NDF RESEARCH

Providing independent research coverage of
ASX-listed Life Science companies

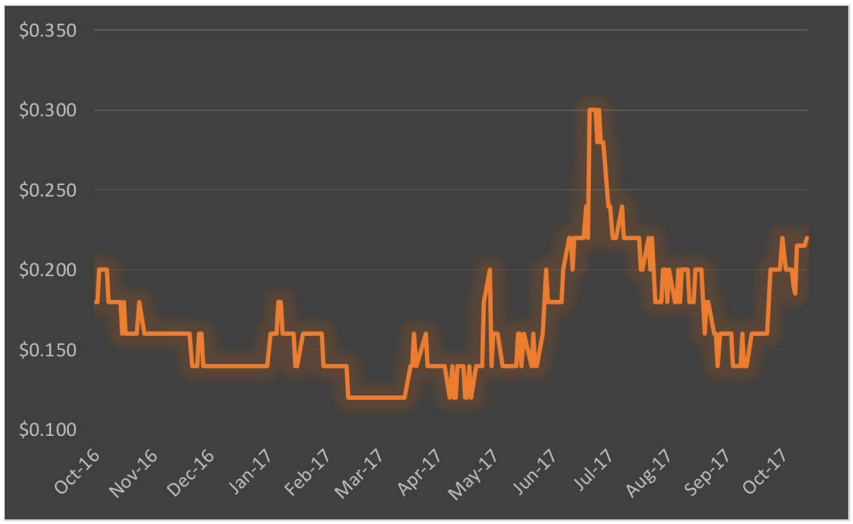
Dimerix (ASX: DXB)

Update note – Wednesday 8 November 2017

Dimerix is now a player in Diabetic Nephropathy

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, earlier this 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, and in new data released last week, Dimerix has found that the majority of patients that completed its study showed a greater than 30% reduction in proteinuria. Dimerix has now performed a sub-group analysis showing that, of the 25% of patients where proteinuria dropped by >50%, 83% of them had a primary diagnosis of Diabetic Nephropathy. Dimerix is now preparing to initiate a Phase 2b early next year recruiting a significant cohort of Diabetic Nephropathy patients, ahead of a potential Phase 3 in an Orphan kidney disease by 2019. We believe Dimerix can find a pharma partner for Diabetic Nephropathy given the market opportunity. Our $0.80 price target (previously 4 cents, before 20:1 share consolidation) for Dimerix stays in place.

Rating	Risk	Current price	Target price
Buy	Speculative	$0.22	$0.80



Stock details

Daily Turnover: ~A$35,000
Market Cap: A20.1m
Shares Issued: 91.5m
52-Week High: $0.30
52-Week Low: $0.12

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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.

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

In this report

Dimerix is now a player in Diabetic Nephropathy

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. Following recent guidance from the FDA, Dimerix is preparing to take DMX-200 into a pivotal study in Focal Segmental Glomerulosclerosis (FSGS), an Orphan kidney disease. Prior to this Phase 3, Dimerix had intended to initiate, in late 2017 or early 2018, a Phase 2b in patients with proteinuria at the optimal dose from Phase 2a. After a favourable sub-group analysis of the Phase 2a patients, Dimerix now intends that the upcoming Phase 2b will have a primary endpoint for a Diabetic Nephropathy cohort, with further exploratory analysis of patients with FSGS and IgA Nephropathy.

Dimerix' Phase 2a study of DMX-200 in patients with proteinuria was successful. As we noted in our 13 July 2017 update on Dimerix, the Phase 2a study of DMX-200 met its primary endpoint of safety, and saw 25% of the patients achieve a >50% reduction in proteinuria. In kidney disease, reductions of this magnitude are generally considered clinically meaningful[1]. We argued that the Phase 2a outcome indicated that Dimerix's drug had strong potential in kidney disease. For one thing, Dimerix's patients were already well managed, as indicated by the average of nine medications other than propagermanium they were receiving. For another, some patients had partial responses (ie <50% proteinuria reductions) or experienced a strong rebound in their proteinuria during the 'washout' period after completion of the trial dosing. Finally, 45% of patients chose, in conjunction with their treating physicians, to stay on DMX-200 after the study via a 'Special Access Scheme' arrangement. All this indicated some clinical benefit for around half of the patients, and in fact we now know that 13 of the 24 patients that completed dosing in the study had a >30% reduction in proteinuria.

Dimerix now has more valuable data from DMX-200's Phase 2a, indicating the drug's potential in Diabetic Nephropathy. Dimerix has now performed a *post hoc* sub-group analysis of the 24 patients that completed dosing in the Phase 2a, finding that

DMX-200 SEEMS TO WORK WELL IN DIABETIC NEPHROPATHY

- of the six patients registering a >50% reduction in proteinuria, five of them had a primary diagnosis of Diabetic Nephropathy.
- in these five Diabetic Nephropathy patients, the reduction in the ACR, that is, the albumin to creatinine ratio commonly used to measure changes in urinary protein excretion[2], 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).

[1] See, for example, Kidney Int. 2004 Jun;65(6):2309-20.
[2] 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.

- the sixth patient had IgA nephropathy, which gives Dimerix a reason to consider this rare kidney disease and may be the basis of another Orphan Drug Designation in addition to FSGS[3].

Dimerix is now preparing for a Phase 2b, guided by the sub-group analysis. Dimerix had previously planned on a ~30-patient Phase 2b in a similar patient population – ie, patients with proteinuria, regardless of the patient's actual disease condition – at the optimal dose established by the Phase 2a. After this the company would move to a Phase 3 in FSGS, a disease where reduction in proteinuria is known to have a meaningful clinical effect[4]. The data on Diabetic and IgA Nephropathy now suggests a Phase 2b of ~90 patients – 60 with Diabetic Nephropathy, 30 with IgA Nephropathy and FSGS.

- This Phase 2b study, to be double-blind, randomised and placebo-controlled, will be initiated in early 2018;
- Patients will be monitored without dosing over the first three months to establish stable disease in terms of ACR, after which they will be dosed for six months;
- The primary endpoint in this study will be reduction in ACR for the Diabetic Nephropathy cohort, with reduction in ACR for the other patients one of the secondary endpoints.

The sub-group analysis is highly encouraging. Diabetic Nephropathy is a large market opportunity of unmet medical need. 20%-40% of all diabetics have kidney disease[5], which suggests the possibility that perhaps 3% of the entire US population has Diabetic Nephropathy[6]. Given the high costs of these patients once they have progressed to dialysis – and up to 45% of new dialysis patients in industrialised countries will arrive there thanks to diabetes complications[7] – the economics of new agents to treat Diabetic Nephropathy are likely to be favourable for their developers, in what would reasonably be a multibillion-dollar market opportunity. Dimerix is now well-placed to develop a drug suitable for this space – consider that >30% reductions in albuminuria are the sort of outcomes that the new SGLT2 inhibitors Jardiance (empagliflozin, Lilly / Boehringer Ingelheim), Invokana (canagliflozin, J&J) and Farxiga (dapagliflozin, AstraZeneca) are showing in large clinical studies[8]. We understand partnering interest in new compounds involved in Diabetic Nephropathy are strong.

~3% OF THE US POPULATION HAS DIABETIC NEPHROPATHY

Dimerix potentially has a better Diabetic Nephropathy drug than ChemoCentryx. We have previously noted that this US drug developer's lead molecule is CCX140, a CCR2 inhibitor that has completed Phase 2 in Diabetic Nephropathy. In that study[9], the lower of two doses of CCX140 over 52 weeks reduced the ACR by 18% for patients that were also on the standard-of-care of either ACE inhibitors or angiotensin receptor blockers. Of course, ChemoCentryx's analysis included 192 patients in a modified intention-to-treat population whereas Dimerix has just 10 patients over ~28 weeks in a *post hoc* analysis in a small Phase 2a. That said, the 36% number from DMX-200 is encouraging. It's worth noting that ChemoCentryx has licensed CCX140 to Vifor (the subsidiary of major

[3] IgA nephropathy, also known as Berger's disease, occurs when the immunoglobulin protein IgA builds up in the kidneys, causing inflammation that damages kidney tissue. There are estimated to be 130,000 cases identified annually in the US (source: NORD).
[4] It is estimated that proteinuria in FSGS patients can be 25 times higher than in diabetic nephropathy patients – see Am J Physiol Renal Physiol. 2008 Dec;295(6):F1589-600. Epub 2008 Jun 25. One Canadian study has found that a reduction in proteinuria is the main factor in renal survival for FSGS patients – see J Am Soc Nephrol. 2005 Apr;16(4):1061-8. Epub 2005 Feb 16.
[5] J Nephropharmacol. 2016; 5(1): 49–56.
[6] For US diabetes estimates see the CDC's 2017 National Diabetes Statistics Report.
[7] Nephrol Dial Transplant. 2008 Dec;23(12):3988-95. Epub 2008 Jul 25.
[8] Diabetologia. 2016 Sep;59(9):1860-70. Epub 2016 Jun 17.
[9] Lancet Diabetes Endocrinol. 2015 Sep;3(9):687-96Epub 2015 Aug 9.

Swiss healthcare company Galenica[10]) for rare kidney diseases. Vifor paid US$50m upfront for this programme with other terms undisclosed. We think this interest by Vifor bodes well for Dimerix in terms of future partnering discussions around 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'*[11].

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

[10] Bern, Switzerland, SIX: GALN, www.galenica.com.
[11] Source: Royal Swedish Academy of Sciences press release dated 10 October 2012.

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 treated with irbesartan. Dimerix is developing an extended-release formulation of propagermanium that will be additive to irbesartan. Dimerix expects to initiate a Phase 2b using the optimal dose in early 2018, recruiting patients with Diabetic Nephropathy, IgA 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 2019 or 2020. 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.
- **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[12], 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

[12] 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).

Valuing Dimerix

We previously valued Dimerix at $0.023 per share base case and $0.057 per share optimistic case using a probability-weighted DCF approach. For details of our approach see our 25 August 2016 note headlined 'Hitting the GPCR spot'. Dimerix has since consolidated its stock on a 20:1 basis. With this note our valuation changes, after the consolidation, to $0.46 per share base case and $1.12 per share optimistic case. Our approach, which we first developed in our 25 August 2016 note, was as follows:

- Our WACC is 15.2% (Speculative)[13].
- 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.

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.

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

Commercial outcomes

- We assume that the product 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 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

- 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$2m at 12 cents per shares (0.6 cents per share before 20:1 share consolidation) in February 2017. However, we believe it will be necessary for Dimerix to raise further capital. For modelling purposes, we assume that the company raises another $10m at 20 cents per share in order to initiate the Phase 2b for DMX-200 as well as move other pipeline elements forward.

[13] 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 2.6%; 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'.

Re-rating Dimerix

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

- Completion of the extended-release formulation of propagermanium;
- 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 INITIATE IN EARLY 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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