

ASX ANNOUNCEMENT

CEO AND MANAGING DIRECTOR

ADDRESS TO SHAREHOLDERS FOLLOWING THE 2014 AGM

13 November 2014

Good morning ladies and gentlemen, both here in Sydney and those joining us via the webcast.

This is the 5th Benitec AGM held since I was appointed CEO in June 2010 and it marks the beginning of the clinical phase of the Company's development.

By any measure this has been a transformational year for Benitec.

Three major events have occurred that have irrevocably altered the Company's future – the FDA giving the green light to the first ever IND application for a systemic ddRNAi clinical trial in January; the \$31.5M capital raising completed in April, and the dosing of a patient in the Company's TT-034 hepatitis C trial, which demonstrated that even at a low dose, the DNA construct reached the patient's liver and expressed short hairpin RNA, with no adverse effects.

When I think back to June 2010, those events seemed a long way away. It is worth spending some time reflecting on the journey we have taken to reach we are today

When the new Benitec Board met to appoint me CEO, I told them that my aim was that Benitec would prove the safety and the efficacy of ddRNAi for human therapeutics.

There were a few hurdles to overcome – lack of money, people, programs and our US Graham patent under rejection. We had no office. No lab. One and a half employees and one licensee – Tacere Therapeutics. And RNAi was at that stage seen as un-investable. Nevertheless, in my address to the Board, I told them that my aim was to get one or more programs into humans within 4 years.

You could excuse them for questioning my grip on reality. However, to their credit, Peter Francis, John Chiplin, Iain Ross and Mel Bridges unanimously agreed to support this vision. Why? Because they shared my belief in ddRNAi to be a transformational therapeutic modality.



The win at the USPTO Appeal on the Graham Patent in October 2010, allowed us to raise around \$7M in May 2011 through Patersons in Melbourne.

This allowed Benitec to commence “Stage 1” of the Benitec revival – the proof of concept stage.

The aim of Stage 1 was to demonstrate the therapeutic potential of ddRNAi in a range of different diseases, and so we started laboratory-based programs in hepatitis B and lung cancer. To do that, I needed the help of Dr Mick Graham, the CSIRO scientist who discovered ddRNAi.

We engaged Mick part time and we started to move forward on hepatitis B with Biomics Biotechnologies in China as well as drug resistant non-small cell lung cancer with the Children’s Cancer Institute Australia at the University of New South Wales.

We had to do these programs as collaborations with external groups because we had no laboratory space, no equipment, and no scientists of our own.

This was soon followed by the concept of a neuropathic pain program based on some very encouraging ddRNAi data from another Chinese group, and, because gene therapy is seen as ideal for orphan diseases, a program in oculopharyngeal muscular dystrophy, in conjunction with Professor George Dickson at the Royal Holloway University of London.

And so we used the \$7M to start to build a company - a team of five, a Board of four and four proof of concept programs.

In November 2012, 18 months after we had raised the money, we acquired our licensee Tacere Therapeutics for \$1.5M in shares.

This followed Pfizer’s merger with Wyeth and the new Pfizer’s decision to de-emphasise anti-infectives, and to close the Sandwich UK plant where the TT-034 program and many other programs were being worked on.

Tacere received the TT-034 asset back from Pfizer, with all of the extensive pre-clinical, IND-ready data, but with no resources to be able to advance the program in an RNAi-averse world.

They turned to us, and the Board and I agreed that acquiring a “clinical ready” program would allow us to get a ddRNAi program into the clinic much faster than any of our Stage 1 proof of concept programs, and to fulfill the aim of proving the safety and efficacy of ddRNAi in people.

So we acquired Tacere, and decided to spend most of our funds on moving TT-034 into the clinic, and put the other programs virtually on hold, as resources did not allow us to significantly advance them.



There is no doubt that acquiring the Tacere assets (TT-034 for hepatitis C and a preclinical AMD program) gave us the ability to attract the interest of local investors to raise another funding round through existing and new shareholders, with the support of Lodge Partners in Melbourne to fund TT-034 into the clinic.

In June 2013, in what was a difficult environment for biotechnology in general and RNAi in particular, Lodge Partners succeeded in raising around \$10M.

That allowed us to fully engage a US-based Contract Research Organisation or CRO, Synteract-HCR, for the hepatitis C trial, and to complete a number of Investigational New Drug Application (IND)-enabling assays for the HCV program. The FDA received the extensive IND in mid-December 2013 and gave the go ahead to commence the first-in-man trial of a systemic ddRNAi drug in mid-January this year. Importantly the Agency released the IND within 30 days of submission with not one single significant question. I believe this highlights the quality of the submission – providing the FDA with the confidence to allow this groundbreaking trial to commence.

At the same time, there was a quantum shift in the RNAi field, with Alnylam, Arrowhead, Tekmira, Dicerna and others working in siRNA announcing good preclinical and clinical data and raising significant funds in the US.

As a result of the renewed interest in this area, Maxim, a New York-based investment bank invited me to come to New York and conduct a non-deal roadshow.

Such was the interest in ddRNAi, TT-034 and other pipeline programs, that it rapidly became clear that there was significant appetite to invest in Benitec, and so we had over \$30M on offer after three days of investor meetings. This was from ten US-based institutional healthcare investors many of whom had never invested in an Australian biotechnology company before.

We decided to accept the funding at a discount to the 15 day V-WAP which was higher than it had been for the past 4 years. The funding was approved by shareholders in April.

That money has been used and is being used to commence “Stage 2” of the Company’s development.

Stage 2 means that we move from proof of concept studies in our pipeline program to IND-ready studies.

To facilitate that we have set up our own laboratory in San Francisco under the leadership of Dr David Suhy, formerly Tacere’s Chief Scientist, who knows what it takes to move a preclinical program into the clinic. The laboratory is named the Bremner Laboratory, recognizing the outstanding support and contribution of Dr Christopher Bremner, whose singlehanded investment in Benitec in 2009, and ongoing support through the following capital raises rescued Benitec financially.



This year we have prioritized three of our pipeline programs – hepatitis B, non-small cell lung cancer, and age-related macular degeneration – as the key programs to advance towards the clinic, based on their potential commerciality and scientific validation. Each of them needs expansion and modification to take them from pre-clinical proof of principle to make them IND ready. We have made significant progress on each of them over the past 6 months. And I will be updating you on each of them shortly.

But before I do that, I want to talk about the TT-034 clinical trial.

It is important to remind everyone that we are conducting a “first in man” clinical trial this is a new therapeutic modality. Many aspects of this trial have never been undertaken before – we are literally breaking new ground at almost every step. Once we administer the compound to the patients, the effect is anticipated to last for up to several years and is non-withdrawable. Therefore in this first trial we need to establish firstly that TT-034 is safe and secondly, the optimal dose at which it is effective. Armed with those pieces of information, this will open the door to a much broader application of this technology in future trials and ultimately on the market.

Although enrolling a second patient to be dosed has taken longer than expected for a variety of reasons, which I have detailed last week in an interview with BRR Media, over the last few months we have taken specific actions to increase the pace of patient recruitment into the trial and those efforts are starting to pay off.

As announced earlier today, the second patient was dosed at Duke overnight. I believe we are on track and the trial will be completed in a timely manner, with the ongoing assistance of Synteract-HCR, Dr David Suhy and Dr Per Lindell who have been working on the trial for the past 9 months, and just recently we have employed Ms Georgina Kilfoil, based in the US, to accelerate recruitment.

Georgina is in the room today and I will now hand over to her to describe the initiatives that the team have put in place.

Thank you Peter.

I am excited to have joined the Benitec family. I have over 24 years of experience in the pharmaceutical and biotech industry – with 8 startup ventures, 4 mid-size biotechs and 3 large pharmaceuticals where I have established a track record of leadership in building, and growing, life-science companies with specific expertise in strategic drug development, operational management, and clinical plan execution.

Along with David Suhy and Per Lindell, I have been working hard over the last couple of months on the TT-034 HCV study, to make sure that we have sufficient patient numbers to screen and to ensure that we reach a timely conclusion to the study.



As Peter mentioned, we have now dosed our second patient. In order to ensure we have a third patient ready to go as soon as we have the green light from the DSMB we are progressing multiple additional patients through the screening process, and have one identified for January.

Both Duke and UCSD continue to work hard to identify patients both through their local databases and through physician referrals. As Peter alluded to, this is a numbers game, the more patients we can get into the top of the funnel, the more likely that we will have eligible patients that can be dosed. With this in mind, we have identified 5 new clinical sites, with the idea of bringing two to three online. The PIs at all of these sites are very enthusiastic about joining the trial and they all have large databases of HCV patients. Two of these sites now have IRB approval for the study and are in the late stages of contract negotiations. We would anticipate having both sites up and running by early January, if not sooner. The third site is in the start-up phase and we hope will be up and running in March or April.

Finally, we have brought a patient recruitment vendor (RESolutions) on board to assist the sites with identifying patients in their local area and with developing targeted advertising materials. RESolutions has been working with both Duke and UCSD and has setup site specific recruitment plans for each site. They have started to engage with the two new sites so these sites will have strong advertising and recruitment plans right out of the gate.

Thanks Georgina.

We have been asked if the difficulty we have experienced in dosing a second patient means that no-one will be eligible for TT-034 when it gets to market.

The answer is absolutely not. This trial, being the first time ddRNAi has been used systemically in humans, is aimed at establishing the safety and optimal therapeutic dose in a necessarily restricted patient group. Once safety has been established, we will have the data needed to be allowed to relax most if not all of the criteria and to offer it to the broader HCV patient community. The data will also have significant positive implications for our hepatitis B program as well. There are numerous clinical remedies to overcome a neutralising antibody which are currently available. We did not want to complicate the first study by introducing those, but they remain an option in subsequent trials.

Another question that we have been asked is “Will there be any market for TT034 in a post Sovaldi/Harvoni world?”

Gilead’s Harvoni drug is the first time that an all oral treatment for HCV has been launched. The big advantage is that it doesn’t need to have regular injections.



The cure rate is reported to be "as high as 99.1%" which whilst very impressive indicates that it is in certain groups, not all patients, and is likely to be lower in real life.

It is a 12 week once a day drug regime which costs \$94,000, so is expensive and subject to patient compliance issues.

If the patient gets reinfected with HCV a few days or weeks later, then they will have to go back on the drug. HCV reinfection rates are reported to be as high as 20% in some patient groups. TT-034 as a single administration treatment should not only be a cure, but should also provide on-going protection against re-infection for months to years. So it really is a totally different proposition.

We are firmly of the belief that TT034, if it works the way we expect it to, will be a superior therapy to existing treatments and as such will take its rightful market share.

However, it is important to remember that Benitec Biopharma is not a hepatitis C company. We are a ddRNAi company with a lead clinical candidate in hepatitis C and an extensive pipeline in other serious diseases, any one of which could be a company-maker in their own right.

I would now like to update the other key programs.

Non-small cell lung cancer program

Earlier this year, the research team at UNSW repeated the *in vivo* experiment demonstrating a doubling in survival of mice with lung cancer when dosed with Benitec's Tribetarna plus the chemotherapy agent cisplatin. As a result, it was decided to advance the program towards a clinical trial. To do that we opened discussions with the United States Food & Drug Administration (FDA) as to what would be required in an IND application.

While the FDA expressed significant interest in this novel approach they requested a number of additional experiments that they would need to see included in the program. When the Bremner laboratory commenced operations in June, we initiated a series of additional preclinical experiments needed to address the FDA's queries. These need to be completed before the appropriate regulatory paperwork can be filed to take the compound into the clinic. Amongst the additional parameters requested by the FDA, these studies will further expand our knowledge and understanding of optimal dosing concentration and timing, and how staggering treatment regimens can impact that ability to sustain maximal knockdown of the target beta-III tubulin gene. As such a series of experiments is underway at third party CROs using an orthotopic model of lung cancer in order to obtain the requested information.

From the published literature, it appears that around 50% of non-small cell lung cancer patients express beta III tubulin in their cancer cells. This group has a life expectancy around 12 months shorter than patients with low levels of beta III tubulin. A critical success factor that we have identified for the Tribetarna clinical trial is to develop a companion diagnostic assay to be used to identify TUBB3 overexpression directly in tumor biopsies and ideally from associated blood samples. The companion diagnostic will not only enable us to identify those patients with the greatest potential to benefit from Tribetarna, it also enables us to correlate Tribetarna efficacy with TUBB3 patient levels.

These developments mean that the proposed clinical trial that we had aimed to commence at the end of this year will proceed when the dose finding, toxicology and companion diagnostic studies have been completed.

To assist in its development, Dr Craig Lewis, an oncologist from Prince of Wales Hospital in Sydney was appointed in the role of Medical Advisor to the lung cancer program. His role is to not only help with the planning and execution of the clinical trial, but to also advise on the development of the companion diagnostic.

Hepatitis B Program

This program was initiated as a joint venture with Biomics Biotechnologies in China. Our strategy with this program is to target the mRNA produced by the hepatitis B virus to knock down viral protein production long term, including the S-antigen gene that the hepatitis B virus utilizes to evade the body's immune system. Long-term suppression of the S-antigen by 48 weeks of conventional drugs has been shown to provide significant therapeutic benefit, and the unique approach of ddRNAi is that we can achieve long term suppression of the target gene from a single, one-time administration. The success of this approach depends upon identifying the best target sequences to silence the S-antigen gene. Whilst some of the sequences identified by Biomics do effectively target the gene, we made the decision earlier this year to use sophisticated database sequence homology searches to broaden the potential pool of effective sequences.

The design of our therapeutic against the Hepatitis B Virus (HBV), is largely based upon mimicking the successful approach used for TT-034. The only changes required are to strip out the anti-HCV sequences from TT-034 and replace them with the new anti-HBV sequences. By taking advantage of the clinical development pathway as well as results of clinical studies from TT-034, we hope to be able to fast track the development of the hepatitis B therapeutic program.

Over the last several months, Benitec's scientists have designed and tested a large number of potential candidate sequences to identify the optimal three sequences that will be inserted into the TT-034 backbone for the final therapeutic. Testing of the sequences is currently on going, and once the final triple construct is identified it will be tested using commercial in vivo and in vitro models of HBV infection.



We are continuing to collaborate with Biomics in the development of this program. We have recently modified the collaboration agreement with Biomics, giving ownership of all developed IP to Benitec and making Benitec the sole commercialising entity.

AMD Program

I would also like to use this opportunity to announce that just yesterday, we executed an agreement with 4D Molecular Therapeutics, a company with a significant amount of expertise for developing next generation AAV vectors with novel properties such as increased tissue specificity or reduced immunogenicity. Specifically, 4D has been engaged to develop novel AAV vectors which in the first instance will be designed to broadly transduce a wide range of retinal cells following an intravitreal injection, a commercially attractive route of administration for ocular therapeutics.

Initially, we intend to employ the novel vector for our Age Related Macular Degeneration program, a disease in which we believe that our ddRNAi technology has the ability to inhibit disease-causing genes for extended periods of time. Currently, the standard of care involves a monthly or bi-monthly intravitreal injection of monoclonal antibodies to be able to prevent progression of the disease. Given that AAV has been clinically demonstrated to produce years of expression following a single administration, including in ocular tissues, we anticipate that this collaboration will deliver exciting advancements and significant competitive advantages for Benitec's AMD program.

If this initial vector performs as anticipated in the retina, we believe that this delivery modality might also provide a clear path for the development of other programs within the same space.

Finally, it should also be noted that the 4D collaboration can also be used to develop other vectors targeting specific tissues apart from liver and neuronal.

doggybone™ DNA

I am also pleased to announce the execution of an Option Agreement with UK based Touchlight Genetics Limited, which provides exclusive worldwide rights to Touchlight's unique closed linear DNA (dbDNA™) platform known as *doggybone*™ DNA, initially for two programs, non-small cell lung cancer and hepatitis B, with the potential to extend it to encompass ddRNAi in general.

doggybone™ is a platform technology that represents the next generation of DNA production and expression.

Touchlight and Benitec are working together to develop and test *doggybone*™-ddRNAi constructs for their use in the lung cancer and particularly hepatitis B programs.

The *doggybone*™ DNA is manufactured without the requirement for bacterial fermentation, and contains no extra sequences traditionally required for DNA plasmid production such as antibiotic resistance genes or extraneous bacterial sequences.



Benitec Biopharma currently employs DNA plasmids in the manufacture of its therapeutic molecules. Given the properties of the *doggybone*[™] DNA technology application of this approach could lead to more effective therapeutic products.

Benitec is also testing the ability of these novel constructs to provide superior expression performance compared to conventional DNA plasmid technology.

I believe that the new technologies that we are in-licensing – *doggybone*[™] and next generation delivery vectors – confirm Benitec as the pre-eminent developer of ddRNAi-based therapeutics. As we and our licensees continue to test ddRNAi based therapies in the clinic, the resulting efficacy and safety data will validate the faith that shareholders, the Board and management have in Mick Graham’s original technology.

I would like to thank my fellow Directors for their on-going support, my team, which now numbers 15, for their hard work, support and dedication over the past year, and of course, you, the shareholders for your support of the Company. I firmly believe that Benitec is in better shape now than at any time in its history, and we look forward with excitement to 2015.

I am happy to answer any questions either from the floor or from the web.

For further information, please contact the persons outlined below, or visit the Benitec website at www.benitec.com.

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About Benitec Biopharma Limited:

Benitec Biopharma Limited is an ASX-listed biotechnology company (ASX:BLT; OTC: BTEBY) which has developed a patented gene-silencing technology called ddRNAi or ‘expressed RNAi’. Based in Sydney, Australia with labs in Hayward CA (USA) and collaborators and licensees around the world, the company is developing ddRNAi-based therapeutics for chronic and life-threatening human conditions including Hepatitis C and B, drug resistant lung cancer and wet Age-related Macular Degeneration. Benitec has also licensed ddRNAi to other biopharmaceutical companies for applications including HIV/AIDS and retinitis pigmentosa. For more information visit www.benitec.com.