

ASX ANNOUNCEMENT

CEO AND MANAGING DIRECTOR ADDRESS TO SHAREHOLDERS

20 November 2014, New York, New York

Good morning ladies and gentlemen.

By any measure 2014 has been a transformational year for Benitec.

Primarily, it was the year which saw the beginning of the clinical phase of the Company's development.

Several major events 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; the first clinical data from the TT-034 hepatitis C trial even at a low dose, the DNA construct reached the patient's liver and expressed short hairpin RNA, with no adverse effects; the opening of the Company's first laboratory since 2006; the in-licensing of two potentially transformational technologies in DNA construct design and AAV delivery technology; and significant interest in Benitec's technology from several major pharmaceutical companies.

When I think back to June 2010, those events all 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.

The win at the USPTO Appeal on the Graham Patent in October 2010, allowed us to raise around \$7M from Australian investors in May 2011. We used the \$7M to start to build a pre-clinical company.

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

with Biomix 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.

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.

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.

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

Acquiring the Tacere assets (TT-034 for hepatitis C and a preclinical AMD program) gave us the ability to raise around \$10M through existing and new Australian shareholders.

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.

At the same time, as a result of the renewed interest in RNAi, 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.



That money 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 the Bremner 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.

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 following discussions with big pharma companies and scientific validation. Each of them needs modification 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 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 took longer than expected for a variety of reasons, which I have detailed elsewhere, last week Duke dosed the second patient. Over the last few months we have taken specific actions to increase the pace of patient recruitment into the trial and those efforts are being coordinated by a new hire, Ms Georgina Kilfoil, based in the US

Georgina has an established track record of leadership in building, and growing, life-science companies with specific expertise in strategic drug development, operational management, and clinical plan execution.

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.

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.



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.

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 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. 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.

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 fundamentally 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* proof of concept 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.

The FDA expressed significant interest in this novel approach and requested a number of additional experiments that they would like to see included – mainly around defining optimal dosing levels and biodistribution. Pleasingly, they were open to conducting simple animal toxicology and biodistribution studies. When the Bremner laboratory commenced operations in June, we initiated a series of additional preclinical experiments needed to address the FDA's queries. A series of experiments is currently underway at a third party CRO using an orthotopic model of lung cancer in order to obtain the requested information. These need to be completed before the appropriate regulatory paperwork can be filed to take the compound into the clinic.



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 identify TUBB3 overexpression. The companion diagnostic will primarily be used to identify those patients with the greatest potential to benefit from Tribetarna™. It is important to note that under current guidelines, the diagnostic does not need regulatory (510(k)) approval before it can be used in conjunction with a trial. For instance, many of our assays currently being used in the TT-034 trial for screening purposes have not gone through the entire 510(k) procedure, but they have to be qualified and/or validated to a certain satisfactory level before they can be used as part of a clinical study.

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

Last week we executed an agreement with 4D Molecular Therapeutics, a US 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. We anticipate that this collaboration will deliver significant competitive advantages and an exclusive IP position for Benitec's AMD program.

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

Last week we also announced the execution of an Option Agreement with UK-based Touchlight Genetics Limited, which provides Benitec with exclusive worldwide rights to Touchlight's unique 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. Touchlight and Benitec are working together to develop and test *doggybone*™-ddRNAi constructs in parallel with the current development of these programs, as potential second generation extensions of these programs.

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

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 firmly believe that Benitec is in better shape now than at any time in its history, and we look forward with excitement to 2015.



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.