NDF RESEARCH

Providing independent research coverage of
ASX-listed Life Science companies

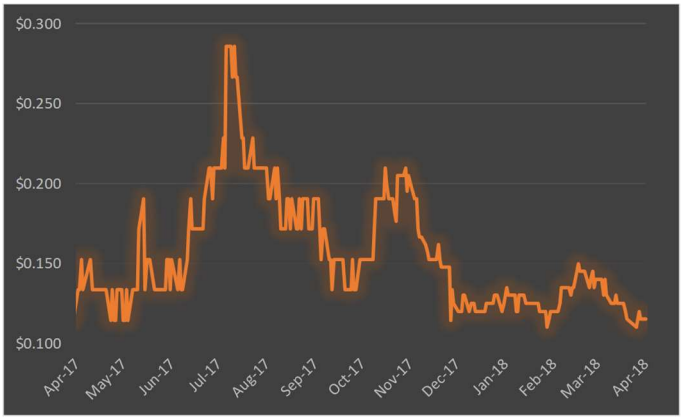
Dimerix (ASX: DXB)

Update note – Thursday 12 April 2018

Dimerix –DMX-200's credibility increases

This note updates our 25 August 2016 note headlined 'Hitting the GPCR spot'. Dimerix's lead DMX-200 candidate, a combination of two existing drugs, irbesartan and propagermanium, last year completed its Phase 2a study in patients with proteinuria, which is symptomatic of a range of kidney problems. We considered the results of this study highly encouraging. Irbesartan is already used to treat kidney disease. Dimerix's investigators found that the majority of patients that completed the Phase 2a showed a greater than 30% reduction in proteinuria, but that the biggest responders were patients with Diabetic Nephropathy. Dimerix is now working towards a Phase 2b of DMX-200 for this condition, as well as a Phase 2 trial for patients with the Orphan indication, Focal Segmental Glomerulosclerosis (FSGS). In this note we profile some recently published work done by scientists working with the US drug developer ChemoCentryx, which we regard as having validated the DMX-200 approach by demonstrating in two animal models of chronic kidney disease that a CCR2 blocker works best to reduce proteinuria when combined with an AT1R blocker. Dimerix had previously demonstrated the same effect in their 2015 publication, and these data were used as the basis for designing DMX-200 as well as for a patent application now granted as US 9,314,450, as outlined in our Update Report of 27 March 2017. Our $0.80 price target for Dimerix stays in place.

Rating	Risk	Current price	Target price
Buy	Speculative	$0.12	$0.80



Stock details

Daily Turnover: ~A$42,000
Market Cap: A18.6m
Shares Issued: 155.0m
52-Week High: $0.28.6
52-Week Low: $0.12

Analyst: Stuart Roberts
stuart@ndfresearch.com
+61 447 247 909

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

In this report

Dimerix –DMX-200's credibility increases

Who is Dimerix? Dimerix is a Melbourne and Perth-based drug discovery company being built around new ways to identify drugs acting on G Protein-Coupled Receptors, the target of a significant number of the world's best-selling drugs. Dimerix's Receptor-Heteromer Investigation Technology (Receptor-HIT) allows druggable GPCR combinations to be identified. Dimerix's lead DMX-200 candidate, an adjunct therapy of two safe and approved drugs, irbesartan and propagermanium, completed, in mid-2017, a Phase 2a study in patients with proteinuria, which is symptomatic of a range of kidney problems. Dimerix is now preparing a Phase 2b for DMX-200, expected to initiate in the second half of calendar 2018, that will recruit patients with Diabetic Nephropathy, where the Phase 2a data was particularly encouraging[1] . Alongside this study, Dimerix intends to conduct a small, 10-patient proof-of-concept study in FSGS, preparatory to taking DMX-200 into a pivotal study in FSGS from late 2019 or early 2020 after the Phase 2b.

DMX-200 WILL LIKELY GO TO PHASE 2B LATER THIS YEAR

The DMX-200 approach has received some encouraging peer-reviewed validation. On 21 March 2018 the online journal PLOS One published a paper from the American drug developer ChemoCentryx[2] entitled *'CCR2 antagonism leads to marked reduction in proteinuria and glomerular injury in murine models of focal segmental glomerulosclerosis (FSGS)'*[3]. In the paper the ChemoCentryx scientists report that one of their small molecule drug candidates, CCX872, which targets an immune system protein called CCR2, worked well as a potential FSGS treatment in two animal models. It worked even better when combined with the blood pressure drug candesartan, whose target, like the irbesartan used in DMX-200, is the Angiotensin II Type 1 receptor (AT1R). We regard this work as providing encouraging peer-reviewed validation of DMX-200, since Dimerix's drug combination also works by targeting CCR2 (propagermanium) and AT1R (Irbesartan).

Why blockading CCR2 and AT1R works in kidney disorders – the findings of Dimerix's Kevin Pfleger and colleagues. Science has known that co-blockade of AT1R and CCR2 could be effective in the treatment of kidney disease since about 2011. In 2007 a group at Tulane University in New Orleans had shown, in rats, that infusion of angiotensin II, the hormone that raises blood pressure, would activate MCP-1, the ligand to CCR2, and induce a rush of inflammatory macrophages into the kidneys[4]. A follow-up study by the same group in 2011 showed that combined treatment with a CCR2 antagonist and an angiotensin receptor blocker could treat a renal condition called crescentic glomerulonephritis in an animal model[5]. Dimerix's scientific founder, Dr Kevin Pfleger, had, by 2011[6], figured out why. Using Receptor-HIT, he and his team were able to show that AT1R and CCR2 form a GPCR heteromer. They then blockaded the heteromer with irbesartan and propagermanium in the 'gold-standard' animal model of kidney disease, the STNx model. The results, as published in PLOS One in March 2015[7], were highly favourable, with each change compared to untreated controls having statistical significance:

[1] Of the six Phase 2a patients registering a >50% reduction in proteinuria, five of them had a primary diagnosis of Diabetic Nephropathy. Of these five patients, the reduction in the ACR, that is, the albumin to creatinine ratio commonly used to measure changes in urinary protein excretion, was 36%. What was particularly encouraging, given the small patient numbers, was that the ACR change had a high degree of statistical significance (p=0.0063).
[2] Mountain View, Ca., Nasdaq: CCXI, www.chemocentryx.com
[3] Miao et. al., PLoS One. 2018 Mar 21;13(3):e0192405.
[4] Am J Physiol Renal Physiol. 2007 Jan;292(1):F330-9. Epub 2006 Jun 27.
[5] Hypertension. 2011 Mar;57(3):586-93. Epub 2011 Jan 31.
[6] See *Combination therapy*, WO/2012/094703, priority date 11 January 2011.
[7] PLoS One. 2015 Mar 25;10(3):e0119803. eCollection 2015.

- a >60% drop in the level of proteinuria in the treated rats. This was something neither irbesartan and propagermanium on their own could achieve, and important given that reductions in proteinuria of greater than 50% have long been considered clinically meaningful[8];
- A >70% drop in macrophage infiltration into the renal area;
- An 40% improvement compared to untreated controls in podocytes, that is, the cells which surround the glomeruli.
- An improvement in fibrosis, in both the glomeruli and the tubules.

The main reason why this data – and ChemoCentryx's – is promising is that until now kidney disease has been widely treated with blood pressure drugs including Irbesartan and candesartan, but there has been relatively little advance in terms of blunting damage to the kidneys caused by inflammation beyond the use of steroids. In the PLOS One paper Pfleger et. al. showed that when AT1R and CCR2 were co-expressed in a cell, the CCR2 signal in terms of G proteins induced by its natural ligand, CCL2, was much stronger when AT1R was being bound by its natural ligand, AngII, at the same time. In other words, the existence of the AT1R/CCR2 heteromer means a stronger level of inflammation notionally being directed towards kidney cells than was previously understood. In addition, in the heteromer form the AT1R and CCR2 signals could each only be completely blocked when both receptors were blocked. By blocking this inflammation, there is potentially much less damage to the glomeruli as well as other tissue.

CCR2 IS A VALIDATED TARGET IN KIDNEY DISEASE

The ChemoCentryx data confirms the findings of Pfleger et. al. ChemoCentryx is currently developing CCX872 as a cancer drug, on the understanding that, since CCR2-bearing cells seem to contribute to immunosuppression in the tumour microenvironment, knocking out such cells can help overcome a cancer's resistance to therapy[9]. The drug is in Phase 1b in patients with advanced pancreatic cancer[10]. In addition, ChemoCentryx used another CCR2 antagonist, CCX-140, in Diabetic Nephropathy and showed a reduction in proteinuria, however at that time they likely did not realise the importance of specifically using an AT1R blocker at the same time, as approximately half of their patients were on another type of medication called an Angiotensin Converting Enzyme inhibitor (ACEi). However, the work of Pfleger and others will have suggested to ChemoCentryx that the potential utility in kidney disease is critically dependant on the use of a CCR2 blocker with an AT1R blocker such as irbesartan or candesartan. To that end ChemoCentryx scientists tried out their proprietary CCR2 antagonist with and without candesartan in the STNx model as well as in another model called the Adriamycin nephropathy model.

- In the **STNx model**, the rat or mouse is 'subtotally nephrectomised', that is, most but not all (generally five-sixths) of its kidneys are removed. STNx is considered the 'gold standard' animal model for chronic kidney disease because typically humans can lose >80% of kidney function before feeling sick. Also, the model is not associated with diabetes or inflammation, which can complicate the picture in terms of tracking kidney function.

[8] See, for example, Kidney Int. 2004 Jun;65(6):2309-20.
[9] Cancer Res. 2013 Feb 1;73(3):1128-41. Epub 2012 Dec 5.
[10] See NCT02345408 at www.clinicaltrials.gov.

- In the **Adriamycin nephropathy model,** the rat or mouse has its kidney damaged via an infusion of Adriamycin, an anti-cancer antibiotic. This model is a good one for FSGS because it causes glomerulosclerosis, that is, inflammation of the capillaries within the kidneys that filter the blood[11].

In each case the ChemoCentryx scientists tracked the UACR, that is, the Urinary Albumin to Creatinine Ratio commonly used to measure changes in urinary protein excretion[12].

- In the Adriamycin nephropathy model, CCX872 alone cut UACR by 56% in week 1 and 58% in week 2, while the addition of candesartan made the UACR reduction 77% and 70%. The change between vehicle and combination was statistically significant in both weeks ($p<0.01$ and $p<0.05$ for weeks 1 and 2 respectively) whereas for CCX872 alone there was only statistical significance in the first week.

- in the STNx model, the ChemoCentryx scientists tracked the change for three weeks rather than 2. What they found here was CCX872 alone reduced UACR by 67% by week 3[13] while candesartan alone reduced UACR by 92% by week 3. When put together, UACR came down by 95% by week 3, with the change highly statistically significant compared to vehicle ($p<0.01$ and $p<0001$ respectively). For CCX872 alone there was only statistical significance in the third week.

These findings represent an encouraging validation of the DMX-200 approach because what they show is that CCR2 blockers really need A1TR blockers in order to work reliably in kidney diseases such as FSGS. It also suggests potential upside for ChemoCentryx should that company take one of its proprietary CCR2 blockers back into the clinic specifically on the background of an AT1R blocker. We have previously noted[14] that US Patent 9,314,450, granted to Dimerix in April 2016, included ChemoCentryx's CCX140 among the list of CCR antagonists covered by the AT1R/CCR2 joint blockade approach described in the patent. The first claim of that patent covers all CCR2 blockers. We await the design of ChemoCentryx's planned FSGS study with interest to see whether patients will be required to be specifically taking one or more of the commercially available AT1R blockers.

[11] Nephrology (Carlton). 2011 Jan;16(1):30-8.
[12] ACR is calculated by dividing the albumin concentration in milligrams by the creatinine concentration in grams. Creatinine is a breakdown product of creatine phosphate in muscle that is routinely excreted through the kidneys. It tends not to be impacted by kidney disease, making it a convenient denominator with which to track protein excretion, which in this case is represented by albumin.
[13] 24.00 ± 7.65 mg/mg compared to 73.36 ± 11.62 mg/mg.
[14] See our update note on Dimerix from 27 March 2017 headlined 'Progress with DMX-200'.

Background to Dimerix (ASX: DXB)

- **What are G Protein-Coupled Receptors and why are they commonly the target of blockbuster drugs?** A great many cellular functions are controlled by molecular signalling pathways that begin with a cell surface receptor and the associated natural binding partner of that receptor, called its 'ligand'. When these two join together, the result is a change in the shape of the interior part of the receptor, which allows it to activate another signalling molecule inside the cell. This signalling molecule in turn passes the signal to other molecules in a cascade of signalling activity until the required changes in the cell's behaviour or characteristics are affected. G Protein-Coupled Receptors, so-called because they pass the signals they receive onto intracellular 'G proteins', are amongst the most important of these cell surface receptors, because they seem to have a role in the whole of physiology. They are present in just about every organ system, and as a result have been considered as targets for a wide range of disease areas including heart disease, cancer, diabetes, inflammation and CNS disorders. This ubiquity explains why the Royal Swedish Academy of Sciences, in awarding the 2012 Nobel Prize for Chemistry to the American scientists Robert Lefkowitz and Brian Kobilka for their work on GPCRs, commented that '*about half of all medications achieve their effect through G protein–coupled receptors*'[15].

ABOUT HALF OF ALL MEDICATIONS ACHIEVE THEIR EFFECT THROUGH G PROTEIN-COUPLED RECEPTORS

- **How is Dimerix a player in the G Protein-Coupled Receptor space?** Dimerix is being built on a platform called Receptor-Heteromer Investigation Technology (Receptor-HIT) that allows druggable 'dimers' of GPCRs, known as GPCR heteromers, to be identified. Until recently the pharma industry had more or less been interested in drugging only individual GPCRs. However, it is now becoming apparent that many different GPCRs complex together, with these heteromers having a different functionality to the constituent GPCRs. This opens up the potential for many new GPCR targets and may also explain some unexpected effects of drugs thought to act on a single receptor. Since Dimerix's platform is cell-based and real-time, it arguably has the most world's most efficient way of identifying GPCR heteromers, and is therefore a corporate 'thought leader' in this new field. Importantly, Dimerix owns granted patents in major jurisdictions protecting its assay.
- **What new drugs has Dimerix discovered with its Receptor-HIT platform?** Dimerix's lead candidate, DMX-200, is the former blockbuster blood pressure drug irbesartan plus a less-well-known anti-inflammatory drug called propagermanium that is approved in Japan for the treatment of Hepatitis B infection. DMX-200 originated from the discovery by Dimerix's scientists that a GPCR called AT1R, which is targeted by irbesartan, forms a GPCR heteromer with CCR2, which is the target of propagermanium, and that this GPCR heteromer is highly relevant in kidney disease. To test its hypothesis that DMX-200 can treat kidney disease, Dimerix has completed a Phase 2a study in patients with proteinuria, that is, excessive protein in the urine, which is symptomatic of a range of kidney problems. Dimerix's clinical data have suggested that it many cases its drug combination can mirror the *in vivo* data and lower proteinuria by at least 50%, a clinically meaningful outcome in kidney disorders such as nephrotic syndrome, which is characterised by damage to the glomeruli that provide part of the kidney's blood filtering function. Patients with nephrotic syndrome and Chronic Kidney Disease are already routinely

DMX-200 IS PATENT-PROTECTED UNTIL 2032

[15] Source: Royal Swedish Academy of Sciences press release dated 10 October 2012.

treated with irbesartan. Dimerix has developed an extended-release formulation of propagermanium that will be additive to irbesartan. Dimerix expects to initiate a Phase 2b using the optimal dose during 2018, recruiting patients with Diabetic Nephropathy and Focal Segmental Glomerulosclerosis (FSGS), a rare nephrotic syndrome disorder for which Dimerix has obtained Orphan Drug Status from the FDA. After this Phase 2b, the company intends to run a single pivotal study in FSGS. Dimerix's original irbesartan-plus-propagermanium product has patent protection until 2032 with further patent life available once the extended-release formulation of propagermanium is completed.

- **What is the upside for Dimerix with DMX-200?** With DMX-200 there is potential for Dimerix to quickly become a Phase 3 drug developer by 2020 or 2021. The actual drug could be game-changing in kidney disease given the lack of new drugs in this space and the fact that ~12% of the US adult population has some sort of Chronic Kidney Disease. Consequently, there is potential for DMX-200 to branch out from FSGS to other larger-market indications including diabetic nephropathy.
- **What is the upside for Dimerix with its Receptor-HIT platform?** Other than DMX-200 we see two main upsides from the platform. Dimerix is currently working on a pipeline of GPCR heteromer-targeting candidates for nonalcoholic steatohepatitis (NASH), diabetic retinopathy, cancer fatigue and multiple sclerosis. In addition to this, it's not unreasonable to expect Big Pharma to be interested in the platform for its own GPCR drug discovery efforts, particular after two GPCR platform companies, Receptos and Heptares, were acquired in 2015. Two 'Top 10' pharma companies, along with Takeda[16], Japan's largest pharmaceutical company, have in the past used Receptor-HIT in paid collaborations with Dimerix scientists.

TWO TOP-TEN PHARMA COMPANIES HAVE IN THE PAST USED DIMERIX'S PLATFORM

Background to DMX-200

DMX-200 is two approved drugs put together. DMX-200 is the well-known hypertension drug irbesartan, adjuncted with a less-well-known anti-inflammatory drug called propagermanium, for the treatment of kidney disease. The first approved indication for DMX-200 is expected to be an Orphan kidney disorder called Focal Segmental Glomerulosclerosis (FSGS). The product originated from work done in the Pfleger lab showing that AT1R and CCR2, both GPCRs, form a GPCR heteromer that is highly relevant in kidney disease. Irbesartan works by binding AT1R, while propagermanium works by binding to CCR2. *In vivo*, DMX-200 has shown a significant reduction in proteinuria, that is, protein leaking into the urine, in an animal model of kidney disease, which is highly indicative of efficacy overall. The product is in Phase 2 in patients with proteinuria, which is symptomatic of a range of kidney problems, and in June 2016 Dimerix obtained FDA guidance related to a pathway for DMX-200 into Phase 3 in FSGS. To understand the potential of DMX-200 in kidney disease, let's look at its two constituent drugs and then kidney disease itself before looking at the combination.

DMX-200 IS TWO APPROVED DRUGS PUT TOGETHER

- **Irbesartan** is the generic name for Avapro, a former blockbuster drug from Sanofi and Bristol-Myers Squibb for the treatment of hypertension which gained its original FDA approval in 1997. Avapro wasn't

[16] Osaka, Japan, TSE: 4502, www.takeda.com. Takeda is the world's 19 largest pharma company with US$12.8bn in 2016 revenue (source: Pharmaceutical Executive magazine).

the first of the angiotensin II receptor blockers – that was Merck & Co.'s Cozaar (losartan), FDA approved in 1995 – but it was more efficient in terms of lowering blood pressure and had a longer half-life[17]. The drug's peak sales were US$2.7bn before the end of patent life in early 2012. Angiotensin II receptor blockers represented a big step forward in the treatment of high blood pressure because they offered better control over the renin-angiotensin system than their predecessor class, the ACE inhibitors[18]. Since high blood pressure tends to damage the kidneys over time they also represented a step forward in the renal area. Avapro gained FDA approval for the treatment of diabetic nephropathy (that is, kidney damage caused by high blood sugar levels) in 2002.

- **Propagermanium** is a much-less well known drug than irbesartan, since it's only approved use to date has been in Japan, for the treatment of Hepatitis B infection. The drug was originally developed by a small Japanese pharmaceutical company called Sanwa Kagaku and gained the Japanese Hepatitis B approval in 1994. Propagermanium, an organic germanium compound[19], doesn't act directly on Hepatitis B virus and its mechanism of action in Hepatitis B is poorly understood but believed to involve restoration of virus-specific cellular immunity[20]. However, much research interest since the mid-1990s has focused on propagermanium's anti-inflammatory properties, which is brought about by blocking the chemokine receptor CCR2[21]. Short for C-C motif chemokine receptor type 2, CCR2 binds to the cytokine MCP-1 (monocyte chemo-attractant protein 1), which in turn promotes migration of monocytes. CCR2 antagonists, by preventing this migration, can blunt a potentially damaging immune response.
- **Why these two drugs?** When Pfleger and his colleagues considered which small molecule would be ideal to drug the constituent GPCRs of their heteromer, it wasn't hard to select irbesartan, as the best of the angiotensin receptor blockers, to drug AT1R, given that by 2012 it was going off-patent. For CCR2 the choice was more complicated since there was no approved drug targeting this GPCR. Propagermanium, however, had gained at least one regulatory approval, and over the years had built a following in the US as a dietary supplement due to its potential anti-cancer properties[22]. This made it relatively easy to source[23]. Apart from the need to provide the drug to Australian patients under Special Access[24], the only downside to using propagermanium was that at the doses suggested from the animal data it would have to be taken three-times daily. Dimerix has worked with consulting chemists on a novel extended-release propagermanium that will also provide some extra intellectual property over the irbesartan/propagermanium combination.

[17] See Can J Clin Pharmacol. 2000 Spring;7(1):22-31.
[18] Renin is a hormone produced by the kidneys whenever the body senses that blood pressure has become too low. Renin then converts angiotensinogen into Angiotensin I, which is then converted by angiotensin-converting enzyme (ACE) into Angiotensin II. This final hormone is a powerful vasoconstrictor, that is, it constricts blood vessels, which increases blood pressure.
[19] That is, the chemical element with symbol Ge and atomic number 32. Propagermanium is a hydrophilic polymer of 3-oxygermyl propionate.
[20] J Gastroenterol. 2003;38(6):525-32. The speed of this immune response can cause liver damage in some patients. When this issue was first identified, around 1995, Japan's Committee on Adverse Drug Reactions ordered a special warning on the drug's packaging but did not withdraw marketing authorisation.
[21] J Interferon Cytokine Res. 2001 Jun;21(6):389-98.
[22] See, for example J Biol Response Mod 1985;4:159-168.
[23] For some background here from a true believer in propagermanium (also called GE-132 or Germanium sesquioxide), see www.germaniumsesquioxide.com. The FDA has a current 'import alert' on this product due to non-US manufacturing issues that date back to the 1980s (See FDA Import Alert 54-07).
[24] Since it is not approved in Australia. For a recent announcement on Special Access see Dimerix's market release dated 19 April 2016 and headlined '*Dimerix Receives TGA Special Access Scheme Approval to Continue to Supply Propagermanium to Kidney Patients on its DMX-200 Phase II trial*'.

If Dimerix is right, >10% of the population of the US and Europe could be helped with DMX-200. Currently around 12% of the US population has CKD and the European experience is probably similar[25]. The reason for this large patient population has to do with the ease with which kidneys can be damaged by Western lifestyles. The major function of the kidneys is to remove waste products and excess fluid from the blood. Within each kidney are up to a million 'filtration units' called nephrons. Each nephron has a capillary feeding into it called a glomerulus which performs the filtration function, after which the excess fluid flows into a tubule that carries the waste out of the body, ultimately in the form of urine. High blood pressure and diabetes will tend to damage the kidneys by exerting pressure on the glomeruli and other parts of the kidney. An early warning sign of kidney disease is proteinuria, that is, the blood protein albumin leaking into the urine, which can happen when the glomeruli become scarred and therefore less effective. This is the main symptom of nephrotic syndrome, which could be described as something of a warm-up act for the headliner of Chronic Kidney Disease (CKD), where the actual filtration function of the kidney, as measured by the estimated Glomerular Filtration Rate (GFR)[26], has noticeably fallen, and continues to do so through four stages of CKD until Stage 5. At that stage, better known as End-Stage Renal Disease (ESRD), there is virtually no kidney function left and the patient has to rely on dialysis if he or she can't find a donor kidney. The decline in kidney function in CKD, which the patients starts to feel by about Stage 3, manifests itself in swelling[27], tiredness and poor appetite among other things, as toxic wastes which should have been filtered by kidney build up in the blood. Eventually the toxic wastes can lead to the death of the patient at the time of ESRD through organ failure of some kind. The reason why there is so much CKD around is that it tends to travel in lockstep with hypertension and Type 2 Diabetes, where prevalence figures are also regrettably high - respectively 29%[28] and 12%[29] in US adults.

12% OF THE US POPULATION HAS CHRONIC KIDNEY DISEASE

ChemoCentryx have previously validated CCR2 as a target in kidney disease. ChemoCentryx's CCX140 CCR2 inhibitor is one of that company's lead programmes. CCX140 has completed Phase 2 in Diabetic Nephropathy. In December 2014 ChemoCentryx reported a statistically significant reduction in proteinuria for patients treated on the lower of two doses of CCX140 of 18% over 52 weeks (p=0.01) that were also on the standard-of-care of either ACE inhibitors or angiotensin receptor blockers. ChemoCentryx's investigators also noted an improvement in eGFR alongside the reduction in proteinuria[30]. The Phase 2 data were published in August 2015[31]. We believe this work also validates the approach that Dimerix is taking with the use of a CCR2 antagonist to reduce proteinuria[32].

Valuing Dimerix

In our 8 November 2017 update of Dimerix we valued the company at $0.46 per share base case and $1.12 per share optimistic case. For details of our basic approach see our 25 August 2016 note headlined 'Hitting the GPCR

[25] J Am Soc Nephrol. 2006 Aug;17(8):2275-84. Epub 2006 Jun 21.
[26] Measured by testing for the blood levels of creatinine, a breakdown product of muscle. Creatinine is normally cleared from the blood by the kidneys. When kidney function is declining the level of creatinine in the blood goes up.
[27] The loss of albumin leads to edema, that is, fluid retention.
[28] NCHS Data Brief. 2013 Oct;(133):1-8.
[29] JAMA. 2015 Sep 8;314(10):1021-9.
[30] See the company's market release dated 12 December 2014 and headlined '*ChemoCentryx Announces Positive Results in Phase II Diabetic Nephropathy Trial With CCR2 Inhibitor CCX140*'.
[31] Lancet Diabetes Endocrinol. 2015 Sep;3(9):687-96. doi: 10.1016/S2213-8587(15)00261-2. Epub 2015 Aug 9.
[32] There are potentially also lessons on patient selection from this study which Dimerix will likely consider, such as the use of biomarkers that indicate the best responses to a CCR2 antagonist.

spot'. With this note our valuation changes to $0.37 per share base case and $0.92 per share optimistic case, however we are leaving our target price unchanged at 80 cents per share. Our approach, which we first developed in our 25 August 2016 note, was as follows:

- Our WACC is 15.3% (Speculative)[33].
- We conservatively modelled a payoff only for DMX-200 and allowed no value for the Dimerix pipeline. We believe *in vivo* data from the pipeline will allow us to gradually add value from this platform.
- We assume another US$5-10m in expenditure for Dimerix to mature the DMX-200 programme.
- We model around 14 years of commercial exclusivity for DMX-200.

Why the valuation range reduction with this note? Since August 2016 we have assumed that DMX-200 can license to a pharma partner in FY19 (base case) or FY18 (optimistic case) for US$30-50m upfront, US$100-200m in milestones and an 8-12% royalty. We are now moving the year of those assumptions back by a year. Basically, preparation for the DMX-200 Phase 2b will now take longer than we originally envisaged due to the larger and more specialised nature of the trial as it is now shaping up. This potentially defers the payday of a licensing transaction. In addition to this, Dimerix recently raised A$7.5m at 12 cents per share. Our model now adjusted for the rights issue and placement involved.

WE MODEL DMX-200's CHANCES OF SUCCESS AT 50%

Why the unchanged target price? Ordinarily our target price sits at the midpoint of our valuation range. This time we are leaving the target price unchanged at the higher end of our valuation range**.** We believe that the DMX-200 story has improved given we now have evidence of its utility in Diabetic Nephropathy.

Risk weighting

- We modelled DMX-200 with a 50% probability of clinical success. This may seem high given the product is still only at Phase 2, however the *in vivo* evidence of efficacy in lowering proteinuria, and the importance of this endpoint to disease outcomes in FSGS, as well as the ease with which DMX-200 can enter Phase 3 in FSGS, suggested a more favourable risk weighting for this product.

Commercial outcomes

- We assume that the product can license to a pharma partner in FY20 (base case) or FY19 (optimistic case) for US$30-50m upfront, US$100-200m in milestones and an 8-12% royalty.
- We assume a product launch in FSGS in FY22 (base case) or FY21 (optimistic case) in the US and FY23 (base case) or FY22 (optimistic case) in Europe.
- We assume peak sales for DMX-200 of US$300-600m, initially in FSGS and then branching out into other kidney disorders.

Further capital

[33] For a relevant discount rate, we use WACCs of between ~11% and ~15% depending on the risk for Life Science companies. This is derived from a RFR of 2.7%; a MRP of 7.5%-11.5% (7.5% for 'medium risk' companies, 9.5% for 'high risk' companies and 11.5% for 'speculative' companies like Dimerix); and an ungeared beta of 1.1. 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'.

- An admirable feature of Dimerix since listing has been the low burn rate, averaging only ~A$165,000 per month for the last twelve months. The company raised A$7.5m at 12 cents per share earlier this year in a rights issue followed by a placement. We therefore assume no further capital to be raised in order to initiate the Phase 2b for DMX-200.

Re-rating Dimerix

We see a number of events helping to re-rate Dimerix to our target price over the next 12 months:

- Research agreements and collaborations related to the Receptor-HIT platform;
- Pre-clinical data from DMX-250 in NASH;
- Data from the other pre-clinical programmes from Receptor-HIT;
- Filing of the IND for DMX-200;
- Ethics approval and initial patient recruitment for the first DMX-200 Phase 2b sites.

DMS-200's PHASE 2B STUDY WILL LIKELY INITIATE IN 2018

Risks related to Dimerix

Risks specific to Dimerix. We see five major risks for Dimerix as a company and as a listed stock.

- **Timing risk.** There is the risk that Dimerix may take longer to complete the clinical work for DMX-200 than the time we have postulated in our research;
- **Clinical risk.** There is the risk that the forthcoming Phase 2b or pivotal study for DMX-200 may miss their primary or secondary endpoints.
- **Regulatory risk.** There is the risk that the FDA and other regulators may decline to approve DMX-200 even if Dimerix consider the data submitted to be adequate.
- **Formulation risk**. There is the risk that propagermanium may not be adaptable in to an extended release formulation.
- **Commercial risk**. There is the risk that DMX-200 may be displaced by other more advance therapies in kidney disease, particularly those related to regenerative medicine.

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 Dimerix.

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