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Midcap players ask Europe to bring it on in 2013

Joanne Fagg

If the European regulator has sometimes given the impression of being a mere rubber-stamper of its US opposite number's decisions, this year it certainly showed that it has a mind of its own.

And in the first half of 2013 it is the EU that will be the battleground for midcap players' key regulatory decisions; many will concern products already given the US green light, such as Medivation's Xtandi, Arena Pharmaceuticals' Belviq and Ariad Pharmaceuticals' ponatinib (see table below). Midcap pharma and biotech will thus watch eagerly for continued signs of independence of thought.

Among the drugs with the highest NPV as calculated by *EvaluatePharma*, it is perhaps the EU decision facing the obesity pill Belviq that should cause most concern. The read-across comes from Vivus's competitor Qsymia, which did at long last secure US approval last year, but then fell over at the CHMP.

Tough stance

As far as obesity goes Europe is clearly taking a tough stance, likely relating to risk/benefit considerations. Although normally EU sales represent no more than a significant minority of revenues, the territory forms a major part of Arena's strategy – hence the importance of the EU verdict on Belviq.

Meanwhile, Xtandi and ponatinib – highly promising cancer drugs – likely have little to fear, although investors will watch eagerly for any additional fallout from the safety issues that recently led the FDA to add a warning to ponatinib's label (*Ariad approval catches bio run-up traders by surprise, December 17, 2012*).

Still, the EMA has shown that it can go boldly where the FDA fears to tread: for instance, although Pfizer's blood thinner Eliquis was hit with a US complete response letter citing data management and verification issues the EU regulator had no qualms about giving it a clean bill of health. This stance could embolden Ariad.

Also awaiting the European green light at some point by mid-2013 is Dendreon's hugely hyped prostate cancer autologous immunotherapy, Provenge.

US triggers too

Meanwhile, of the most important midcap US catalysts in the next six months the biggest is surely the FDA decision on Theravance's LABA/steroid combination Breo. This will face a US panel for the COPD indication before a US decision due by March 12. Breo, formerly known as Relovair, carries an NPV of $4.1bn, according to *EvaluatePharma* data, and could become Theravance's first approved drug and transform the company.

Analysts still see considerable risk, given the heterogeneity of phase III data and LABA dose concerns; it is uncertain when a US filing for asthma – a problematic indication – might later be made. Breo also faces an EU decision, under the name Relvar, for use both in asthma and COPD.

A broader consideration is that Theravance's partner GlaxoSmithKline will likely manage the launch process carefully given the current dominance in both asthma and COPD of its own blockbuster, Advair. The companies' follow-up COPD combination of umeclidinium and vilanterol has just been filed in the US.

Also in the US, ImmunoGen is looking forward to approval of its antibody-drug conjugate Trastuzumab-DM1, following its extension of both progression-free and overall survival in metastatic Her2-positive breast cancer. The product's approval is a major catalyst for ImmunoGen's partner Roche, too (*Key regulatory decision for big pharma in the first half of 2013, December 20, 2012*).

And rare diseases continue to feature on investors' radars. Here, a duo of small companies – Isis Pharmaceuticals and Aegerion Pharmaceuticals – await regulatory verdicts in the tiny indication of hereditary familial hypercholesterolaemia. The latter's lomitapide has just secured US approval – hardly surprising given its strong advisory panel endorsement – and awaits an EU ruling.

For Isis's Kynamro, however, the jury in the US is still out. Not only was its panel backing more cautious, but to add to Isis's woes the CHMP recently issued a negative opinion on Kynamro, citing safety concerns – another clear example that a positive US outcome is no longer a reliable indicator of the regulatory verdict on the other

side of the pond.

The table below is drawn from *EvaluatePharma's* Calendar of Events, and highlights some of the biggest regulatory decisions facing mid and micro-cap pharma and biotech companies in the first half of 2013.

H1 2013 regulatory decisions, companies capitalised at <$30bn							
Product	**Company**	**Pharmacology class**	**Event**	**Indication**	**Date**	**Product NPV ($m)**	**N M**
Xtandi	Astellas Pharma	Androgen receptor antagonist	EU approval	Prostate cancer	Q1	7,871	1
Xtandi	Medivation	Androgen receptor antagonist	EU approval	Prostate cancer	Q1	4,664	1
Breo/ Relvar	Theravance	Beta 2 adrenoreceptor agonist & corticosteroid	EU (COPD, asthma), adcom (COPD), US approval (COPD	COPD, asthma	Q1, Mar 7, May 12	4,113	1
Belviq	Arena Pharmaceuticals	5-HT2C (serotonin) agonist	EU approval	Obesity	Q1	2,533	1
Provenge	Dendreon	Prostate cancer vaccine	EU approval	Prostate cancer	Mid-2013	2,437	2
Remsima	Celltrion	Anti-tumour necrosis factor alpha MAb	EU approval	rheumatoid arthritis, ankylosing spondylitis, ulcerative colitis, Crohn's disease and psoriatic arthritis	Q1	2,169	4
Ponatinib	ARIAD Pharmaceuticals	BCR-ABL inhibitor & pan-FGFR inhibitor	EU approval	Chronic myeloid leukemia, acute lymphoblastic leukemia	Mid-2013	1,794	5
Vortioxetine	Lundbeck	5-HT3 & 5-HT7 (serotonin) antagonist, 5-HT1B partial agonist, 5-HT1A agonist & 5-HT re-uptake transporter inhibitor	EU approval	Major depressive disorder	Apr	1,747	6
Opsumit	Actelion	Endothelin receptor antagonist	EU approval	Pulmonary arterial hypertension	Jun	1,730	2
Bronchitol	Pharmaxis	Respiratory agent	Adcom, US approval	Cystic fibrosis	Jan 30, Mar 18	1,625	4
Myrbetriq	Astellas Pharma	Beta 3 adrenoreceptor agonist	EU approval	Urinary incontinence	Q1	1,598	
		Anti-HER2 (ErbB-					

Trastuzumab-DM1	ImmunoGen	2) MAb-DM1 maytansinoid conjugate	US approval	Breast cancer	Feb 26	1,496	1
Defibrotide	Gentium	Cathepsin G inhibitor	EU approval	Hepatic veno-occlusive disease	Q1	1,419	8
Jetrea	ThromboGenics	Plasmin	EU approval	Vitreomacular adhesion	H1 2013	1,366	
Herceptin SC	Halozyme Therapeutics	Anti-HER2 (ErbB-2) MAb	EU approval	Breast cancer	Q1	1,101	1
Levadex	MAP Pharmaceuticals	5-HT1B (serotonin) & 5-HT1D agonist	US approval	Migraine	Apr 15	914	1
Nuedexta	AVANIR Pharmaceuticals	N-methyl-D-aspartate & sigma-1 agonist	EU approval	Pseudobulbar affect	Q1	778	2
Cometriq	Exelixis	VEGFr2, RET & Met tyrosine kinase inhibitor	EU approval	Thyroid cancer	Mid-2013	720	8
Augment Bone Graft	BioMimetic Therapeutics	Platelet-derived growth factor	US approval	Bone graft for treatment of foot and ankle fusions	May 13	686	3
Xiaflex	Auxilium Pharmaceuticals	Collagenase	US approval	Peyronie’s disease	May 7	683	
Rytary	IMPAX Laboratories	Dopamine precursor & dopa decarboxylase inhibitor	US approval	Parkinson's disease	Jan 21	663	4
Lyxumia	Zealand Pharma	Glucagon-like peptide 1 agonist	EU approval	Diabetes	Q1	628	1
Zelrix	NuPathe	5-HT1B (serotonin) & 5-HT1D agonist	US approval	Migraine	Jan 17	418	8
ChemoSAT	Delcath Systems	Alkylating agent	US approval	Metastatic melanoma in the liver	Jun 14	417	4
Abilify Depot	Lundbeck	5-HT1A (serotonin) & dopamine D2 partial agonist & 5-HT2 antagonist	US approval	Schizoprenia	Feb 28	406	1
Procysbi	Raptor Pharmaceutical	Cystine-depleting agent	US and EU approval	Nephropathic cystinosis	Jan 30, H1 2013	340	1
Amitiza	Sucampo Pharmaceuticals	Chloride channel activator	US approval	Opioid-induced constipation	Apr	286	8
Kynamro	Isis Pharmaceuticals	Apolipoprotein B-100 antisense	US approval	Homozygous familial hypercholesterolemia	Jan 29	275	2
Uceris	Santarus	Corticosteroid	US approval	Ulcerative colitis	Jan 16	250	1
Lomitapide	Aegerion Pharmaceuticals	Microsomal triglyceride transfer protein	EU approval	Homozygous familial hypercholesterolemia	H1 2013	242	1

		inhibitor					
Probuphine	Titan Pharmaceuticals	Opioid agonist	US approval	Opioid addiction	Apr 29	215	2
Uceris	Cosmo Pharmaceuticals	Corticosteroid	US approval	Ulcerative colitis	Jan 16	192	
Lemtrada	BTG	Anti-CD52 MAb	EU approval	Multiple sclerosis	Q2	124	
Zevtera	Basilea Pharmaceutica	Cephalosporin	EU approval	Community-acquired and hospital-acquired pneumonia	Feb	98	
Zaltrap	Regeneron Pharmaceuticals	VEGFr kinase inhibitor	EU approval	Colorectal cancer	Q1	90	
Crofelemer	Salix Pharmaceuticals	Cystic fibrosis transmembrane conductance regulator channel & calcium-activated chloride channel blocker	US approval	HIV-associated diarrhea	Q1	85	
Stendra	VIVUS	Phosphodiesterase V inhibitor	EU approval	Erectile dysfunction	Q1	55	
Serada	Depomed	GABA agonist	Adcom, US approval	Menopause	Mar 4, May 31	46	

To contact the writers of this story email Jacob Plieth or Joanne Fagg in London at news@epvantage.com or follow @JacobEPVantage and @JoEPVantage on Twitter