



# NDF RESEARCH

Providing independent research coverage of  
ASX-listed Life Science companies

## Anatara (ASX: ANR)

Initiation of Coverage – Monday 23 January 2017

### A good gut feeling

Anatara Lifesciences is nearing the market with its first product, called Detach, a treatment for production animals such as cattle and pigs designed to reduce gastrointestinal disorders in these animals, thereby increasing meat yield. Anatara filed for Australian approval of Detach in October 2016 and expects to be selling the product commercially to pig farmers in 2017. We see significant upside for Anatara from an option granted last year to the animal health major Zoetis over a worldwide license for Detach's use in production animals. Anatara has argued that Detach's mechanism of action, which doesn't involve killing pathogens directly, makes the product one potential solution to the emerging problem of antibiotic resistance. Anatara is currently looking at human applications for Detach, where the market opportunity in Inflammatory Bowel Disease and other gastrointestinal diseases in need of new anti-inflammatory approaches is significant. We value Anatara at \$2.22 base case and \$5.94 optimistic case using a DCF approach. Our target price of \$4.00 sits at around the midpoint of our valuation range.

**Rating**  
Buy

**Risk**  
Speculative

**Current price**  
\$1.02

**Target price**  
\$4.00



#### Stock details

Daily Turnover: ~A23,600  
Market Cap: A\$50.4m  
Shares Issued: 49.4m  
52-Week High: \$1.78  
52-Week Low: \$1.00

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**Please note:** Please refer below for risks related to Anatara Lifesciences as well our General Advice Warning, disclaimer and full disclosures. Also, please be aware that the investment opinion in this report is current as at the date of publication but that the circumstances of the company may change over time, which may in turn affect our investment opinion.



## About NDF Research

NDF is an independent equity research firm based in Sydney, Australia. It focuses on Life Science companies that are publicly traded on the Australian Securities Exchange (ASX), most of which are headquartered in Australia and New Zealand. ASX hosts one of the world's premier equity markets for biotech and medical device companies, and is home to world-beating companies such as CSL and ResMed and emerging pioneers such as Mesoblast and Impedimed.

NDF's Founder and Senior Analyst, Stuart Roberts, has been involved in Life Sciences since 2002 as a sell-side analyst as well as an executive of two ASX-listed immuno-oncology drug developers.

NDF believes that ASX-listed companies have been largely overlooked in the global Life Sciences boom that began in late 2008, partly because of insufficient quality research. NDF's goal is to provide such research, and introduce investors around the world to potential future billion dollar companies from 'Down Under'.

To learn more about the Life Sciences sector on the ASX and our firm, please visit [ndfresearch.com](http://ndfresearch.com).



*Ferry at the end of a rainbow on Sydney Harbour, August 2014*



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## Financial summary

### Financial summary

Code	ANR
Analyst	Stuart Roberts
Date	23 January, 2017
Share price	\$1.02
Market capitalisation	\$50m
Year end	30 June

Rating	BUY
Price target	\$4.00
Upside/downside	292.2%
Valuation	\$2.221 / \$5.943
Valuation method	Probability-weighted DCF
Risk	Medium

#### PROFIT AND LOSS (A\$m)

Y/e June 30 (A\$m)	FY15A	FY16A	FY17E	FY18E	FY19E
Revenue	0	2	0	5	11
EBITDA	-2	-1	-8	-2	7
D&A	0	0	0	0	0
EBIT	-2	-1	-8	-2	7
Net interest	0	0	0	0	0
Pre-tax profit	-2	-1	-8	-2	7
Tax	0	0	0	0	0
NPAT	-2	-1	-8	-2	7
Minority interests	0	0	0	0	0
Net profit after minorities	-2	-1	-8	-2	7

#### BALANCE SHEET (A\$m)

Y/e June 30	FY15A	FY16A	FY17E	FY18E	FY19E
Cash	6	14	6	4	11
Current receivables	0	0	0	0	0
Inventories	0	0	0	0	0
Other current assets	0	0	0	0	0
<b>Current assets</b>	<b>6</b>	<b>14</b>	<b>6</b>	<b>4</b>	<b>12</b>
PPE	0	0	0	0	0
Intangible assets	0	0	0	0	0
Other non-current assets	0	0	0	0	0
<b>Non-current assets</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>
<b>Total assets</b>	<b>6</b>	<b>14</b>	<b>6</b>	<b>4</b>	<b>12</b>
Payables	0	0	0	0	1
Debt	0	0	0	0	0
Other liabilities	0	0	0	0	0
<b>Total liabilities</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>1</b>
Shareholders' equity	5	13	6	4	11
Minorities	0	0	0	0	0
<b>Total shareholders funds</b>	<b>5</b>	<b>13</b>	<b>6</b>	<b>4</b>	<b>11</b>
<b>Total funds employed</b>	<b>6</b>	<b>14</b>	<b>6</b>	<b>4</b>	<b>12</b>
<b>W/A shares on issue</b>	<b>31</b>	<b>49</b>	<b>34</b>	<b>34</b>	<b>34</b>

#### CASH FLOW (A\$m)

Y/e June 30	FY15A	FY16A	FY17E	FY18E	FY19E
NPAT plus discontinued ops.	-2	-1	-8	-2	7
Non-cash items	0	0	0	0	0
Working capital	0	0	0	0	0
Other operating cash flow	0	0	0	0	0
<b>Operating cashflow</b>	<b>-2</b>	<b>0</b>	<b>-8</b>	<b>-2</b>	<b>7</b>
Capex	0	0	0	0	0
Investments	0	0	0	0	0
Other investing cash flow	0	0	0	0	0
<b>Investing cashflow</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>
Change in borrowings	0	0	0	0	0
Equity raised	6	9	0	0	0
Dividends paid	0	0	0	0	0
Other financing cash flow	0	0	0	0	0
<b>Financing cashflow</b>	<b>6</b>	<b>9</b>	<b>0</b>	<b>0</b>	<b>0</b>
<b>Net change in cash</b>	<b>4</b>	<b>8</b>	<b>-8</b>	<b>-2</b>	<b>7</b>
<b>Cash at end of period</b>	<b>6</b>	<b>14</b>	<b>6</b>	<b>4</b>	<b>11</b>

#### EARNINGS (A\$m)

Y/e June 30	FY15A	FY16A	FY17E	FY18E	FY19E
Net profit (\$m)	-1.8	-0.7	-8.1	-2.3	7.1
EPS (c)	-5.8	-1.5	-23.4	-6.7	20.7
EPS growth (%)	N/A	N/A	N/A	N/A	N/A
P/E ratio (x)	-17.5	-68.5	-4.4	-15.1	4.9
CFPS (c)	-6.3	-0.6	-21.8	-6.4	21.0
Price/CF (x)	-16.3	-177.0	-4.7	-15.9	4.9
DPS ( c )	0.0	0.0	0.0	0.0	0.0
Yield (%)	0.0%	0.0%	0.0%	0.0%	0.0%
Franking (%)	N/A	N/A	N/A	N/A	N/A
EV/EBITDA	-23.2	-34.5	-5.4	-19.9	5.5
EV/EBIT	-23.2	-34.0	-5.4	-19.8	5.5

#### PROFITABILITY RATIOS

Y/e June 30	FY15A	FY16A	FY17E	FY18E	FY19E
EBITDA/revenue (%)	-3173.8%	-43.3%	-6384.4%	-44.7%	64.9%
EBIT/revenue (%)	-3173.8%	-44.0%	-6386.8%	-44.8%	64.8%
Return on assets (%)	-31.9%	-5.2%	-132.0%	-54.1%	59.9%
Return on equity (%)	-32.7%	-5.4%	-140.0%	-60.9%	63.1%
Return on funds empl'd (%)	-32.7%	-5.4%	-140.0%	-60.9%	63.1%
Dividend cover (x)	N/A	N/A	N/A	N/A	0%
Effective tax rate (%)	0.0%	0.0%	0.0%	0.0%	0.0%

#### LIQUIDITY AND LEVERAGE RATIOS

Y/e June 30	FY15A	FY16A	FY17E	FY18E	FY19E
Net debt/(cash) (\$m)	-6	-14	-6	-4	-11
<b>Net debt/equity (%)</b>	<b>-101.3%</b>	<b>-102.6%</b>	<b>-109.2%</b>	<b>-107.0%</b>	<b>-99.8%</b>
Net interest cover (x)	N/A	N/A	N/A	N/A	N/A
Current ratio (x)	38.1	31.2	17.5	8.9	19.2

#### INTERIMS

Y/e June 30 (\$m)	2H15A	1H16A	2H16A	1H17F	2H17F
Revenue	0	0	2	0	0
EBITDA	-2	-1	0	-4	-5
D&A	0	0	0	0	0
EBIT	-2	-1	0	-4	-5
Net interest	0	0	0	0	0
Pre-tax profit	-2	-1	0	-3	-5
Tax	0	0	0	0	0
NPAT	-2	-1	0	-3	-5
Minority interests	0	0	0	0	0
Net profit after minorities	-2	-1	0	-3	-5

#### VALUATION

	Base	Optim.
Detach Global (A\$m)	92.3	237.2
Value of tax losses	1.1	1.1
Underlying R&D cost	-9.6	-9.6
Cash now (A\$m)	12.3	12.3
Cash from options and cash to be raised	2.5	2.5
<b>Total value (A\$m)</b>	<b>114.2</b>	<b>305.4</b>
Total diluted shares (million)	51.4	51.4
Value per share	\$2.22	\$5.94
Valuation midpoint	\$4.08	
Share price now (A\$ per share)	\$1.020	
Upside to midpoint	300.2%	



## Introducing Anantara (ASX: ANR)

Anantara Lifesciences is a Brisbane-based drug developer, initially focused on the use of a natural product called bromelain in animal health. Its lead product, a bromelain formulation called 'Detach', has been demonstrated in various field trials to be able to reduce gastrointestinal disorders in cattle and pigs, thereby increasing the meat yield of these 'production animals'. Detach can do this by harnessing the notable anti-infective properties of bromelain. Anantara has completed registration studies for Detach in Australia and submitted its dossier to the regulators ahead of a 2017 commercial launch. In January 2016 Anantara granted the animal health major Zoetis an option over an exclusive worldwide license for Detach's use in production animals. Anantara is currently looking at human applications for Detach, where the market opportunity is significant. Anantara has argued that Detach's mechanism of action, which doesn't involve killing the pathogens directly, makes the product one potential solution to the emerging problem of antibiotic resistance.

**ANATARA  
OPTIONED ITS  
LEAD  
PRODUCT TO  
ZOETIS IN 2016**

**What is bromelain, and how can it potentially ameliorate the scourge of antibiotic resistance?** Bromelain is one of several protein-digesting enzymes that can be obtained from the fruit or stem of pineapples<sup>1</sup>. Over the years, researchers have identified numerous potential therapeutic applications of bromelain in conditions as diverse as osteoarthritis, angina and even cancer<sup>2</sup>. One of the product's specific anti-infective properties arise from its ability to prevent the attachment of pathogenic gut bacteria to various receptors located on the intestinal mucosa. Ordinarily such attachment would allow efficient delivery of bacterial enterotoxins, resulting in diarrhea. When unable to bind these receptors, such bacteria are rendered harmless, and since bromelain doesn't kill the offending bacteria, there is no opportunity for drug resistant strains to emerge.

**Why is Anantara's Detach bromelain formulation different from previous formulations?** Detach is a patented formulation of bromelain protease where the bromelain has been obtained from the stem of pineapples<sup>3</sup>. It's fair to say that bromelain is far from novel, having first been isolated in 1891<sup>4</sup> and first marketed commercially from the late 1950's<sup>5</sup>. Moreover, the original formulation of bromelain, also called Detach, was developed in the late 1980s and early 1990s<sup>6</sup> for use in the animal health market. However, the current Detach formulation, developed shortly after the 2010 startup of Anantara and patent protected from 2014<sup>7</sup>, differs from its predecessor in that it does not contain phthalates – excipients now no longer used due to their potential toxicity<sup>8</sup> – while the bromelain used in the new product is different in composition from commonly available bromelain. Also, in the years since the early 1990s no other company has advanced the use of bromelain in animal health in a serious way, so Anantara is arguably a leader in this field.

**What is the evidence that Detach can increase meat yield in production animals?** Numerous field trials in pigs in the late 1980s and early 1990s showed that the original Detach formulation could improve weight gain in the

<sup>1</sup> People encounter bromelain any time they place a slice of pineapple onto steak to tenderise it – proteolytic work which is performed by this enzyme.

<sup>2</sup> Biotechnol Res Int. 2012;2012:976203. Epub 2012 Dec 10.

<sup>3</sup> Fruit bromelain is substantially different from stem bromelain but the latter has greater anti-infective and anti-inflammatory properties.

<sup>4</sup> Marciano, Bull. Pharm. 5, 77 (1891).

<sup>5</sup> After researchers in Hawaii funded by pineapple growers discovered efficient ways to obtain the bromelain – see Heinicke and Gortner, Economic Botany July 1957, Volume 11, Issue 3, pp 225–234.

<sup>6</sup> See *Use of enzymes, especially bromelain, in the treatment of diarrhoea*, WO/1994/000147, priority date 30 June 1992, invented by Tracey Mynott.

<sup>7</sup> See *Anti-diarrhea formulation which avoids antimicrobial resistance*, WO/2016/032944, priority date 25 August 2014, invented by Tracey Mynott and John Walsh.

<sup>8</sup> See *Phthalates are everywhere, and the health risks are worrying. How bad are they really?* by Amy Westervelt, The Guardian, 11 February 2015.



herd, as well as cut mortality and the level of antibiotic use, all of which had demonstrable economic benefits<sup>9</sup>. A field trial of the new Detach formulation in 2012 showed that this product could lower the incidence of scour in post-weaning pigs by 40%, as well as increase weight gain while reducing antibiotic use. In addition to this, the product could also increase the 'feed conversion ratio' of the piglets – the quantity of feed compared to the meat yield. Subsequent studies have confirmed this original 2012 study, allowing Anantara to file for Australian registration of the product.

**What is the potential human uses of Detach?** Diarrhea in humans is a potentially lucrative indication for Detach given the incidence of this condition, and Anantara believes that there is a potential new military indication here. However, bromelain also has anti-inflammatory properties, making Detach potentially useful in large market prescription opportunities such as Inflammatory Bowel Disease. An initial safety study has shown Detach to be very well tolerated, and Anantara envisages the potential for partnering discussions around various human indications in 2017.

**ANATARA MAY  
HAVE AN Rx  
PRODUCT FOR  
IRRITABLE  
BOWEL  
SYNDROME IN  
ITS PIPELINE**

## Ten reasons to consider Anantara

1. **Anantara is getting ready to launch its first commercial product.** With various field trials having shown the safety and efficacy of Detach in pigs, Anantara has now filed for Australian registration of the product. Subject to approval, the company envisages launching Detach commercially in 2017.
2. **Anantara has optioned Detach to Zoetis for production animal use.** Zoetis, formerly a unit of Pfizer<sup>10</sup>, is the world's largest animal health company, with US\$4.8bn in revenue and US\$889m<sup>11</sup> in net income in 2015. Anantara will therefore have a significant marketing partner should Zoetis choose to exercise the option which it took in January 2016 over an exclusive worldwide license for Detach in production animals.
3. **Detach is likely to be attractive given worries about antibiotic resistance.** The rising incidence of drug-resistant bacteria or 'superbugs' around the world has in recent years excited the interest of policy-makers and food producers alike, with many key opinion leaders advocating for lower use of antibiotics in the food chain. This adds to the appeal of Detach as a product that can replace antibiotics while still preventing infectious diseases of production animals.
4. **Detach potential represents an important productivity tool for farmers.** Given that the global demand for meat is expected to grow significantly over the next two decades, producers of cattle and pigs are looking for new tools to lower the rate of infectious diseases that don't involve antibiotics. Detach represents one such tool.
5. **The human uses of Detach are significant.** The prevalence of Inflammatory Bowel Disease (1.2-1.6 million US patients) and Irritable Bowel Syndrome (11% of the global population) suggests a significant payoff for Anantara should Detach have utility in this setting.

<sup>9</sup> See Lyndsay, Milne's Pork Journal 1991:13;32-34.

<sup>10</sup> Florham Park, NJ, NYSE: ZTS, www.zoetis.com..

<sup>11</sup> Non-GAAP, adjusted.



6. **There is potential for US government help related to military medicine.** Given the potentially debilitating effects of diarrhea in combat zones, we believe Detach could attract US Department of Defence funding.
7. **Detach's mechanism of action is well understood and the safety profile is excellent.** Dr Tracey Mynott, Chief Scientific Officer and co-founder of Anantara, has spent the best part of two decades working on bromelain and has built up a strong knowledge base on how it works as an anti-infective and an anti-inflammatory. We think this increases the product's potential to gain partnering interest for human use, helped by the fact that bromelain is Generally Regarded as Safe (GRAS).
8. **Anantara is fully funded through to first revenues.** With Anantara having raised A\$9m in a placement at 78 cents per share in July 2015, the company has a good runway through to first revenues from Detach in 2017.
9. **Anantara has a solid management team.** Chairman and CEO Dr Mel Bridges has a track record of success in a variety of Life Sciences ventures running back to the 1980s. Chief Scientific Officer Dr Tracey Mynott has been intimately involved in the science behind Anantara running back to the 1980s and brings considerable corporate memory regarding the Detach project, as well as significant 'skin in the game' through her 9% stake in the company. Backing Mel Bridges and Tracey Mynott is a board with the background suitable to an early stage Life Sciences company.
10. **Anantara is undervalued on our numbers.** We value Anantara at \$2.22 base case and \$5.94 optimistic case using a DCF approach. Our target price of \$4.00 sits at around the midpoint of our valuation range. We see Anantara being re-rated by the market as further data emerges on the utility of Detach in pig farming, and as first regulatory approval nears.

**TRACEY  
MYNOTT HAS  
BEEN  
WORKING ON  
BROMELAIN  
SINCE THE  
1980s**

## Anantara's Detach product – The story so far

**There is a long history of development behind the current Detach formulation.** When Anantara Lifesciences went public on the ASX in October 2014<sup>12</sup> it was the third public company to have been involved in the development of bromelain as an anti-infective in animal health. We think Tracey Mynott's willingness to persevere with the Detach project through all three companies, including putting up her own money, bodes well for an eventual commercial payoff for Anantara shareholders.

**Cortecs (1991-2002).** Back in the mid-1980s Tracey Mynott, then a trainee microbiologist, became interested in the potential of bromelain to treat diarrhea. She spent the next decade or so demonstrating that crude bromelain extracts could be effective in this setting because of their ability to stop bacteria attaching to gut wall receptors. Tracey ultimately worked for the UK biotech company Cortecs in commercialising the approach with an anti-scouring product for piglets that the company trademarked 'Detach'<sup>13</sup>. That product was launched in Australia in

<sup>12</sup> After raising \$7m at 50 cents per share.

<sup>13</sup> The original Detach formulation was developed by Dr David Chandler of the Victorian Department of Agriculture, with a company called Enzacor Technology Pty Ltd. Enzacor had a world-wide marketing and distribution agreement with Ciba Geigy and was later acquired by Cortecs. Tracey Mynott was a PhD student of Chandler's and was involved with all the original Detach trials and development. Following the initial Detach work, Tracey discovered the bioactive components within bromelain and new uses for bromelain, including applications for humans.





1991 by Ciba-Geigy and was popular with pig farmers –it gained a 40% market share<sup>14</sup> - but was eventually discontinued after the 1996 merger of Ciba-Geigy and Sandoz that created Novartis. Anantara believes that Detach's exit from the market represented a strategic corporate decision on the part of Novartis rather than any matter of safety or efficacy, as evidenced by the fact that Novartis focused more on human rather than animal health after its formation<sup>15</sup>. In addition to developing Detach, Cortecs also ran a Phase I study of bromelain in humans to explore its use in the treatment of travellers' diarrhea. Tracey Mynott eventually acquired the intellectual property related to Detach from Cortecs before returning to Australia<sup>16</sup>.

**THE ORIGINAL  
DETACH  
PRODUCT  
GAINED A 40%  
MARKET  
SHARE**

**Incitive Ltd (2006-2010).** This company was formed in 2005 to take over the Detach project from Tracey Mynott<sup>17</sup>, and listed on the ASX in May 2006 after raising \$3m. With Incitive the focus was on two individual therapeutic fractions within bromelain – one called CCS that was a bromelain fraction capable of suppressing an immune response<sup>18</sup> and another called CCZ that could boost an immune response<sup>19</sup>. The company chose CCS, then called ICV0019, as its lead compound with intended indications in Inflammatory Bowel Disease (IBD) and other inflammatory diseases, such as GvHD<sup>20</sup>. By 2006 Incitive could produce ICV0019 as a recombinant protein<sup>21</sup> and had started pre-clinical testing of the protein in animal models of immunosuppression<sup>22</sup> and IBD<sup>23</sup>. However due to the difficult funding environment for Life Sciences characteristic of the mid 2000s, Incitive struggled to make progress with Detach and its other programmes, and eventually handed back the IP to Tracey Mynott<sup>24</sup>.

**Anantara Lifesciences (2010 - ).** This company was formed in 2010 by Tracey Mynott and Mel Bridges, who had been Chairman of Incitive, to pick up where Incitive left off.

## The evidence of Detach's effectiveness in pig health

The main evidence of the effectiveness of Detach in animal health comes from field trials in pig herds, where the product has been demonstrated to reduce 'scour', that is, diarrhea. Scour can reduce weight gain in pigs as well as reduce herd numbers through mortality, and the same is true of other production animals. Since pathogenic *E. coli* and other bacteria are often the cause of scour<sup>25</sup>, farmers often feed antibiotics daily to their animals as a prophylactic measure. Detach, by contrast, has been found to reduce scour with two oral doses only<sup>26</sup> - a 2 ml 'drench' as a sucker (when the piglet is between two to five days old), and a 4 ml drench as a weaner (ie

<sup>14</sup> See Anantara's 22 October 2014 presentation, slide 7.

<sup>15</sup> The Ciba/Sandoz merger was only approved by the EU on the condition that the companies divest several of their animal health businesses.

<sup>16</sup> Where she worked as a Business Development Manager at the Queensland Institute of Medical Research between 2002 and 2006. Maintaining the bromelain patent families in good standing cost ~A\$150,000.

<sup>17</sup> As well as a project from the Peter MacCallum Cancer Centre in Melbourne centred on the perforins, which are targets for autoimmune disease and transplant rejection drugs.

<sup>18</sup> See *Component of bromelain*, WO 1998/038291, priority date 25 February 1997.

<sup>19</sup> See *Component of bromelain*, see WO 1998/038320, priority date 25 February 1997.

<sup>20</sup> Short for Graft-versus-Host-Disease, a condition where the patient's own immune system rejects transplanted tissues or cells. This results in skin inflammation, diarrhoea and jaundice.

<sup>21</sup> See the Incitive market release dated 27 July 2006 and headlined '*Incitive achieves first development milestone*'. This was no easy task. The original CCS was three different proteins with a combined molecular weight of around 68 kDa, which was large for many bacterial cell culture systems, although not for yeast culture. An additional problem was the fact that proteases like bromelain are rich in the amino acid cysteine, which often forms disulphide bonds with itself that can alter the shape and therefore the function of the proteins of which it forms a part.

<sup>22</sup> See the Incitive market release dated 14 November 2006 and headlined '*Incitive's ICV0019 causes immunosuppression in animal model*'.

<sup>23</sup> See the Incitive market release dated 26 June 2007 and headlined '*Incitive reports successful results for lead compound*'.

<sup>24</sup> Incitive is now Hawkey Oil and Gas Ltd, ASX Code HOG.

<sup>25</sup> J Vet Intern Med. 2004 Jan-Feb;18(1):8-17.

<sup>26</sup> Delivered by mouth using a measured dosing applicator.





after the piglet has been weaned from its mother, around day 21). Multiple studies have demonstrated the effectiveness of this 2+4 ml regime over the years:

- **Cortecs field trials, 1988-2001.** In analysing 19 field studies in both suckers and weaners that covered >7,500 animals, Anantara has found that Detach, on average, improved daily weight gain by 11%, reduced mortality by over 40%, and more-or-less cut antibiotic use in half<sup>27</sup>. That these results are relatively easy to replicate is demonstrated by an Australian challenge trial where the results were published in the journal *Gut* in 1998<sup>28</sup>.
- **Anantara 2012 study in weaners**<sup>29</sup>. This study, in 288 weaner pigs on a commercial pig farm in Spain, saw Detach reduce the incidence of post-weaning scour in treated pigs by 40% and reduced antibiotic use by 55%. In each case these results had statistical significance ( $p < 0.05$ ). Detach also improved average daily weight gains by 22%.
- **Anantara 2012 weaner study focused in feed conversion.** A key metric in pig farming historically has been the 'feed conversion ratio', which measures the kilograms of feed required to produce one kilogram of pig meat. Two studies in 2012, one in Spain and one in France, showed that Detach could improve the feed conversion rate by 33% over Colistin, an antibiotic known to help engender antimicrobial resistance in humans<sup>30</sup>, and by 4% over zinc oxide<sup>31</sup>.

**DETACH CAN  
POTENTIALLY  
IMPROVE FEED  
CONVERSION  
IN PIGS**

**Studies completed since 2014.** Anantara completed two field trials of Detach in 2015 which, with the 2012 data, the company considers sufficient for gaining Australian regulatory approval, having shown non-inferiority to antibiotics in both suckers and weaners<sup>32</sup>.

- **Study in suckers, February 2015**<sup>33</sup>. This randomised, blinded and controlled study was conducted on a commercial pig farm in northern Victoria that had a problem with pre-weaning scour despite the use of prophylactic antibiotics<sup>34</sup> as well as sow vaccines. In 233 treated suckers versus 229 untreated controls, Detach administered two days after birth<sup>35</sup> cut piglet mortality in the treated pigs to 8% compared to 16% for the untreated controls. This was statistically significant ( $p < 0.02$ ), while treated pigs also registered an average daily weight gain to weaning (at day 21) of the surviving pigs by 5.2%.

**Study in weaners, September 2015**<sup>36</sup>. This study evaluated Detach on a commercial pig farm in southeast Qld. In 280 treated weaners who were dosed at day 21 versus 280 untreated controls, Detach reduced the frequency of scour by 41%, while the severity of scour<sup>37</sup> came down by 45% over the next 28 days. This outcome was statistically significant in each case ( $p < 0.02$ ). The treated pigs, however, experienced only a 1%

<sup>27</sup> Source: Lyndsey, 1991. Milnes Pork Journal article on Detach and Anantara Lifesciences prospectus dated 4 September 2014, page 21.

<sup>28</sup> Gut. 1998 Aug;43(2):196-202.

<sup>29</sup> Anantara code name ANR 12-001.

<sup>30</sup> See Appl Environ Microbiol. 2016 Jun 13;82(13):3727-35.

<sup>31</sup> See Anantara's 22 October 2014 presentation, slide 11.

<sup>32</sup> Another study had been announced in June 2016, this one in suckers to expand the proposed label that would give the pig farmer the option to either dose once or twice. However, this study was terminated by Anantara on 23 June 2016 when various 'extreme conditions' including power and water shortages caused the removal of substantial numbers of pigs from the trial site.

<sup>33</sup> Anantara code name ANR 14-001.

<sup>34</sup> Such as neomycin, trimethoprim and sulfadiazine.

<sup>35</sup> Since scouring tends to show up in suckers at days 3 or 4.

<sup>36</sup> Anantara code name ANR 15-001.

<sup>37</sup> Where each scour occurrence was rated 1 or 2, the more severe being 2.



increase in average daily weight gain. Unlike the study in suckers, the piglets in this study had no antibiotic use.

## Why Detach is a big step forward for pig health

Like all really good drugs, Detach has multiple mechanisms of action:

- **Preventing bacterial attachment.** We noted above that one of bromelain's mechanism's as an anti-infective is its ability to prevent the attachment of bacteria to the gut wall. It achieves this by proteolytically modifying specific glycoprotein receptor attachment sites<sup>38</sup>.
- **Interfering with bacterial enterotoxins.** Should bacteria still attach to enterocytes, Detach is able to interfere with the enterotoxins that cause fluid secretion. It does this by blocking the cellular signalling molecules that the toxins would normally activate - cyclic AMP, cyclic GMP and calcium in the form of  $Ca^{2+}$ <sup>39</sup>.
- **Modulating inflammation.** We noted above that at least one protein within Detach has strong anti-inflammatory properties<sup>40</sup>. Taking inflammation down reduces tissue damage to the intestinal wall, thereby reducing the potential for diarrhea.

**Detach has broad spectrum activity.** The combination of these three mechanisms means that Detach can act against a wide variety of pathogens – not just *E. coli*, but other bacteria such as *V. cholerae*<sup>41</sup>, as well as protozoa and viruses.

**Detach is stable at room temperature,** meaning that it can be used in markets that don't have cold chain pharmaceutical infrastructure.

**Detach is very safe.** We noted above that bromelain is Generally Regarded as Safe. Anantara announced in September 2016 that the drug had been safe and well-tolerated in a safety study in pigs when five times the recommended dose was administered, on multiple occasions before day 21 of the piglet's life<sup>42</sup>.

**Detach is better than the alternatives.** As we note below, antibiotics have become very unpopular in recent days due to concerns over antimicrobial resistance. Zinc oxide, known to be effective as an anti-microbial in pigs<sup>43</sup>, is banned in some countries, not just because of its potential for antimicrobial resistance but because of its environmental implications as a heavy metal. Copper sulphate has yet to be banned, but is also considered to have the potential for environmental hazard.

- **Is there other competition?** There are various oral vaccines for *E. coli* as well as probiotics, but these approaches tend to be expensive. Also, low protein diet or organic acids seem to work but may also affect

**DETACH CAN  
ACT AGAINST  
A VARIETY OF  
PATHOGENS**

<sup>38</sup> Gut. 1996 Jan;38(1):28-32

<sup>39</sup>Gastroenterology. 1997 Jul;113(1):175-84.

<sup>40</sup>J. Immunol. 1999;163:2568-2575

<sup>41</sup> Gastroenterology. 1997 Jul;113(1):175-84.

<sup>42</sup> See the company's market release dated 8 September 2016 and headlined 'Anantara successfully completes target safety study'.

<sup>43</sup> Res Vet Sci. 1998 May-Jun;64(3):225-31.



the quality of the meat that is produced. When compared with these two alternatives we think that Detach is a superior option.

## Modern medicine's antibiotic resistance problem

**Bacteria tend to become resistant to antibiotics after a while.** Antibiotics are simply drugs that can kill bacteria. Historically antibiotics have been very important in terms of reducing mortality from infectious disease, ever since Florey et. al. helped bring the first one, penicillin, to market in the 1940s<sup>44</sup>. However, bacteria can quickly become resistant to antibiotics when overused. That's because bacteria naturally mutate over time, and such mutations can confer on bacteria the ability to resist the drug<sup>45</sup>. Antibiotic overuse speeds this process up applying selective pressure for the survival of resistant strains.

**Antibiotic resistance is on the rise.** For some years now antibiotic resistance has been of increasing concern to policy makers. The World Health Organisation estimates that in the EU ~400,000 patients present with an antibiotic-resistant strain, resulting in ~25,000 deaths<sup>46</sup>. The comparable figures for the US are 2 million infections and 23,000 deaths<sup>47</sup>.

**There is growing evidence that antibiotics in production animals has contributed to the antibiotic resistance problem.** Traditionally antibiotic resistant bacteria, such as methicillin-resistant *Staphylococcus aureus* (MRSA) and multi-drug resistant *Mycobacterium tuberculosis*, have been generated by antibiotic use in man. In recent decades, however, evidence has emerged that high antibiotic use in production animals is a contributing factor by causing antibiotic resistance to move through the food chain<sup>48</sup>. While this evidence is not totally definitive<sup>49</sup>, the fact that most antibiotics are used in animals – in the United States, production animals consume around four fifths of all antibiotics consumed<sup>50</sup>, with humans only accounting for the last 20% or so – has a lot of policy-makers worried.

**The push is on to remove antibiotics from the food chain.** For the last couple of decades, antibiotic use in production animals has been gradually coming down, because of public concern over the issue. The trend started in the 1990s in Europe<sup>51</sup> and by 2007, when the major US chicken producer Purdue eliminated antibiotic use for growth promotion, the trend was noticeable in the US. In 2012 a survey from Consumer Reports in the US found that 60% of respondents would be willing to pay more for meat raised without antibiotics<sup>52</sup>, at which point the Quick Service Restaurant (QSR) chains began to respond. Chick-Fil-A, the US chicken restaurant chain with >2,000

**>20,000  
PEOPLE DIE  
EACH YEAR IN  
AMERICA  
BECAUSE OF  
ANTIBIOTIC  
RESISTANCE**

<sup>44</sup> The Australian Howard Florey (1898-1968) won the Nobel Prize in Physiology or Medicine in 1945 alongside Sir Alexander Fleming (1881-1955) and Sir Ernst Chain (1906-1979) for the discovery of penicillin.

<sup>45</sup> Through either (1) enzymatic degradation of antibacterial drugs, which is what generally happens with bacteria resistant to penicillins and cephalosporins, (2) alteration of bacterial proteins that are antimicrobial targets (which is what causes methicillin resistance), and (3) changes in membrane permeability to antibiotics.

<sup>46</sup> Nat Rev Microbiol. 2011 Nov 2;9(12):894-6.

<sup>47</sup> Source: CDC.

<sup>48</sup> See Nutr Res Rev. 2000 Dec;13(2):279-99 and Int J Antimicrob Agents. 2000 Nov;16 Suppl 1:S19-24.

<sup>49</sup> Foodborne Pathog Dis. 2007 Summer;4(2):115-33.

<sup>50</sup> Proc Natl Acad Sci U S A. 2015 May 5;112(18):5649-54. Epub 2015 Mar 19.

<sup>51</sup> Environ Health Perspect. 2014 Jun;122(6):A160-5.

<sup>52</sup> Source: Consumer Reports, *Meat on Drugs*, June 2012.



stores, publicly committed to antibiotic-free chicken in February 2014<sup>53</sup>. Then in March 2015 McDonalds, far and away the world's biggest QSR operator with >36,000 restaurants system-wide<sup>54</sup>, announced that it would phase out all meat sources that contained antibiotics<sup>55</sup>. Many competitors have followed suit, most notably Subway (October 2015<sup>56</sup>), In-N-Out Burger (March 2016<sup>57</sup>) and Taco Bell (April 2016<sup>58</sup>). No wonder that suppliers are now hastening to cut loose from antibiotics, as evidenced by Tyson, another US chicken producer, which intends to eliminate the use of human antibiotics from broiler chicken flocks by September 2017<sup>59</sup>.

**RESTAURANT  
CHAINS ARE  
NOW ACTIVELY  
WORKING  
AGAINST  
ANTIBIOTICS IN  
THEIR SUPPLY  
CHAINS**

**Public policy has started to become more concerned.**

- In 2006 the EU banned antibiotic growth promotants in animal feed.
- In 2011 the EU announce an 'Action Plan' designed to move against antimicrobial resistance.
- In 2012 the US Congress passed the GAIN Act to encourage the development of new products that would fight antimicrobial resistance. Short for 'Generating Antibiotics Incentives Now', GAIN provides new 'qualifying infectious disease products' or QIDPs with an extra five years' US market exclusivity on top of whatever exclusivity they would otherwise have been granted.
- In June 2014, a Ministerial Conference on Antibiotic Resistance held in The Hague addressed, among other issues, the need for reduced antimicrobial use in production animals<sup>60</sup>.
- In September 2016, various Heads of State and Governments met at the UN Headquarters for a General Assembly on Antimicrobial Resistance and agreed that resistance to antibiotics is 'the greatest and most urgent global risk'<sup>61</sup>.

**Anatara is well placed with Detach.** The two recently-completed field trials of Detach has shown that the product serves the same purpose as antibiotics. We therefore see the potential, should Zoetis be able to replicate Anatara's findings, for Detach to become the standard of care for managing scour in pigs.

## Detach – the path to market in pigs

**Anatara has filed for Australian regulatory approval in October 2016.** The relevant oversight body, the Australian Pesticides and Veterinary Medicines Authority (APVMA) is expected to grant the approval in 2017 given that that agency typically turns around the necessary dossiers in a 9-12 month period. After this approval, Detach will be re-launched in Australia for use in treating piglet scour.

**The market opportunity is significant.** Pig production is significant as an initial sector to target with Detach, because pork is currently the most consumed meat on the planet. Every year on average humans eat around 41

<sup>53</sup> See *Chick-fil-A commits to stop sales of poultry raised with antibiotics* by Stephanie Strom, New York Times, 11 February 2014.

<sup>54</sup> Source: McDonalds 10-K and 10-Q reports. Since the start of 2015 McDonalds has opened a new restaurant somewhere in the world every 1.8 days.

<sup>55</sup> See the McDonalds policy document headlined 'McDonald's Global Vision for Antimicrobial Stewardship in Food Animals' at mcdonalds.com.

<sup>56</sup> See the Subway press release headlined 'Subway Restaurants Elevates Current Antibiotic-Free Policy' and dated 20 October 2015.

<sup>57</sup> See *In-N-Out vows to veer away from beef raised with antibiotics* by Bradley Zint, LA Times, 4 March 2016.

<sup>58</sup> Source: Statement Regarding Antibiotics, 18 April 2016 at tacobell.com.

<sup>59</sup> See the Tyson press release headlined 'Tyson Foods Strives to Eliminate Human Antibiotics From Broiler Chicken Flocks by 2017' and dated 28 April 2015.

<sup>60</sup> Source: World Health Organisation press release dated 27 June 2014 and headlined 'Global call made to take action on antimicrobial resistance'.

<sup>61</sup> Source: UN document headlined 'Draft political declaration of the high-level meeting of the General Assembly on antimicrobial resistance' and dated 21 September 2016.



kg of meat, and ~37% of that is pork, followed by poultry at 33%, beef at 24% and lamb/mutton at 5%. FAO projections out to 2030 suggest that per capita pork consumption will decline marginally in favour of more expensive meat sources, but that pork will remain at least 33% of total meat consumption at that time. On FAO's estimates, global pork production – currently 110 million tonnes p.a. – will rise at roughly global population growth, which is around 1% p.a.<sup>62</sup>.

**The economics of the earlier Detach formulation were significant.** Analysing the weight gain of the pigs treated with Cortec's formulation, a study published in the trade publication *Milne's Pork Journal*<sup>63</sup> in 1991 suggested at least A\$5 per pig could be realised from the use of Detach. While this is an old study, we believe that favourable economics can be realised for the current Anantara formulation. With around half of the world's pork production coming from China<sup>64</sup>, and another 10% coming from five other less-developed countries – Brazil, Russia, Vietnam, the Philippines and Mexico – the economics of Detach for a significant portion of the world's pig producers are compelling.

**DETACH IS  
LIKELY TO BE  
VERY COST  
EFFECTIVE  
FOR FARMERS**

## Detach – the path to market for other animals

**Anantara has optioned the use of Detach in production animals.** In January 2016 Anantara announced that Zoetis had taken an option to licence the use of Detach in production animals globally, excluding only Australia and New Zealand, which Anantara will retain. The option fee was undisclosed however Anantara reported A\$2.28m income in its June 2016 cash flow report so the upfront option fee was probably ~US\$1.75m. There will be subsequent cash payments during the option period. This option period was also undisclosed, however we assume it is two years, during which time we expect Zoetis will conduct studies of Detach across multiple species.

**Zoetis is a great partner to have.** Zoetis was the animal health business of Pfizer until its 2013 spin-out. The company is the No 1 player in animal health globally, with US\$4.8bn in revenue and US\$889m<sup>65</sup> in net income in 2015. We see three reasons why Zoetis can potentially be a great partner to have should the option exercise:

- The company gets only half its revenue from the US, so there is considerable 'international' growth that Detach can tap into should Zoetis take it forward;
- Around two-thirds of Zoetis' revenue related to production animals, so the fit of Detach is right;
- Zoetis consistently spends 7-9% of revenue on R&D, for an annual budget of US\$350-400m

**We expect US and European field trials to commence in 2017,** with calves and chickens an early priority for Zoetis. These are also big markets. In field studies of the old Cortec's Detach formulation, the product was shown to be effective against scour in calves, reducing death from 25% to 4%, the number of days of scouring by 37% (from 2.33 days to 1.46 days), and the use of antibiotics by 66%.

<sup>62</sup> Source: Food and Agriculture Organization, *World agriculture: towards 2015/2030*, 2003.

<sup>63</sup> Milne's Pork Journal 1991:13;32-34.

<sup>64</sup> Source: *Top 10 Pork-Producing Countries*, pork.org.

<sup>65</sup> Non-GAAP, adjusted.



**Demand for meat is on the rise.** We noted above that the world demand for pork rises at around 1% p.a. On FAO's numbers, overall meat demand will probably rise at around 1.6% p.a., meaning that meat producers are going to require significant productivity tools to keep up. Obviously Detach represents one such tool given its widespread potential utility across multiple production systems.

**Anatara can still license the companion animal opportunity,** which can potentially be significant. We estimate that the world market for veterinary products for companion animals is around US\$25bn, growing 3% p.a.

## Detach – the path to market for humans

**Anatara is currently exploring the human therapeutic potential of Detach,** which makes sense given that the product has anti-inflammatory and anti-infective properties relevant to a wide range of human diseases. The company will further the opportunity originally pioneered by Cortecs of a Detach formulation for the treatment of human diarrhea, distributed OTC. For significant blue sky beyond this, Anatara will also continue the work done by Incitive on an anti-inflammatory protein fraction of Detach, aiming for an early OTC product followed by a potential Rx indication.

**Travellers' diarrhea is a major market opportunity for Detach.** The risk of traveller's diarrhea for a two-week stay is between 8% and 20% in some parts of the world<sup>66</sup>. Anatara has also identified travellers' diarrhea in soldiers as an opportunity. The incidence of diarrhea among deployed military personnel from industrialized countries to lesser developed countries is approximately 30% per month overall<sup>67</sup>. We believe there is potential for Anatara to gain US government funding to pursue research in this area.

**DETACH  
COULD HAVE  
APPLICATION  
IN MILITARY  
MEDICINE**

**Anatara will develop ANA0019 in Irritable Bowel Syndrome and Inflammatory Bowel Disease.** We noted above that Incitive did a good deal of work to show the effectiveness of ICV0019, an anti-inflammatory fraction of Detach, in animal models. As ANA0019, this product will now re-enter pre-clinical development. Anatara announced in June 2016 that it was collaborating on the product with a group at Melbourne's LaTrobe University. ANA0019 is known to block the MAP kinase pathway<sup>68</sup>, which has long been regarded as a valuable target for anti-inflammatory drugs due to its position upstream from other inflammatory processes. Anatara believes that, potentially, the company can go after an Rx indication with ANA0019 for both Inflammatory Bowel Disease<sup>69</sup> and Irritable Bowel Syndrome, although in the near term it is more likely to pursue Irritable Bowel Syndrome with an OTC product.

<sup>66</sup> JAMA. 2015 Jan 6;313(1):71-80.

<sup>67</sup> Curr Opin Infect Dis. 2012 Oct;25(5):546-54.

<sup>68</sup> Specifically, the ERK, JNK and p38 components of the pathway. T cells recruit other T cells through the cytokine interleukin 2 (IL-2). MAP kinases are the tail end of the chemical pathway in the T-cell through which the signal to generate IL-2 is passed.

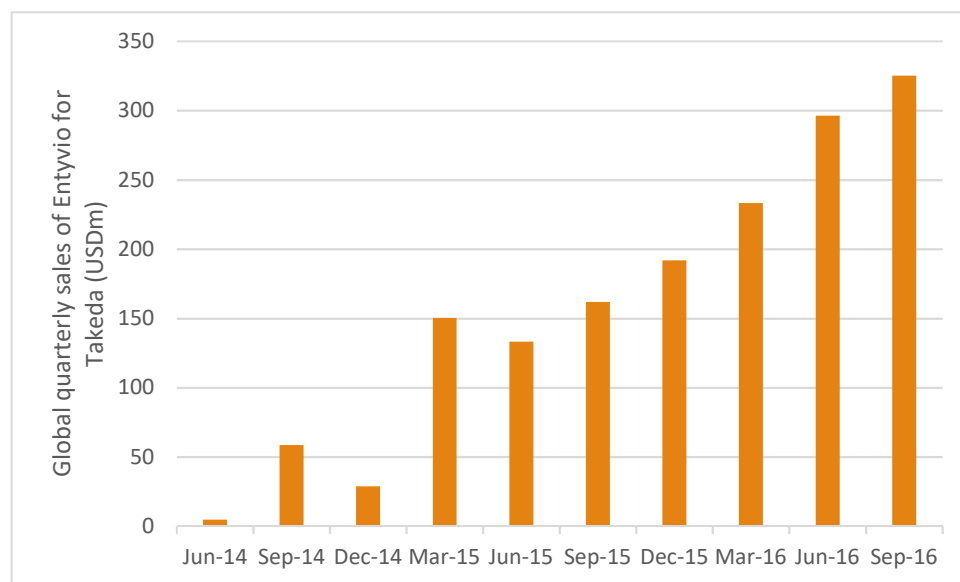
<sup>69</sup> Where the role of MAP kinases have long been noted – see Clin Chim Acta. 2011 Mar 18;412(7-8):513-20. Epub 2010 Dec 23.



## Anatara's 'blue sky' in the human gut

**Big Pharma is seriously interested in Inflammatory Bowel Disease.** Inflammatory Bowel Disease (IBD) is basically chronic inflammation of all or part of the digestive tract, characterised by severe diarrhea, pain, fatigue and weight loss. There are two major types of IBD - ulcerative colitis, in which the inflammation impacts the inner lining of the gut, and Crohn's disease, in which the whole wall of the gut is inflamed. Both represent large market opportunities. We estimate that between 1.2 million<sup>70</sup> and 1.6 million Americans<sup>71</sup> have IBD, roughly 40% of them with Crohn's disease and 60% with ulcerative colitis. This burden of disease, traditionally managed with anti-inflammatories such as the corticosteroids and mesalazine<sup>72</sup>, has more recently seen increased use of biological agents such as the TNF inhibitors that appear to have disease-modifying capabilities<sup>73</sup>. The anti-TNF drugs, however, are expensive, however, and after about 12 months fail to work in around 20-40% of IBD patients<sup>74</sup>. The most recent advance in the field, Takeda's Entyvio (vedolizumab), which binds to the  $\alpha_4\beta_7$  integrin<sup>75</sup>, gained FDA approval in 2014 in both ulcerative colitis and Crohn's and took only two years to become a blockbuster<sup>76</sup>. So, while mesenchymal stem cell therapies, known for their anti-inflammatory properties, are probably coming over the horizon for IBD<sup>77</sup>, we think that more straightforward drug approaches will be favoured by pharma, particularly if the product can notionally be less expensive than monoclonal antibodies. For an indication of the potential upside should Anatara take a bromelain derivative into the clinic for IBD, consider Protagonist Therapeutics<sup>78</sup>, a developer of oral peptides for gastrointestinal disorders. That company's lead candidate, another  $\alpha_4\beta_7$  antagonist, is moving into Phase 2 in ulcerative colitis. Protagonist is now a ~US\$287m company<sup>79</sup>.

**MORE THAN A  
MILLION  
AMERICANS  
HAVE  
INFLAMMATORY  
BOWEL DISEASE**



<sup>70</sup> See Inflamm Bowel Dis. 2013 Jun;19(7):1421-7

<sup>71</sup> Extrapolated from Loftus et. al., Updated Incidence and Prevalence of Crohn's Disease and Ulcerative Colitis in Olmsted County, Minnesota (1970-2011). ACG 2014 Annual Scientific Meeting. October 2014.

<sup>72</sup> An aminosalicic drug similar in structure to aspirin.

<sup>73</sup> Am J Gastroenterol 2013; 108:859-860.

<sup>74</sup> Autoimmun Rev. 2014 Jan;13(1):24-30. doi: 10.1016/j.autrev.2013.06.002. Epub 2013 Jun 19.

<sup>75</sup> And thereby reduces inflammation by inhibiting the adhesion of T lymphocytes to gastrointestinal tissues.

<sup>76</sup> Sales in the twelve months to September 2016 - source: Takeda.

<sup>77</sup> Inflamm Bowel Dis. 2015 Nov;21(11):2696-707

<sup>78</sup> Milpitas, Ca, Nasdaq: PTGX, www.protagonist-inc.com.

<sup>79</sup> 20 January 2017 close on Nasdaq.





**Irritable Bowel Syndrome is also a major opportunity.** The difference between Inflammatory Bowel Disease and Irritable Bowel Syndrome (IBS) is that the latter is a functional disorder in which the bowel, while not badly inflamed<sup>80</sup> or ulcerated, still doesn't work as it should. Patients typically report symptoms such as bloating, gas, mucus in the stool, diarrhea and constipation. The market opportunity here is the massive prevalence numbers. Possibly 14% of the US population<sup>81</sup> and 11% of the global population<sup>82</sup> appears to have IBS, and for most the condition is undiagnosed. While a lot of people seek OTC remedies for their IBS, pharma has in recent years introduced several Rx drugs such as two products from Allergan - Viberzi (eluxadoline), FDA approved in 2015 for patients where the IBS is characterised by diarrhea<sup>83</sup>, and Linzess (linaclotide), FDA approved in 2012 for IBS with constipation<sup>84</sup>. The market opportunity for Detach in IBS probably lies in IBS patients with diarrhoea, due to Detach's anti-secretory capacity.

## Valuing Anantara

**We valued Anantara on a probability-weighted DCF basis.** We value Anantara at \$2.22 base case and \$5.94 optimistic case using a probability-weighted DCF approach. Our target price of \$4.00 sits at around the midpoint of our valuation range. We valued only two aspects of the Anantara story using probability-weighted DCFs, to with 1) Detach in Australia and New Zealand; 2) The Detach option to Zoetis. We left the value of a future OTC or Rx product for IBS/IBD unvalued, but would look to revisit this once Anantara's clinical plans are announced.

**WE VALUE  
ANATARA AT  
>\$2.00 PER  
SHARE BASE  
CASE**

### General assumptions.

- **Discount rate.** We used a WACC of ~11%, appropriate in our view for a 'Medium' risk rating<sup>85</sup>;
- **Probability of success.** For Detach in Australia and New Zealand, 85%. For the Zoetis option transitioning into a license from Anantara and then into a commercial product, 50%;
- **Time horizon.** We used a 14-year time horizon in our DCFs followed by a terminal value;
- **Currency.** We assume the AUD/USD exchange converges on 0.7 over a three-year period from now.
- **Capital.** We assume no further capital needs to be raised, with Anantara in a position to fund itself from Detach-related revenues from FY18.

### Valuing Detach in Australia and New Zealand

- We assume a commercial launch in FY18;
- We assumed peak sales of ~A11m (base case) to A\$34m (optimistic case)

<sup>80</sup> There is some low-grade inflammation involved in the pathophysiology of IBS – see World J Gastroenterol. 2016 Feb 21; 22(7): 2242–2255.

<sup>81</sup> Aliment Pharmacol Ther. 2005 Jun 1;21(11):1365-75.

<sup>82</sup> Clin Epidemiol. 2014 Feb 4;6:71-80. eCollection 2014.

<sup>83</sup> The drug is both a  $\mu$ - and  $\kappa$ -opioid receptor agonist and  $\delta$ -opioid receptor antagonist. This mechanism means that the drug is marketed with restrictions, being a scheduled substance as per the Drug Enforcement Administration.

<sup>84</sup> It's a selective agonist at the guanylate cyclase-C (GC-C) receptor on the luminal surface of intestinal enterocytes.

<sup>85</sup> For a relevant discount rate, we use varying WACCs depending on the risk for Life Science companies. We start with an RFR of the Australian ten year bond rate and an ungeared beta of 1.1 but use a variable MRP of 7.5%-11.5% (7.5% for 'medium risk' companies, 9.5% for 'high risk' companies and 11.5% for 'speculative' companies). We regard Life Science companies with existing businesses, or who have enough capital to reach the market with their products, as 'Medium' risk. Companies that have small revenue streams from marketed products but that are still potentially in need of capital are 'High' risk. Everything else is 'Speculative'.



- We assume 65-75% gross margins for Detach at launch, alongside SG&A expenses equal to 20-25% of sales. We assume both COGS and SG&A decline by 0.1%-0.2% of revenue annually;
- We assume that Anantara sources the product from contract manufacturers or from Zoetis on commercial terms for modelled no capex requirements.

### Valuing Detach globally

- We assume a minimum two-year option period for Zoetis, transitioning into a licensing agreement in FY18 (optimistic case) or FY19 (base case);
- We assume upfront payments post the licensing agreement of US\$5-10m;
- We assume milestone payments as products are developed of US\$20-40m;
- We assume first commercial launch in FY20 (optimistic case) or FY21 (base case).
- We assume peak sales globally of ~US\$90m (base case) to US\$170m (optimistic case).
- We assume a royalty to Anantara of 8% (base case) to 10% (optimistic case).

## Re-rating Anantara

We see a number of events helping to re-rate Anantara stock towards \$4.00 per share:

- APVMA approval of Detach;
- Commercial launch of Detach in Australia;
- Potential transition of the Zoetis option into an outright licensing agreement;
- Further pre-clinical data on the efficacy of Anantara's Bromelain fractions in humans;
- Potential US military grant funding related to traveller's diarrhea;
- Other partnering or collaboration events related to human use for the Bromelain fractions.

## Anantara's seasoned leadership team

We think Anantara has the skill and experience among its people to build a world-beating animal health company:

**Dr Mel Bridges** (Chairman and CEO), is a veteran of multiple Life Science companies over many years. His first company, Pacific Diagnostics, was sold to Baxter in 1986, after which he built Panbio, a successful supplier of diagnostic kits for various infectious diseases including Dengue and Ross River fever. That company was ultimately sold in late 2007 to Inverness Medical Innovations<sup>86</sup> for US\$37m. Among other Bridges achievements since he stepped down from leadership at Panbio in 2003 has been negotiating royalty agreements over anti-TNF antibodies for Peptech<sup>87</sup>, and helping to grow other early stage companies such as Benitec (ASX: BLT) and Oventus (ASX: OVN). During his career Bridges has raised more than A\$400m in biotech investment capital.

**DR MEL  
BRIDGES HAS  
RAISED OVER  
A\$400m FOR  
LIFE SCIENCES  
COMPANIES**

<sup>86</sup> Now Alere, NYSE: ALR.

<sup>87</sup> Later Arana, sold to Cephalon for A\$318m in 2009.



**Dr Tracey Mynott** (Chief Scientific Officer) has been intimately involved in the science behind Anantara since the early 1990s and therefore brings both determination as well as strong corporate memory to the Detach project.

**Dr Michael West** (Chief Operating Officer), who worked at the Brisbane-based drug developer Alchemia from the late 1990s until 2015, brings valuable experience in technology transfer and intellectual property management which will be vital as Anantara moves to introduce Detach into its first markets.

**The Anantara board** has the right kind of experience for a successful biotech company

- **Iain Ross** brings a background working with established UK Life Science companies including Sandoz, Fisons, Roche and Celltech, as well as valuable experience turning around early-stage companies on behalf of banks and private equity groups.
- **Dr Tracie Ramsdale**, founder of Alchemia, brings valuable experience from the science side in the building of drug development platforms;
- **Dr Jay Hetzel** knows a good deal about animal health, from his CSIRO academic background in animal genetics to his work commercialise genomics technology in livestock through Genetic Solutions, which was sold to Pfizer Animal Health in 2008.
- **Paul Grujic** also has an animal health background, as a former President of CSL Animal Health.

## Major shareholders

Anantara currently has three substantial shareholders:

- **Mel Bridges** (11.6%), the current Chairman and CEO.
- **Tracey Mynott** (8.9%), the current Chief Scientific Officer.
- **Thorney Investment Group** (5.1%), the institutional investor, which went substantial in August 2016.



## Risks related to Anataro Lifesciences

**Risks specific to Anataro Lifesciences.** We see five major risks for Anataro as a company and as a listed stock:

- **Regulatory risk.** There is the risk that Anataro may take longer to gain Australian regulatory approval for Detach than the time we have postulated in this note.
- **Partnering risk.** There is the risk that Zoetis may not exercise the option it took over a license from Anataro at the start of 2016
- **Scale-up risk.** There is the risk that Anataro may not be able to produce enough Detach under GMP to complete field and clinical trials in animal and human applications. Ameliorating this risk is the fact that Anataro has been performing production runs of Detach since late 2014<sup>88</sup>.
- **Commercial risk.** There is the risk that Detach may fail to gain adequate reimbursement even if the product is deemed safe and effective in field trials and clinical studies and gains regulatory approval.
- **Clinical risk.** There is the risk that Detach may prove ineffective in IBD and IBS given the complexity of these disease conditions.

**Risks related to pre-revenue Life Science companies in general.**

- The stocks of biotechnology and medical device companies without revenue streams from product sales or ongoing service revenue should always be regarded as speculative in character.
- Since most biotechnology and medical device companies listed on the Australian Securities Exchange fit this description, the 'term' speculative can reasonably be applied to the entire sector.
- The fact that the intellectual property base of most biotechnology and medical device lies in science not generally regarded as accessible to the layman adds further to the riskiness with which the sector ought to be regarded.

**Caveat emptor.** Investors are advised to be cognisant of the abovementioned specific and general risks before buying any the stock of any biotechnology and medical device stock mentioned on this report, including Anataro Lifesciences.

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<sup>88</sup> See Anataro's 17 October 2014 market release headlined 'Manufacturing, clinical trial and European SME status update'.



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## **Recommendations**

NDF Research issues a BUY recommendation in case of an expected total shareholder return (TSR, share price appreciation plus dividend yield) in excess of 25% within the next twelve months, an ACCUMULATE recommendation in case of an expected TSR between 5% and 25%, a HOLD recommendation in case of an expected TSR between -5% and +5% within the next twelve months and a SELL recommendation in case of an expected total return lower than -5% within the next twelve months.



## Appendix I – Anantara’s capital structure

		% of fully diluted	Note
Ordinary shares, ASX Code ANR (million)	49.4	96.1%	
Unlisted options (million)	2.0	3.9%	Exercise price 125.3 cents, average expiry date 16-Jan-2020
Fully diluted shares	51.4		

Current market cap:	A\$50.4 million (US\$38.0 million)
Current share price	\$1.02
Twelve-month range	\$1.00 - \$1.78
Average turnover per day (last three months)	23,600 shares

## Appendix II – An Anantara glossary

**Adhesins** – Proteins used by bacteria to adhere to the gut wall. Adhesins are often in the form of fimbriae, that is, appendages on the bacterium (fimbria is the Latin word for fringe).

**ANA0019** – An anti-inflammatory component of Detach.

**Antibiotic resistance** – The ability of bacteria to avoid being killed by antibiotics.

**APVMA** – The Australian Pesticides and Veterinary Medicines Authority, the government agency overseeing drugs for veterinary use in Australia.

**Bromelain** – A mixture of enzymes found in pineapples that have proteolytic properties. Anantara’s Detach product is a modified-release formulation of bromelain.

**Chloride** – Negatively charged chlorine ions (Cl<sup>-</sup>), vital for keeping the amount of fluid inside and outside of cells in balance.

**Cyclic AMP, Cyclic GMP** – Two ‘secondary messengers’ that help send signals into cells. They are cyclic in terms of their shape. AMP is adenosine monophosphate while GMP is guanosine monophosphate.





**Detach** – Anantara's lead compound, a modified release formulation of bromelain that prevents bacterial adhesion to the gut wall.

**Drench** – A dose of medicine administered to an animal.

**Enterotoxigenic *E. coli* (ETEC)** – The gut bacterium *Escherichia coli*, where the bacterial strain produces toxins which stimulate the lining of the intestines, causing excessive fluid secretion and, thus, diarrhea.

**Enzyme** – A protein that helps speed up biochemical reactions in the body. Enzymes generally have the suffix 'ase' in their name.

**Excipient** – An inert substance used to prepare a drug for administration rather than being an active part of the drug itself.

**Feed conversion ratio** – A measure of the efficiency with which a production animal converts food into protein. It is measured by kilograms of feed required to produce 1 kg of pig meat, where the meat is measured either as dressed weight or liveweight.

**Good Manufacturing Practice (GMP)** – The set of standards that have been laid down by regulators regarding pharmaceutical production.

**GRAS** – Short for 'Generally Regarded as Safe', a product with a long history of use and therefore with a well-known safety record.

**Inflammatory Bowel Disease (IBD)** – Inflammation in the gut, where the inflammation affects either just in the inner lining of the gut (ulcerative colitis) or the whole wall of the gut (Crohn's disease).

**Irritable Bowel Syndrome (IBS)** – A functional disorder in which the bowel, while not inflamed or ulcerated, still doesn't work as it should. Symptoms of IBS include pain, bloating, gas, mucus in the stool, diarrhea and constipation.

**Natural product** – A drug that occurs in an unmodified form in nature. For example, penicillin is a natural product from the mould *Penicillium chrysogenum*. Bromelain is a natural product.

**Phthalates** – Chemicals commonly used as 'plasticisers', increasing the flexibility of plastics so they are harder to break. Phthalates are often used as excipients in orally available medicines.

**Proteolytic** – Capable of breaking down proteins.

**Scour** – Another name for diarrhea in livestock.

**Sucker** – A piglet before it has been weaned, which generally happens at or around day 21.

**Weaner** – A piglet that has been weaned. Historically piglets become weaners between three and five weeks of age. For study purposes Anantara has used day 21 as the day a piglet becomes a weaner.



## Appendix III – Anantara's IP position

Anantara's core intellectual property is covered by one published patent family<sup>89</sup>:

- **Anti-diarrhea formulation which avoids antimicrobial resistance**, WO/2016/032944, priority date 25 August 2014, invented by Tracey Mynott and John Walsh.

This patent family covers Anantara's modified release formulation of bromelain. The formulation comprises stem bromelain plus sodium carboxymethyl cellulose as a gelling agent, lecithin as an emulsifier and EDTA and citric acid anhydrous as chelating agents.

## Appendix IV – Papers relevant to Anantara

There are eight peer-reviewed papers that are relevant to Anantara.

**Mynott et. al., 1991.** *Efficacy of enteric-coated protease in preventing attachment of enterotoxigenic Escherichia coli and diarrheal disease in the RITARD model.* Infect Immun. 1991 Oct;59(10):3708-14 (full text available for free online).

- This paper covers an early animal study of bromelain in which the product, when administered to rabbits prior to infection with ETEC, reduced diarrhea and diarrhea-induced death in six of seven treated rabbits, whereas seven of eight rabbits not protected by protease treatment died or developed severe diarrhea. The bromelain took the levels of bacteria down 2,000-fold ( $p < 0.001$ )<sup>90</sup>.

**Mynott et. al., 1996.** *Oral administration of protease inhibits enterotoxigenic Escherichia coli receptor activity in piglet small intestine.* Gut. 1996 Jan;38(1):28-32 (full text available for free online).

- This paper shows that bromelain could alter adhesin ETEC attachment sites in the guts of piglets, thereby preventing attachment. Oral administration of the bromelain took down ETEC attachment via an adhesin called K88 in a dose-dependent manner ( $p < 0.05$ ).

**Mynott et. al., 1997.** *Bromelain prevents secretion caused by Vibrio cholerae and Escherichia coli enterotoxins in rabbit ileum in vitro.* Gastroenterology. 1997 Jul;113(1):175-84.

- This paper describes experiments with Ussing chambers<sup>91</sup> showing that bromelain pre-treatment could inhibit the secretion of bacterial toxins. This showed the effectiveness of bromelain not just on ETEC but also on cholera toxins.

<sup>89</sup> Anantara's second patent application was filed in August 2016 and so will publish in February 2017. This will cover composition of matter for the active components within the company's therapeutic bromelain.

<sup>90</sup> The animal model used here, the RITARD model, is a commonly used one for studying the pathogenesis of diarrhea caused by *E. Coli* among other bacteria. Short for 'Removable Intestinal Tie-Adult Rabbit Diarrhea', it involves isolating the terminal ileum - the distal end of the small intestine that intersects with the large intestine – using a tape, and injecting the occluded segment with *E. Coli* or another bacterium of choice.

<sup>91</sup> In which a chamber is divided into two with an epithelial tissue stretched across the middle, to measure what ions get transported across the membrane.



**Chandler and Mynott, 1998.** *Bromelain protects piglets from diarrhea caused by oral challenge with K88 positive enterotoxigenic Escherichia coli.* Gut. 1998 Aug;43(2):196-202 (full text available for free online).

- This paper reports a field test of bromelain in piglets, where weaned piglets were fed bromelain and then challenged with K88+ ETEC. Bromelain reduced the incidence of diarrhea, with treated pigs experiencing a statistically significant increase in weight gain compared with untreated pigs, however the effect of bromelain treatment was temporary, with enterocytes regenerating within 30 hours of treatment.

**Mynott et. al., 1999.** *Bromelain, from pineapple stems, proteolytically blocks activation of extracellular regulated kinase-2 in T cells.* J Immunol. 1999 Sep 1;163(5):2568-75 (full text available for free online).

- This paper shows that bromelain has an inhibitory effect in T cell activation by blocking a kinase called ERK-2.

**Engwerda et. al., 2001.** *Bromelain activates murine macrophages and natural killer cells in vitro.* Cell Immunol. 2001 May 25;210(1):5-10. Cell Immunol. 2001 May 25;210(1):66-75.

- This paper shows that bromelain enhances the performance of two key elements of the innate immune system - the macrophages and the natural killer cells.

**Engwerda et. al., 2001.** *Bromelain modulates T cell and B cell immune responses in vitro and in vivo.* Cell Immunol. 2001 May 25;210(1):66-75.

- This paper shows that bromelain has not only the direct inhibitory action on T cells noted in Mynott et. al., 1999 above, but also an indirect stimulatory action on T cells, effected by increasing the costimulatory activity of accessory cell populations.

**Mynott et. al., 2002.** *Proteolytic inhibition of Salmonella enterica serovar typhimurium-induced activation of the mitogen-activated protein kinases ERK and JNK in cultured human intestinal cells.* Infect Immun. 2002 Jan;70(1):86-95 (full text available for free online).

- This paper shows that bromelain is an inhibitor of MAP kinase signalling pathways. Such pathways are used by *Salmonella* and similar bacteria in inducing intestinal barrier dysfunction.



## Appendix V – Comparable companies to Anantara

Company	Location	Code	Market cap (US\$m)	Web
Achaogen	South San Francisco, Ca.	Nasdaq: AKAO	555	achaogen.com
Paratek Pharmaceuticals	Boston, Ma.	Nasdaq: PRTK	333	paratekpharma.com
Aratana Therapeutics	Watertown, Ma.	Nasdaq: PETX	285	aratana.com
Tetraphase Pharmaceuticals	Watertown, Ma.	Nasdaq: TTPH	182	tphase.com
Oasmia Pharmaceutical	Uppsala, Sweden	Nasdaq: OASM	119	oasmia.com
Kindred Biosciences	San Francisco, Ca.	Nasdaq: KIN	124	kindredbio.com
CorMedix	Bedminster, NJ	Nasdaq: CRMD	66	cormedix.com
Nexvet Biopharma	Dublin, Ireland	Nasdaq: NVET	41	nexvet.com

### Antibiotic drug developers

**Achaogen.** This company develops new antibacterials for the treatment of gram-negative infections. The company's lead compound, Plazomicin, is in Phase III in complicated urinary tract infections as well as in *Enterobacteriaceae* infections where the bacteria have become carbapenem-resistant. The company announced favourable data from both studies in December 2016.

**CorMedix.** This company is working on a new formulation of taurolidine, an antimicrobial agent that was originally used in the local treatment of peritonitis but was subsequently shown to be effective in the prevention of catheter-related bloodstream infections. CorMedix's product, called Neutrolin, combines taurolidine with heparin so as to decrease both the infection and the blood clot threats. Neutrolin, which is CE Marked in Europe, is in Phase III in the US in patients undergoing chronic hemodialysis via a central venous catheter.

**Paratek Pharmaceuticals.** This company, which includes the Nobel laureate Wally Gilbert as a co-founder, is in Phase III with Omadacycline, the first in a new class of antibiotic called the aminomethylcyclines. The first two indications for Omadacycline are bacterial skin and skin structure infections, and community-acquired bacterial pneumonia. Paratek's second product, a once-daily oral tetracycline-derivative called Sarecycline, is in Phase III in acne and rosacea. The US rights to Paratek are held by Allergan.

**Tetraphase Pharmaceuticals.** This company is being built on a synthetic chemistry platform inspired by the core chemical structure of tetracycline. The company's lead Eravacycline compound, a fully-synthetic tetracycline antibiotic, is in Phase III for the treatment of complicated intra-abdominal infections and complicated urinary tract infections.

### Animal health companies.

**Aratana Therapeutics.** This company develops medicines for pets with chronic diseases. The company has three FDA-approved products – Entyce, a selective ghrelin receptor agonist for appetite stimulation in dogs; Nocita, a bupivacaine local anaesthetic formulation for dogs; and Galliprant, a prostaglandin receptor antagonist for canine pain and inflammation associated with osteoarthritis.



**Kindred Biosciences.** This pet biotech company is getting ready to launch its first products: Mirataz, a transdermal ointment to deliver the antidepressant mirtazapine as an appetite stimulant for cats; and Zimeta, an injectable version of the pain drug Metamizole for treating fever in horses.

**Nexvet Biopharma.** This company, whose CEO is the Australian Dr Mark Heffernan although the company is headquartered in Dublin, has been built on a platform for the 'PETization' of monoclonal antibodies so they can be used in companion animals. Nexvet has two anti-NGF antibodies in late-stage development for the treatment of chronic pain.

**Oasmia Pharmaceutical.** This Swedish company is being built on Apealea, which is a formulation of paclitaxel based on an excipient called XR-17 that allows Cremophor, a cause of hypersensitivity reactions in some patients, to be dispensed with. For human use this product has completed Phase III and is now at the regulatory stage. A veterinary version of the same product is currently marketed under the name Paccal Vet-CA1.