

# INVESTOR UPDATE

by  PRIMA BIOMED

EDITION  
NOVEMBER 2015

# 15



Lucy Turnbull, AO

## Message from the Chair

Dear Fellow Shareholders,

As this constitutes the first newsletter since shareholders approved the A\$15m investment in our Company by US-based Ridgeback Capital Investments, I would like to thank you for your support as I regard this as a big step forward for Prima.

The Ridgeback investment provided significant funding for the exciting immuno-oncology programs we acquired late last year with the Immutep SA transaction. In addition, as stated at the EGM, I believe that having Ridgeback as a shareholder elevates the reputation of our Company with key opinion leaders in the Life Sciences investment field. As we highlight in the Investor Relations Update, US activity in our stock has increased markedly since Ridgeback's involvement was announced.

The shareholder vote on 31 July came shortly after completion of a Share Purchase Plan that raised A\$10m at 5 cents per share. This SPP closed oversubscribed, which I think reflects the enthusiasm with which many of Prima's long-standing shareholders in Australia have welcomed the Immutep programs into our Company. Gratifyingly, the funds from the SPP, when combined with the Ridgeback investment and more recent smaller institutional placements provide us funding certainty into 2017, by which time we expect to have made considerable progress with our new lead compound, IMP321.

Prima BioMed today is a company that is in very good shape; commercially, clinically and financially. Commercially, we have products that are partnered with GlaxoSmithKline and Novartis, two of the largest pharmaceutical companies in the world, where both programs have entered the clinic, and we also have a partnership over IMP321 with Eddingpharm, one of the fastest growing pharma companies in China. Clinically, we are on track to commence two studies of IMP321 in the next few months, one of them having recently received Scientific Advice from the European Medicines Agency (EMA). And financially, we have sufficient cash to allow us to make good progress with our existing programs.

That is not to say that the Board and management team at Prima can relax now that Immutep is integrated and the company is well funded. Far from it. Our CEO, Marc Voigt, and his team continue to work hard making sure that the Company realises the potential of IMP321 and our other programs. The team also continues to work on new intellectual property and business development opportunities.

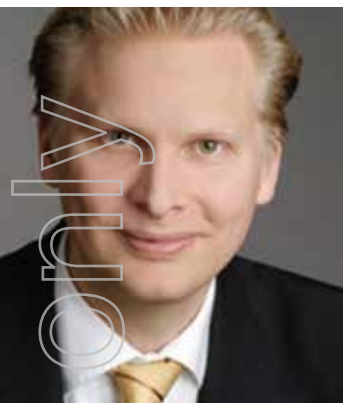
We are frequently asked about the state of play with CVac™, the immunocellular therapy that was Prima's foundation product. As we announced on 27 February 2015, we have ceased recruitment into our CVac studies and are seeking partners for further development. Especially since mid of this year we have had various discussions with potential partners and these are ongoing.

Prima will be holding its 2015 Annual General Meeting in Sydney on 25 November. In addition to the meeting formalities, CEO Marc Voigt will be updating shareholders on our Company's tremendous progress. I would encourage you, if you can, to attend.

Yours sincerely,  
Lucy Turnbull

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Marc Voigt, CEO

## Message from the CEO

### Dear Fellow Shareholders,

Probably the biggest news of the year for Prima BioMed, in my opinion, has been our unveiling in July 2015 of the 'AIPAC' trial for our lead compound, IMP321. In my section of this Investor Update I would like

to focus on AIPAC's importance to Prima BioMed and on its potential to create considerable value for shareholders.

To begin, let me give you some background on IMP321 and the Phase I/IIa data which was generated a few years ago in metastatic breast cancer.

IMP321 is a soluble form of a 'checkpoint' molecule called LAG-3. Checkpoints are key intersections in cell signalling mechanisms that either turn up an immune response (stimulatory checkpoints) or turn it down (inhibitory checkpoints). On the T cells designed to eliminate cancer or infected or abnormal cells, LAG-3 is an inhibitory receptor. However, on the Antigen Presenting Cells (APCs) which help direct our immune systems, Prima's soluble LAG-3 is an activator, meaning that IMP321 can boost T cell responses.

In the past, Immutep showed in a study of 30 women with metastatic breast cancer, that IMP321 as an APC activator could double the response rate of patients being administered a conventional chemotherapy drug called paclitaxel.

AIPAC, short for 'Active Immunotherapy PAclitaxel', will recruit the same cohort of HER-2 negative metastatic breast cancer patients as the previous Phase I/IIa trial, which is described in more detail in the adjacent box, and dose them in the same format. Whereas the original Phase I/IIa had no control group, this multicentre study will be randomised, double blind and placebo-controlled.

After a smaller safety run-in phase (15 patients) that will extend into 2016 and will yield valuable safety, pharmacokinetic and pharmacodynamic data, AIPAC will recruit 196 patients with HER-2 negative metastatic breast cancer, randomising them 1:1 to either standard-of-care paclitaxel or paclitaxel plus IMP321. Progression-Free Survival will be Primary Endpoint, but response rates according to the RECIST criteria and Overall Survival will be among the secondary endpoints. The study has been powered to increase PFS advantage for the treatment group. Clinical data from the safety run in phase

can be expected from mid-2016 onwards. Allowing time for patient recruitment and follow-up, AIPAC's expected duration is approximately three years.

Initiating any clinical study requires being on top of a myriad of details and co-ordinating activities with multiple site administrators, regulators and other stakeholders, not to mention collaborators at the Clinical Research Organisations. I want to thank the team for all the hard work they are putting into AIPAC as well as the very exciting Phase I immuno-oncology combination we intend to initiate shortly in Australia.

Looking back one year since we first announced the acquisition of Immutep, I am very pleased that now all three programs (IMP321, IMP731, and GSK 2831781 derived from IMP701) are at clinical stage, instead of just one (IMP321) at the time of the acquisition. Our partners GSK and Novartis have been advancing the programs to clinical stage and we look forward to further milestones being reached.

Active business development continues to be an important part of our strategy moving forward, with a number of interesting activities which are ongoing. We will of course keep shareholders updated on any significant events.

### Prima's financial position

As at September 2015 Prima held A\$24.4m cash, which reflects the impact of the May 2015 Ridgeback transaction and the SPP. The A\$5.1m of cash spent during the quarter mainly represented increased costs to prepare for the clinical studies and higher G&A costs related to the capital raising.

Since the end of the first fiscal quarter Prima has raised €1m (A\$1.55m) through a small placement at A\$0.05 per share to Nyenburgh Investment Partners, a Netherlands-based health-care fund. We also secured a A\$2m placement with similar conditions to an Australian institutional investor. The growth in institutional investor interest in Prima is a very welcome and positive indication of the strength of Prima's asset portfolio.

These transactions, with selective and credible long term institutional investors, further strengthen our share register while providing opportunities to raise further funds on attractive terms and at a low cost of capital. As a micro-cap company, it is important that we take advantage of efficient financing opportunities that allow us to deliver our growth plans and create long term value for shareholders. Also helping Prima's cash position has been the recent receipt of approx. €306,000 (A\$475,000)

in grant funding for the 2015 financial year from the European Union and the German Free State of Saxony.

Together, these transactions provide Prima with cash reach into 2017. We continue to be vigilant in managing our cash. One example of this is the recent relocation of our head office to Pitt Street. Finance Director Karl Pechmann did an outstanding job in facilitating the move with minimal disruption to the business.

#### Outlook

I believe AIPAC can potentially create considerable value for shareholders. Firstly, hormone receptor positive but HER-2 negative metastatic breast cancer, which represents 65-75% of all breast cancer, has not had many treatment options specifically developed for it in recent years, so this represents a large market opportunity. Secondly, AIPAC is being conducted under the auspices of Scientific Advice from the European Medicines Agency. The legally non-binding Agency's communication to

Prima has suggested that the achievement of certain clinical endpoints may lead to full Marketing Authorisation for IMP321 in the EU based on this one pivotal study.

In addition, we are looking forward to starting a Phase I study with IMP321 in combination with a checkpoint inhibitor in melanoma in Australia early next year and will go into more detail regarding this exciting initiative soon.

I look forward to speaking with many of you again at our Annual General Meeting in November if you are able to attend. On behalf of Prima, I also wish you and your family a very happy Christmas!

Yours sincerely,  
Marc Voigt

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<sup>1</sup>In HER2-negative metastatic breast cancer PFS can be as low as 6 months - see Miller et. al., N Engl J Med. 2007 Dec 27;357(26):2666-76.

## Explaining our Phase I/IIa trial of IMP321 in metastatic breast cancer

When cancer patients receive paclitaxel, their actively dividing cancer cells die and the result is 'tumour debris' produced as cancer cells are destroyed. Adding an APC activator like IMP321 after chemotherapy should boost the patients' APC's to activate more T cells specific against the patients' own tumour antigens present in the debris. As a result, the immune system should kill more cancer cells. In Immutep's Phase I/IIa trial, patients received IMP321 the day after paclitaxel for two of the three doses during a four week cycle when paclitaxel was being administered.

After six months, half of the patients had experienced a reduction in tumour size measured by the sum of diameter of the target lesions by at least 30% (a 'response' as measured by the RECIST criteria<sup>2</sup>). A 30% reduction of the diameter would represent a shrinkage of app. 70% of the tumour volume. 90% of the patients (i.e. 27 out of 30) had seen clinical benefit where at least the tumour was not larger

than it was at the beginning of the study or shrinking by less than 30%. Ordinarily paclitaxel was only expected to get a 25% response rate based on results of a comparable unrelated study called ECOG2100<sup>3</sup>, but IMP321-plus-paclitaxel produced a 50%<sup>4</sup> response rate.

What was even more impressive was the fact that the patients in our trial were much older than those in ECOG2100 (averaging 64 years old vs 55 for ECOG2100) and had a much greater percentage of patients with disease in three or more sites (73% vs 46%). This historical comparison had a p value of 0.007, meaning that it was highly unlikely to have happened by chance.

**Basically, IMP321 seemed to double the response rate for metastatic breast cancer patients even after the patient recruitment process had made it less likely that this could happen.**

<sup>2</sup> Short for the Response Evaluation Criteria in Solid Tumours, RECIST is a set of rules that define when a tumour has responded to treatment, is stable, or has progressed.

<sup>3</sup> See Gray et. al., J Clin Oncol. 2009 Oct 20; 27(30): 4966-4972.

<sup>4</sup> See Brignone et.al., J Transl Med. 2010 Jul 23;8:71.

## Investor Relations Update

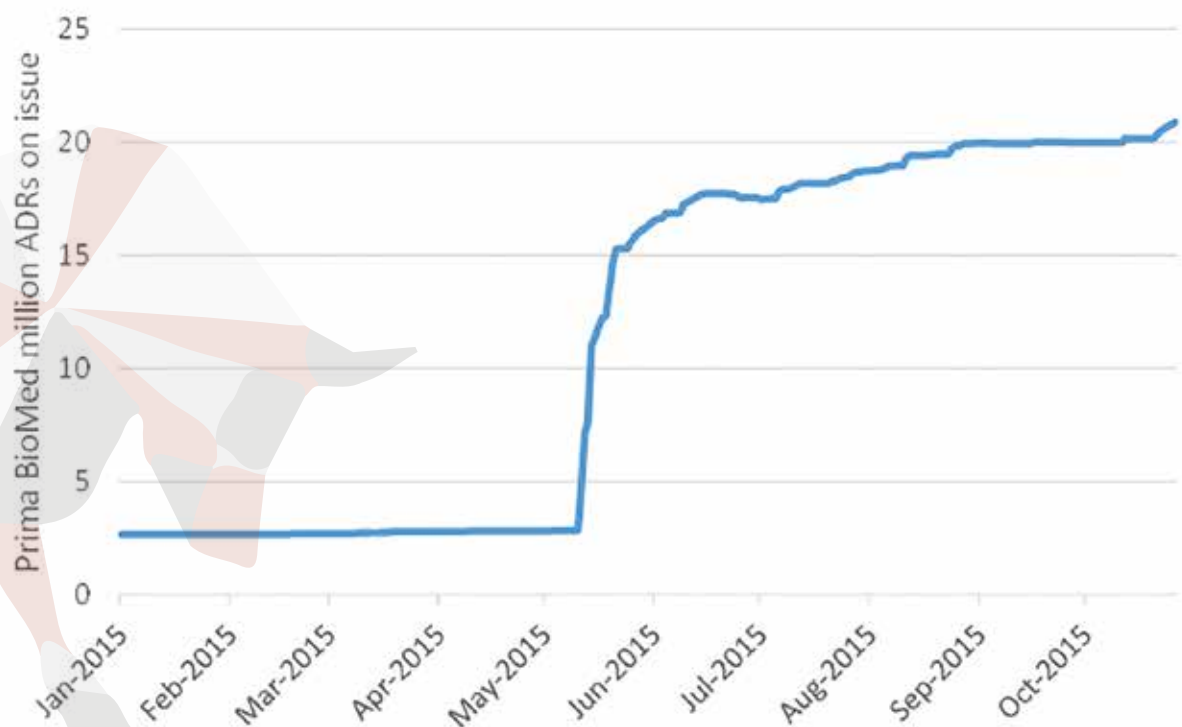
One of the more interesting aspects of our stock over the last couple of months has been the involvement of US investors. Prima BioMed is traded on two markets – the Australian Securities Exchange in the form of ordinary shares (ASX Code: PRR), and on the Nasdaq Global Market in the form of American Depositary Receipts (ADR), in which each ADR represents 30 ordinary shares (Nasdaq Code: PBMD).

Since May 2015 the number of ADRs on issue and available for trading on Nasdaq, and the activity of those ADRs, has increased markedly. On 14 May, when Prima announced the A\$15m Ridgeback investment, there were approximately 2.8 million ADRs representing approximately 6% of the total ordinary shares on issue. On average 10,300 ADRs had been traded each day on Nasdaq over the month prior to the announcement. At the end of October 2015 there were approximately 20.2 million ADRs on issue – a near sevenfold expansion on mid-May - and during the month of October the average turnover on Nasdaq was around 560,000 ADRs per day. More than 30% of Prima's share register is now held in the form of ADRs.

The increased ADR activity has meant that a good part of the liquidity in Prima BioMed stock since May has been generated by US investors. Indeed, Nasdaq has consistently represented more than 80% of the combined daily turnover in Prima stock since May. In August it was a massive 92%.

Nasdaq has been a natural market for biotechnology risk capital ever since the early 1980s, and in the US one can find large numbers of knowledgeable professional biotech investors, both private and institutional, as well as analysts (many of them with PhDs), in a way unknown in other parts of the world. These US investors have seen, since the end of the Global Financial Crisis, a boom in biotechnology investment, and part of the fuel driving that boom has been the rise of companies focused on immuno-oncology. It's fair to say that Prima has now been 'discovered' by US investors.

We have begun the process of harnessing this emerging US interest by introducing our Company to US biotech investors more directly. CEO Marc Voigt presented at the Rodman and Renshaw Global Investment Conference in New York



(8-10 September), and at the Leerink Partners 4th Annual Rare Disease Roundtable in New York (30 September).

Our IR plan involves further visits to continue marketing to the kind of investors that have backed other cancer immunotherapy companies like Juno, Kite, Celldex, NewLink and Aduro (each of whom now has a current market capitalisation in excess of US\$1billion).

Having a bigger US shareholder base will only in turn benefit Australian shareholders because it is likely to lend greater stability to the share register. However, as we have seen with the recent placement announcement, we are also beginning to attract the attention of Australian institutional investors.

We believe that the deep pools of institutional money that can build our Company into one considerably larger than it is today are mostly in the US, so we need to be actively going after it. As a result and in light of our expanded US

shareholder base, it is important that we have someone on the ground in New York City and in the same time zone. We have therefore appointed a specialist investor relations firm, Trout Group, which has considerable expertise in supporting Nasdaq-listed biotech companies.

Our Head of Investor Relations, Stuart Roberts was brought on board following the acquisition of Immutep to help explain the benefits of our LAG-3 based immuno-oncology assets, primarily to the Australian investment community. We were encouraged by the strong shareholder support for our recently oversubscribed SPP, and with Trout now supporting Prima in the US, Stuart is leaving Prima. We thank him for his contribution to our investor relations efforts and wish him well.

## Do we have your correct email address?

We recently checked the email addresses registered against shareholders at our share registry, Boardroom Ltd, and found that over **8%** of them were no longer valid. If Boardroom has a valid email address for you then you can receive all communication from Prima, including investor newsletters like this one, electronically. To add an email address to your account, or change the email registered there, please call Boardroom Ltd on **1300 737 760** within Australia or **+61 2 9260 9600** outside Australia.

## Focus on checkpoints

When Prima BioMed acquired Immutep in December 2014 it became a player in the emerging field of checkpoints as targets for cancer immunotherapy agents. In our July 2015 Newsletter, Professor Frederic Triebel gave us some insight into understanding immune checkpoints and how they work. Here we present some further information and commercial background on checkpoints and why they're helping to create a cancer treatment revolution.

**What are checkpoints?** Checkpoints are intersections in the process of cell signalling that occurs when the receptors and ligands on the various cells that make up the immune system communicate with one another. The signals created at these checkpoints either turn down an immune response (inhibitory checkpoints) or turn up an immune response (stimulatory checkpoints). Checkpoints are vital to the proper functioning of the immune system – for example, when the body can't switch off an immune response that is no longer required, the result can be autoimmune diseases like Rheumatoid Arthritis. However, cancer knows how to interfere with checkpoints to prevent an anti-cancer immune response. In recent years drug developers have started to use the checkpoints to maintain such a response, leading to what we think is a cancer treatment revolution.

**Therapies that work through checkpoints are coming on the market.** The first cancer therapy that worked through interacting with a checkpoint was Yervoy®, an antibody from Bristol-Myers Squibb for the treatment of metastatic melanoma that gained FDA approval in 2011. Yervoy, by binding to a receptor called CTLA-4 present on T cells, blocks an inhibitory signal from being delivered by the tumour to protect itself. The drug was able to increase survival times by >50% in the late stage patients in which it was trialled prior to approval<sup>5</sup>. In 2014 Yervoy was a blockbuster with US\$1.3bn in net sales. There have been similarly good clinical results from two therapies which target another inhibitory checkpoint called PD-1 - Keytruda®, from Merck & Co., and Opdivo®, also from Bristol-Myers Squibb – and pharma companies are working on many more drugs that target the various checkpoints which immunologists have identified.

**Why are people so excited about checkpoints?** The most powerful anti-cancer treatment known to mankind is the human immune system, since it can normally identify and eliminate cancerous cells with exquisite specificity and without any side effects. The approved checkpoint inhibitors

have been among the first drugs that can harness this ability, pointing to long-term functional cures for many patients, where 'functional cure' is the ability to live well beyond the usual life expectancy for the relevant cancer. With approved drugs now targeting the CTLA-4 and PD-1 checkpoints, the search is on for the next checkpoints with clinical relevance. Four checkpoints that are often mentioned as 'coming soon' are TIM-3, GITR, OX40, and Prima's checkpoint, LAG-3.

**How is Prima BioMed a player in the checkpoint space?** Immutep's technology pipeline was built around a checkpoint called LAG-3. This checkpoint is unique in that it can have either an inhibitory or a stimulatory function on the immune system depending on the cells and receptors involved (unlike CTLA-4 and PD-1, which have an inhibitory role only).

From an inhibitory perspective, LAG-3 is now being targeted with antibodies by a number of companies including Novartis, which licenses its LAG-3 antibodies from Immutep. Prima is also working on another property of LAG-3, which is its stimulatory function. On Antigen Presenting Cells LAG-3 is an activator, causing increased antigen presentation when it binds to a molecule called MHC Class II. This function, which Prima harnesses through IMP321, a soluble LAG-3 protein, makes LAG-3 ideal for an immunotherapy agent since it can work with other checkpoint blockers as well as cancer vaccines and conventional chemotherapy.

**Prima will initiate a Phase I trial in an immuno-oncology combination during FY16.** Back in late May, Prima announced that it had filed a provisional patent application over the use of IMP321 in combination with immune checkpoint inhibitors. This meant that the combination could theoretically 'push the gas pedal' on tumour-specific CD8 T cells (IMP321) and then 'release the brake' on these T cells (the checkpoint inhibitors). Beginning in 2016 we plan to initiate a pilot open-label Phase I study of IMP321 in patients with metastatic melanoma. Prima envisages that this study will be run in Australia. We believe that good data from this study can considerably widen the commercial opportunity for IMP321.

<sup>5</sup> See N Engl J Med. 2010 Aug 19;363(8):711-23. Epub 2010 Jun 5.



*Dr Frank Fliegert*

## Meet Dr Frank Fliegert

Dr. Frank Fliegert is Prima BioMed's Global Medical Director, overseeing the medical aspects of the Company's clinical programs related to IMP321. Frank, who joined Prima in June 2014 in Germany, brings experience working with a variety of different drugs at large companies such as Grünenthal and Boehringer Ingelheim as well as small companies such as Noxxon Pharma and the Contract

Research Organization SynteractHCR. A German national, he received his medical degree in 1993 from the Medical School Hannover and went on to specialise in experimental and clinical pharmacology at the University of Aachen before getting involved in commercial drug development.

**Question: You have worked in various drug development teams in a commercial setting since the late 1990s. What do you like about working at Prima BioMed?**

**Answer:** I like the way in which our Company is evolving to go after higher-value products. When I first joined in the middle of last year the Company's lead compound was CVac. That immunocellular therapy certainly has merit as a cancer treatment, as we've seen with the data on second remission ovarian cancer. However, when Prima acquired Immutep and I and my colleagues started work on IMP321, I quickly realised that we have a product that has much lower development cost with bigger upside potential given the Phase I/IIa data.

**Question: What's the most challenging part of your job right now?**

**Answer:** Definitely getting IMP321 ready for the AIPAC trial. The amount of paperwork and co-ordination required by the various stakeholders in this study is immense so there have been a few times when I've been kept up past midnight working on trial design and clinical protocols.

**Question: You have previously worked at the German pharma companies Grünenthal and Boehringer Ingelheim. What are the big lessons you learned at these companies?**

**Answer:** Both these companies have been around a long time – Boehringer since 1885 and Grünenthal since 1946 – and have been very successful so they are well resourced in both clinical and R&D. Working for them allowed me to learn a lot

about how good drugs get off the benchtop. For example, Grünenthal has a great franchise in drugs that treat acute and chronic pain. I was part of the team that helped develop the opioid analgesic Tapentadol® (FDA approved in 2008), and working on this and related products showed me that even in a tough area of drug development like pain – where there are great demands on a physician and a high level of anxiety by regulators given the concerns over side effects and addiction – it's still possible to bring great new products to market. When I was at Boehringer I was involved in the early clinical development strategy of six new drug candidates in various therapeutic areas.

**Question: You've spent some time working in healthcare economics. Any lessons for Prima there?**

**Answer:** Absolutely. Between 2007 and 2009 I worked in Munich as a Drug Management Expert for the private health insurance arm of Allianz AG. While I was there I led a group that was analysing the cost-effectiveness of various drug therapies. What I realised was that drugs which seemed expensive on paper were actually quite cheap when you considered the costs they took out of the system, or the additional years of life they added to patients. Companies looking to get reimbursed for their drugs in the future – and Prima may be there if AIPAC goes well – are likely to be well paid – especially if one is dealing with a biological like IMP321 - for their products so long as they do the homework on cost effectiveness.

**Question: It's often said that good Medical Directors are hard for emerging biotech companies to find. Is that true?**

**Answer:** The job of a Medical Director is to craft and oversee a company's clinical strategy so that it fits in with current best clinical practice in the countries of interest as well as gets the data which the companies and the regulators are looking for. So a Medical Director needs to be up-to-date on standard of care for treatment and also needs to understand the current regulatory environment as well the science – much of it relatively new – behind the product they are working on. This can often vary from country to country. It involves skills from a number of disciplines beyond the practice of medicine, and sometimes involves creating new science. I believe my diverse background, in terms of companies and roles, has helped give me the necessary skills, and that we're putting them to good use getting ready for IMP321's next couple of studies.

## Coming up for Prima in Calendar Year 2016

- Ongoing Phase IIb trial with IMP321 (AIPAC)
- Start of immuno-combination study with IMP321
- Ongoing Phase I trials for IMP701 & GSK 2831781
- Continued expansion of intellectual property
- R&D for new products
- Ongoing: Business development

## Follow Prima's progress

Prima BioMed is dedicated to maintaining consistent and clear communications with our investors. In addition to our quarterly newsletter, we encourage our shareholders to continue following Prima's progress in a number of ways:

► **www.primabiomed.com.au**

The company website is a treasure trove for those in search of details about our company, our management team, and archived information. We encourage everyone to check it out regularly.

► **www.clinicaltrials.gov**

Prima registers all of our clinical trials, and the details of enrolling doctors, on the ClinicalTrials.gov website, a service of the United States National Institutes of Health. This register is the largest such repository of clinical trial information around the world.

► **Twitter**

[twitter.com/PrimaBioMed](https://twitter.com/PrimaBioMed)

► **Facebook**

[www.facebook.com/PrimaBioMed](https://www.facebook.com/PrimaBioMed)

► **LinkedIn**

<http://us.linkedin.com/company/prima-biomed-ltd>

## Prima BioMed – Fast Facts

### Listings

Australian Securities Exchange (ASX), NASDAQ

### Stock Codes

ASX: PRR, NASDAQ: PBMD

### Issued Capital – Ordinary shares

2.06B (approximate as of 19 November 2015)

### Issued ADR's

20.16M (approximate as of 31 October 2015)

### Market Capitalization

A\$105M (approximate as of 19 November 2015)

## Board of Directors

<b>Ms Lucy Turnbull, AO</b>	Non-executive Chairman
<b>Mr Albert Wong</b>	Non-executive Deputy Chairman
<b>Mr Marc Voigt</b>	Executive Director and Chief Executive Officer
<b>Dr Russell J Howard</b>	Non-executive Director
<b>Mr Pete A Meyers</b>	Non-executive Director

## Senior Management

<b>Ms Deanne Miller</b>	General Counsel and Company Secretary
<b>Prof Dr Frédéric Triebel</b>	Chief Medical Officer and Chief Scientific Officer

[www.primabiomed.com.au](http://www.primabiomed.com.au)