MEDIUS DEAL WATCH

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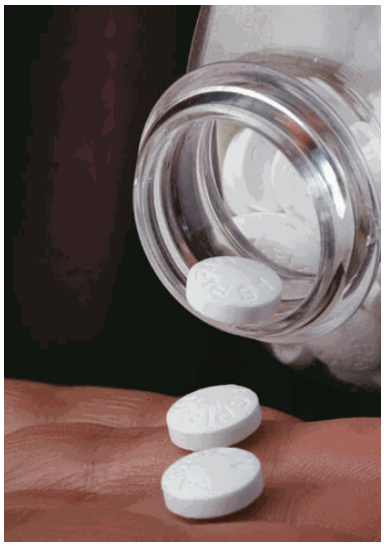
September 2015

September saw an interesting mix of deal types and structures, disease areas and companies hitting our Deal Watch radar. Oncology deals continue to be prominent, but the month also saw CNS-focused deals in vogue; with chronic, post-operative and neuropathic pain centre-stage. Ophthalmic, metabolic, dermatological, autoimmune and anti-infective based deals also featured.

The loudest noise, however, was the ricochet created by Turing Pharma's newly acquired, 62 year old drug, daraprim, to treat toxoplasmosis, being given a 5,000 % price increase ($13.50 per pill to $750), to "fund future research into the disease " and the subsequent backlash against its CEO Martin Shkreli and the biotech sector as a whole.

Share prices across the industry were rocked over the last 10 days of the month as investors demonstrated their concern that US legislators may do something drastic to rein in the cost of drugs as politicians and presidential candidates clamour for answers and reforms. In addition to Turing Pharma, Deal Watch favourite, Valeant is under the spotlight and, this time, not just for its exuberant deal making.

However, we do need to keep some perspective, although by the end of the month, the Nasdaq biotech index is approx. 25% down on the year's high of 4,165 (20th July), at 3,033, it is still higher than this time last year and only 5% down on where it started 2015 at 3,203.



It will be interesting to see how much of this is knee-jerk, how much will result in a new world order and the impact it has on the industry's deal makers and their willingness to continue to shell-out vast premiums and multiples. In all this uncertainty, one thing that is certain is this is not going to be easily brushed under the carpet as we head into election year in the US.

Let's deal with the pain first …

After last month's deal with Eisai for lemborexant, a phase 3 insomnia treatment, Purdue Pharma is refocusing on its pain portfolio by in-licensing a mid stage asset and spinning out some earlier stage assets. Purdue licensed VM Pharma's allosteric selective tropomyosin receptor kinase A (TrkA) inhibitor programme for chronic pain. The lead product is VM-902A, which demonstrated strong safety and efficacy profile in a 72-patient phase 1 study. Purdue will start the phase 2 study in early 2016. Under the terms of the agreement, VM is entitled to receive undisclosed upfront and milestone fees of $213m, plus royalties on sales.

With the aim of accelerating some in-house early stage programmes, Purdue has spun-out its pipeline targets in NAV1.7 sodium ion channel products into a JV with AnaBios, which has a propriety discovery platform ("Phase X") that uses human tissue in pre-clinical development. No financial terms were disclosed.

Targeting the same NAV1.7 ion channel, Astellas has in-licensed Chromocell's CC8464 for neuropathic pain for up to $515m. Under the terms of the deal Chromocell will receive $15m upfront and will continue to undertake the development through to the first phase 2a POC study, thereafter Astellas will progress the development. Chromocell retains the right to develop the candidate for indications other than neuropathic pain and Astellas can opt into any of these projects at an incremental cost.

Show me the money

The final deal in the pain space, is less about the pain and more about the money! PDL BioPharma is buying out the majority of the expected royalty stream from EU sales of AcelRX's phase 3 product, Zalviso™ for $65m. Zalviso™ is a combination drug and device product which uses a patient controlled dispenser to deliver a sub-lingual formulation of sufentanil, an opioid with a high therapeutic index. It is licensed to Grunenthal in Europe. The drug is being evaluated for the treatment of moderate to severe post-operative pain in hospitals and could be used to replace intravenous patient-controlled analgesia. It has received a positive EMA CHMP opinion and Grunenthal expects to launch Zalviso™ in the first half of 2016 and PDL expects to start to receive royalties thereafter.

Specifically, PDL will receive 75% of the EU royalties under the Grunenthal licence as well as 80% of the first four commercial milestones, subject to a capped amount. AcelRx will receive 25% of the royalties, 20% of the first four commercial milestones, 100% of the remaining commercial milestones and all development milestones, including a potential $15m payment for the approval of the Zalviso™ MAA. The non-dilutive cash injection, will provide AcelRx with additional operating capital, to complete regulatory submissions for another product, ARX-04, in the US and EU, and any additional work on Zalviso, ahead of re-submitting the NDA.

For PDL this represents the 15th transaction it has completed since embarking on the strategy of building a portfolio of income generating assets.

In a similar, but more complex financing deal transaction, Agenus is selling future royalties on a GlaxoSmithKline (GSK) -partnered vaccine adjuvant, QS-21, used alongside malaria and shingles vaccines, in exchange for up to $115m. Agenus will invest the proceeds in its growing pipeline of pre-clinical immuno-oncology treatments which include a series of PD-1 and CTLA-4 inhibitor programmes.

Agenus is giving the royalty rights to Oberland Capital in exchange for a $100m loan, (recouping the other $15m if and when the shingles vaccine gets FDA approval) and GSK will service the loan (accruing interest at 13.5% per year). If and when GSK's repayments satisfy the loan terms, Agenus will regain full rights to QS-21; if after 12 years, the adjuvant doesn't live up to its potential, Agenus will have to pay Oberland the difference.

This move sees an 18 month turn-around for Agenus as back in early 2014, the company had only $25m in cash and its share price was under $3 a share after a clinical setback to the GSK product. During this period, Agenus acquired 4-Antibody and its discovery platform for $10m upfront ($40m more in milestones) and has done deals with Merck ($100m) and Incyte ($140m) to generate $120m in net cash to fund its near-term development needs and more than double its share price (before the Shkreli crisis).

Oncology continues to attract

Continuing the interesting deal structures to build oncology platforms, Celgene is continuing its march; this month with a partnering deal with Third Rocks' freshly launched company, Nurix. In a raft of other oncology deals announced in September, we have seen a range of targets and platforms including mitochondrial agonists, bispecific targets and dendrimer drug delivery.

Celgene is paying Nurix $150m up-front plus an undisclosed equity investment for the right to license some of its ubiquitin proteasome system (UPS)-focused projects. The UPS is a network of enzymes that regulate cell growth and death, and it is believed that through these programmes it will be possible to modulate the production and breakdown of proteins within cells, thereby potentially having wide reaching implications in oncology, inflammation and immunology. Under the agreement, in typical Celgene style, Nurix remains in control of all R&D through to the end of phase 1 before bringing in its new partner. At that stage, Celgene can have worldwide rights to certain Nurix programs by paying an option fee and milestone payments totalling up to $405m each, plus royalties. On other projects, Nurix will retain some US rights, giving Celgene the opportunity to split development costs in exchange for a half US generated profits and all of the proceeds from other countries.

After several deals sharing rights to its checkpoint inhibitor indoleamine 2,3-dioxygenase 1 (IDO1 - epacadostat), to big pharma, Incyte is getting its own seat at the immuno-oncology table, by taking rights (outside China) to a PD-1 inhibitor (POC ready) from Jaingsu Hengrui Medicine (SHR-1210) for advanced solid tumours paying a modest $25m upfront but up to $770m in milestones and royalties if all goes well.

This month saw Takeda form a partnership with Gencia to develop two mitochondrial agonists of the glucocorticoid receptor (MAGR) drugs for the treatment of cancer and inflammatory diseases. Standard glucocorticoid drugs (steroids) can be effective in haematological and inflammatory diseases, but their serious side effects limit use, and can often lead to a resistance that eventually renders the treatments useless. MAGR therapies, chemically distinct from steroids, may have the benefits without the downsides. Gencia could receive up to $500m in milestone payments. Takeda will make the decision which treatments will enter clinical trials. Gencia is also at the discovery phase in mitochondrial therapies in neurodegeneration, cardiovascular disease and other areas.

Amgen's busy month (part 1)

In a month that saw Amgen announce 5 deals, 2 were in oncology. Amgen is collaborating with Xencor, which has a proprietary bispecific antibody technology (simultaneous targeting of two biological targets; tumour-expressed antigens and the immune system's T cells), on 6 early-stage programmes in immuno-oncology and inflammation.

Licensor Acquired	Licensee Acquirer	Product / Technology	Deal Type	Headline ($m)
Amdipharm Mercury Company	Concordia Healthcare	Speciality pharma company	Acquisition - company	3,500
ZS Pharma	Actelion	ZS-9 to treat hyperkalemia under review with FDA	Acquisition - company	2,500
Xencor	Amgen	Proprietry bi-specific antibody platform for use on 6 early stage programmes for immuno-oncology and inflammation	Collaboration - licence	1,700
Dezima	Amgen	TA-8995 an oral CETP inhibitor to treat dyslipidemia (phase 2b)	Acquisition - company	1,550
UCB	Lannett	Kremers Urban Pharmaceuticals - speciality generics business	Acquisition - company	1,230
Jiangsu Hengrui Medicine	Incyte	anti-PD-1, checkpoint inhibitor SHR-121 (POC ready)	Licence *	795
Nurix	Celgene	Early stage pipeline to target ubiquitin proteasome system (UPS) for potential in oncology / inflammation and immunology	Collaboration - option to license **	555
Hetero Drugs	Cipla	Generic US based companies; InvaGen Pharmaceuticals and Exelar Pharmaceuticals	Acquisition – 2 companies	550
Mitsuibishi Tanabe	Biogen	MT-1303, an oral S1P modulator (phase 2 complete) for multiple sclerosis	Licence ***	544
Chromocell	Astellas	NaV1.7 ion channel - blocker to treat neuropathic pain, phase 1 ready	Licence	515
Gencia	Takeda Pharmaceuticals	Development of 2 small-molecule mitochondrial agonists of the glucocorticoid receptor, or MAGRs	Collaboration - discovery	500
AstraZeneca	Valeant Pharmaceuticals	Brodalumab for psoriasis, ready for submission to regulators in EU and US	Acquisition - product	445
Aquesys	Allergan	Implantable shunt for glaucoma	Acquisition - company	300
AstraZeneca	US Dept of Health & Human Services	Combining antibiotics to tackle multi-drug resistant bacterial infections	Collaboration -public private partnership	220
VM Pharma	Purdue Pharma	VM902A a signalling protein tropomyosin receptor kinase A (TrkA) inhibitor in phase 1	Licence	213
California Cancer Centre (City of Hope)	Sorrento Therapeutics	Antibody platform that allows MAbs to enter the cytoplasm	Joint venture	170
Link Healthcare	Clinigen Group	Regional speciality business in Australia, Asia and Africa	Acquisition - company	155
Starpharma	AstraZeneca	DEP dendrimer-conjugate platform applied to specific targets	Licence	126
Agenus	GlaxoSmithKline	QS-21 vaccine adjuvant used alongside malaria and shingles vaccines	Royalty monetisation	110
AcelRx Pharmaceuticals	PDL BioPharma	Zalviso™ sub-lingual formulation of sufentanil	Royalty monetisation ****	65
Insite Vision	Sun Pharmaceuticals	Ophthalmology portfolio	Acquisition - company	65

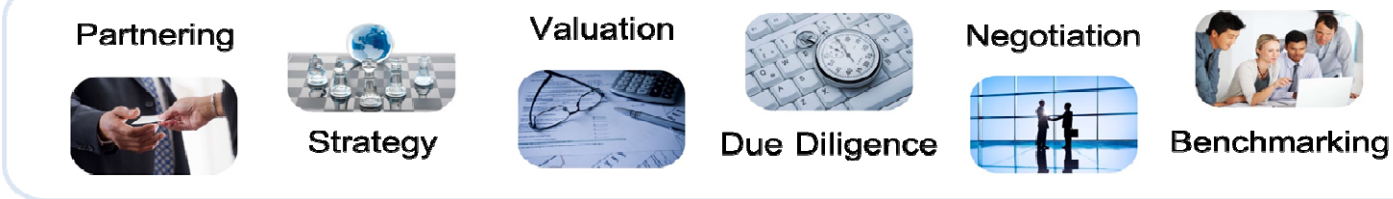
All deals global unless otherwise stated:

* Worldwide excluding China (and related territories)

** Worldwide on some candidates and Worldwide (excluding US) on others … not disclosed

*** Worldwide excluding Asia

**** European sales only



Amgen is paying $45m up-front to use Xencor's R&D technology on some pre-clinical antibodies designed to harness the body's natural defences. Xencor could potentially receive an additional $1.7bn tied to regulatory and sales milestones, plus royalty payments on future sales. Xencor will earn mid to high single-digit royalties on the Amgen-selected targets and high single- to low double-digit royalties on its internally developed candidate, a multiple myeloma treatment.

Amgen, has had success with in-house bispecifics already, such as acute lymphoblastic leukaemia (ALL) treatment, Blincyto; the in-development acute myeloid leukaemia (AML) therapy AMG 330; and multiple myeloma drug Kyprolis, acquired in the $10bn purchase of Onyx Pharmaceuticals.

Building on a previous collaboration AstraZeneca (AZ) is again partnering with Australian Starpharma on its DEP dendrimer-conjugate platform with an oncology candidate. The platform consists of a large molecule made of layers of monomers, most often the amino acid lysine, to create the dendrimer. The drug is conjugated to the dendrimer with various linker molecules between the drug and the dendrimer that can be used to achieve different drug delivery feats. A permanent linker can be used if the dendrimer does not affect efficacy (i.e. insulin), or an unstable linker that degrades at a specified half-life can be used for sustained release, or linkers that degrade at a low pH or exposure to a certain enzyme can be used for targeted release, such as the site of a tumour. In this way, the technology can result in improved solubility, less off-target toxicity, and ultimately, improved efficacy.

Starpharma is receiving an upfront of $2m with milestones of up to $124m. For subsequent drugs targeting a defined (but undisclosed) family of targets, using the platform, Starpharma could earn milestones up to $93m plus tiered royalties on net sales. AZ will fund all development and commercialisation costs under the agreement.

Pre-loved asset

Following Amgen's abandoning of brodalumab (an IL-17 for psoriasis) earlier this year, development partner AZ has now sold it on to Valeant. This is Valeant's first biologic but apart from that, it fits with the tried and tested strategy of taking on "close to launch", daunting assets (see last month's acquisition of Sprout familiar as a case in point) and going on the offensive against rivals.

Brodalumab is phase 3 complete, but is thought to have been cast off due to concerns raised over links to the drug and suicidal thoughts.

For a company that has built its business to a large extent on acquiring drugs and pushing prices, given the current Shkreli ricochet effect this may not be the best time to pursue a "robust" pricing model. In fact Valeant's Michael Pearson has already been asked to outline the rationale for price increases in two cardiovascular drugs Isuprel (525%) and Nitropress (212%) after acquiring them from Marathon Pharmaceuticals. He has also written a letter to employees to assuage their concerns over company's business model, potential exposure and the fall in the company's stock price (it fell 20 % in five days from $240 on 18th September and by 29th it was as low as $158, but rallied slightly to $178 by 30th September. It is worth noting that the share price has increased by 600% in 5 years).

Bridget Lacey has over 18 years of corporate finance and business development experience within the Healthcare industry in Pharmaceuticals, Biotech, Vaccines and Life Sciences roles in the UK, Singapore and Japan. She has experience across a wide range of transactions including leading company and product acquisitions, business divestments and licensing deals, with a focus on due diligence and valuations, most recently in the orphan and rare diseases space.

Amgen's busy month (part 2)

Following FDA approval for its novel PCSK9 treatment for "bad cholesterol", Amgen is moving onto tackle dyslipidemia, an asymptomatic disease in which serum lipid levels deviate from the normal level, by acquiring Dutch biotech Dezima for $1.55bn. Dezima's TA-8995 (phase 2b-complete), is an oral cholesterol ester transfer protein (CETP) inhibitor that has demonstrated dramatic LDL-C lowering, reducing levels of LDL-C by up to 48%, while boosting healthy HDL.

It was originally in-licensed from Mitsubishi Tanabe. Amgen is paying $300m upfront and $1.25bn in potential milestones, but this is competitive field and several of the industry players have invested heavily in the space. Whilst Roche and Pfizer failed to overcome efficacy and safety concerns regarding their candidates, Eli Lilly's (evacetrapib) and Merck's (anacetrapib), products are looking to raise HDL levels and these companies will be looking over their shoulders as Amgen moves into the space.

Transformational deals

The two largest deals announced this month were Cinven's sale of Amdipharm Mercury (AMCo) to Concordia Healthcare and Actelion's move to acquire ZS Pharma, at $3.5bn and rumoured to be $2.5bn, respectively.

In an attempt to be hunter rather than hunted, and to diversify its portfolio from just PAH (pulmonary arterial hypertension), Actelion has acknowledged it is holding "preliminary discussions with ZS Pharma". The US based company's lead experimental drug, ZS-9, is aimed at treating hyperkalemia; a build-up of potassium in the body that could lead to heart failure and would complement Actelion's PAH portfolio. In phase 3 studies, ZS-9 succeeded in reducing the dangerously high blood potassium concentrations that characterise hyperkalemia, and the FDA has promised to hand down a final decision on it by May 2016, but in the meantime rival products are expected to receive FDA feedback before the of the year; watch this space.

Canadian-based Concordia announced it is buying AMCo for about $3.5bn, including debt, in a transformational deal that will give it a platform to take its business to the next level. AMCo's commercial footprint reaches across 100 countries and its diverse line-up of almost 200 products will help Concordia become a "leading, international pharmaceutical company". This intention alone may have had fellow Canadian player Valeant concerned, but following last month's events, Valeant may have a few other concerns. The rationale for the deal offers long-term revenue and EPS growth, but in the short term will increase EPS by more than 35% in the first full year.

It will be interesting to see how things play out in October … whether some companies are snapped up at relatively low prices, or whether deals are delayed as the industry watches the Shkreli ricochet continue to echo.

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