a Human Papilloma virus (HPV) vaccine. HPV is responsible for venereal warts and 99 per cent of women who develop cervical cancer are infected with the virus. The work on this vaccine was developed in

CSL CSL



conjunction with the University of Queensland and CSL has partnered early with one of the largest pharmaceutical companies in the world, Merck (US). Merck has one of the most respected biotech research programs within the pharmaceutical industry.

One of the difficulties with this program is the multiple strains of the virus that exist. There are more than 70 different types of HPV and of these 13 are believed to be associated with cervical cancer. CSL and Merck have focused on developing a vaccine for the four key strains linked with the cancer formation.

Current methods for prevention of cervical cancer involve regular Pap smears with testing for HPV also being conducted in the US and Britain. Although CSL has partnered early, and as a result will receive a lower royalty stream from future sales of the vaccine, the market for an effective (and economical) vaccine would be massive – vaccination of half of the population in the Western world with a possible booster shot every few years. CSL may also manufacture and market the vaccine in certain regions of the world.

Vaccination on such an enormous scale of a healthy population, however, means that it must be exceptionally safe – a reason the trials may be lengthy.

Phase II trials are being conducted in the US by Merck, and results can be expected towards the middle of 2001. Phase III trials will take another three years and the vaccine may be on the market by 2005. With CSL capitalised at more than \$5 billion, positive results from Phase II are not expected to significantly move CSL's share price, but it will reinforce the company's position as one of the largest vaccine companies this side of the equator.

GroPep

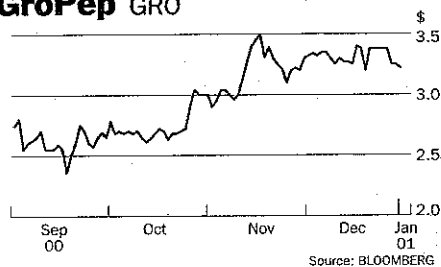
Listed on the ASX in August, GroPep is similar to its counterpart Bresagen, and is also a diversified biotech company. It has a broad pipeline of compounds supported by a biopharmaceutical manufacturing division.

It has three compounds in Phase II clinical trials. One for the treatment of diabetic neuropathy, one compound to stimulate the growth of wounds as a result of venous ulcers, similar to Pi2, and the other for the treatment of burns. None of the compounds have been partnered out at this stage.

GroPep's model is quite standard in that it intends to partner the projects following successful Phase II trials, although the company will market the products independently where the markets are smaller. GroPep's expertise is in the manufacture and development of growth factors. It supplies growth factors to companies, such as CSL, that blend the growth factors with cells infected by viruses to generate large volumes of vaccines in cell cultures.

It is also using its knowledge in growth

GroPep GRO



factors to develop new therapeutics. These include growth factors to regrow wounds that diabetics commonly suffer due to loss of nerve function (nerve endings in diabetics absorb excess glucose in the bloodstream, reducing nerve function); to promote wound healing of skin ulcers as a result of poor blood circulation; and to accelerate skin grafts for patients with burns or major wounds.

The largest market for these compounds is in diabetic neuropathy. About 50,000 diabetics in the US have limbs amputated each year due to chronic nerve ending damage. GroPep may initiate a second Phase II trial following completion of the existing trial. The expected market for treatment of burns and major wounds is not expected to be very large. And the market for venous leg ulcers may be significant, however, it is difficult to judge with no biologically active compounds on the market in this area.

The trials are being conducted in 10 hospitals throughout Australia on 132 patients with results expected in July 2002.

Amrad

Amrad has three drugs expected to complete Phase II trials this year. The first of these to report results is AM424, known as Emfilermin, with test data expected around March. AM424 is a recombinant human growth factor that was initially proposed as a treatment for motor neurone disease (MND) or Amyotrophic Lateral Sclerosis (AMS).

Emfilermin has been shown to stop neurons from dying. AMS is characterised by the rapid acceleration of motor neurone death. Emfilermin has a role in preventing nerve damage, almost by building a "protective coat" around nerves.

Clinical trials for MND can be difficult and protracted, so Amrad opted for developing AM424 to treat nerve damage (peripheral neuropathy) that results from chemotherapy. AM424 entered 18-month Phase II trials in September 1999.

AM336 is a potential treatment for chronic intractable pain. This molecule is derived from the toxins of marine cone snails. Molecules in this class are a thousand times more effective than morphine in treating pain. A similar drug, Elan Pharmaceutical's ziconotide, has received tentative approval from the US Food and Drug Administration.

This is positive news, because it confirms the regulatory and scientific position of this new class of compounds at the highest level. Amrad began combined Phase I/Phase II trials last year, but results should be revealed later this year. Determinations from these trials in the case of chronic pain are quickly and easily determined.

Amrad's third drug in Phase II trials is AM365, designed to treat chronic hepatitis. AM365 is a nucleoside inhibitor, which means it is designed to work inside the nucleus of the cell, where genetic material is located. This compound, if successful, will enter a therapeutic line-up where there is only one partially useful drug available, Lamivudine.

The Hepatitis B virus (HBV) causes chronic infection because it can escape detection by the immune system's "police" by hiding in places inaccessible to the immune system, such as in the brain, testes and liver.

HBV is also a "sloppy" virus. It lacks a reproduction proof-reading capacity, allowing it to mutate very easily. More importantly, HBV, like HIV, encodes a protein called a reverse transcriptase that allows the virus to integrate its DNA with the host DNA. This makes it highly invisible to the host's immune system. Inhibiting transcription is therefore a highly desirable goal for drug designers. Efficacy results for AM365 depend not only on clearing HBV infections, but sustaining the clearance for a long period. (See Amrad story on page 50.)

Mark Pachacz (info@bioshares.com.au)
is the co-author of *Bioshares*, an
independent investment publication
specialising in biotech stocks