EDISON

Zeltia

H115 results

Yondelis approvals in US and Japan pending

Pharma & biotech

Zeltia is approaching a number of significant catalysts, with approval decisions for Yondelis in the US and Japan due before the end of the year, and Phase III data for Aplidin expected early in the New Year. Plans to seek an IPO in the US in H216 following the group's restructure (through a reverse merger whereby its PharmaMar division absorbed the parent company, Zeltia) could strengthen its financial and commercial abilities. We maintain our valuation of €1.03bn or €4.65 per share, ahead of these catalysts.

Year end	Revenue (€m)	PBT* (€m)	EPS* (€)	DPS (€)	P/E (x)	Yield (%)
12/13	141.8	15.6	0.06	0.0	54.8	N/A
12/14	149.7	16.3	0.07	0.0	47.0	N/A
12/15e	163.1	15.2	0.06	0.0	54.8	N/A
12/16e	198.2	35.9	0.15	0.0	21.9	N/A

Note: *PBT and EPS are normalised, excluding intangible amortisation, exceptional items.

Yondelis: Approvals pending

Key near-term catalysts for Zeltia are the pending approval decisions in major markets for Yondelis, which is already marketed in 80 countries. The PDUFA date is 24 October for a decision on US FDA approval as a second-line treatment for soft tissue sarcoma (STS), while a decision on the same indication in Japan could be announced any time from mid-September onwards. Approvals could significantly boost revenues through milestones and royalties from its partners (Janssen in the US, Taiho in Japan). Another significant potential catalyst is results from the Phase III study of Aplidin in multiple myeloma, which are due in Q116.

PM01183: Phase III begun in ovarian, pending in lung

PM01183 (a Yondelis follow-on) has generated highly encouraging clinical data in ovarian cancer and SCLC, which was presented at ASCO in June. A Phase III trial in platinum-resistant ovarian cancer was initiated in June. The company is finalising the design of a proposed Phase III trial in small cell lung cancer (SCLC) after positive data from a Phase Ib study; the Phase III is expected to start Q415.

H115: Sales revenue up, milestones down

H115 net revenues rose by 8% to €84.4m. EBITDA was 57% lower at €9.5m, reflecting the smaller US$10m Yondelis milestone received from Janssen, compared with US$25m in H114, as was expected in line with the deal terms. With Yondelis approval milestones worth $20m ($10m for US, $10m for Japan) potentially receivable in the second half, we forecast FY15e EBITDA to be €27.0m, 5% ahead of FY14.

Valuation: Unchanged at €4.65 per share

Our valuation is unchanged at €1.03bn (€4.65/share), with increased R&D and capex spending offset by the roll-forward of the DCF model. We see significant potential upside from Yondelis approvals in the near term, and Aplidin data in Q116.

25 August 2015

Price	**€3.29**
Market cap	**€731m**
	US$1.10/€
Net debt (€m) at 30 June 2015	61.7
Shares in issue	222.2m
Free float	73.3%
Code	ZEL
Primary exchange	Madrid
Secondary exchange	N/A

Share price performance

%	1m	3m	12m
Abs	(18.4)	(17.7)	16.5
Rel (local)	(5.4)	(2.5)	25.4
52-week high/low		€4.32	€2.38

Business description

Zeltia is a Spanish biopharmaceutical group with a core focus on the development of marine-based drugs for cancer. Yondelis is approved in the EU and partnered with Janssen (J&J) in the US and Taiho in Japan. The group also has subsidiaries commercialising and developing consumer chemicals, molecular diagnostics and RNAi.

Next events

Yondelis: PDUFA review in STS	October 2015
Yondelis: Japan approval in STS	Q415
Aplidin: Phase III ADMYRE data in multiple myeloma	Q116
Potential US IPO	H216

Analysts

Christian Glennie	+44 (0)20 3077 5727
Lala Gregorek	+44 (0)20 3077 5700
Dr Dennis Hulme	+61 (0)2 9258 1161

healthcare@edisongroup.com

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Reverse merger brings oncology portfolio to the fore

Historically, Zeltia was a Spanish biopharma/chemicals group comprising a number of subsidiaries: PharmaMar (oncology drug development and commercialisation), Genómica (molecular diagnostics), Sylentis (RNAi gene silencing technology development) and two consumer chemicals companies, Zelnova and Xylazel.

A shareholders' meeting in June 2015 approved a reverse merger whereby the oncology division PharmaMar absorbed Zeltia, with one PharmaMar share exchanged for each Zeltia share. Friday 30 October will be the last trading day for Zeltia shares. PharmaMar shares are expected to begin trading on Monday 2 November on the same official markets on which Zeltia shares are currently listed (primarily Bolsa de Madrid – BME).

One of the key outcomes of the corporate restructure is the intention to seek a US IPO under the PharmaMar name, possibly in H216. If the US listing occurs it could strengthen the company's financial position, and potentially also enable the group to expand its US operations. Janssen (J&J) is already a key partner for Yondelis in the US, but there would be scope to build a US business commercialising pipeline oncology products, most likely PM01183, but possibly also Aplidin, if pivotal trials are successful.

Yondelis – two potential approvals in H215

The PDUFA date for the FDA review for Janssen's (J&J) NDA application to market Yondelis in the US as a second-line treatment for soft tissue sarcoma (STS) is 24 October. In July Zeltia announced that it had successfully cleared another hurdle in the approval process, with the manufacturing facility for the Yondelis active ingredient trabectedin having passed FDA inspection as acceptable for supply to the US market.

FDA approval would trigger a $10m milestone payment from J&J. Zeltia will also receive tiered double-digit royalties on net US sales from J&J, and in our model we apply an effective blended annual royalty rate of 15%. J&J is also conducting a pivotal Phase III trial with Yondelis in third-line ovarian cancer, although the study is not expected to read-out until 2018.

Partner Taiho Pharmaceutical filed for approval in Japan in January 2015 for the use of Yondelis to treat advanced STS. With orphan drug designation in Japan, a decision could be made as early as September 2015. Zeltia would receive a $10m milestone on Japanese approval.

ASCO data highlight PFS benefit of Yondelis in STS

Janssen presented data at ASCO 2015 from the interim analysis of the Phase III trial of Yondelis in second-line treatment of STS. These data were a key component of the NDA submission in October 2014.

Exhibit 1 shows that treatment with Yondelis reduced the risk of disease progression or death (PFS) by 45% compared to dacarbazine (hazard ratio (HR) 0.55, $p<0.0001$). Median progression-free survival (PFS) was 4.2 months for Yondelis-treated patients vs 1.5 months for dacarbazine.

At the interim analysis the trial had not yet met the primary endpoint for overall survival (OS). The OS data are not yet mature, with 64% of patients censored (non-informative) in the analysis. Nonetheless, there was a numerical trend consistent with a 13% reduction in the risk of death in patients treated with Yondelis (HR 0.87, P=0.37), although this trend was not reflected in the median OS, which favoured dacarbazine by two weeks (12.4 months for Yondelis vs 12.9 months for dacarbazine). The study is ongoing to determine the final OS results.

Safety findings were consistent with the known toxicity profiles of both drugs. The most common grade 3-4 toxicities for Yondelis vs dacarbazine were neutropenia (40% vs 25%) and transient

increases in liver enzymes (ALT, 29%vs 1%). Drug related deaths occurred in 2.1% of patients in the Yondelis group vs none on dacarbazine.

Encouragingly, in February the FDA granted priority review status to Janssen's NDA application to market Yondelis in the US. Priority review is a designation for a drug that treats a serious condition and may offer major advances in treatment when compared to existing options. The FDA's decision to grant priority review status to Yondelis reflects the fact that there are no effective treatment options for patients who have failed treatment with doxorubicin and ifosfamide.

The FDA will be assessing whether the 2.7 month increase in PFS leads to a better life for patients, when weighed up against the known toxic side effects. We maintain our assumption that there is a 90% likelihood that the FDA decision in October will be positive.

Exhibit 1: Interim data from Yondelis Phase III in STS show PFS benefit

			Median (mths) or %	
	Hazard ratio	p	Yondelis	Dacarbazine
Secondary endpoints (mature data)				
Progression-free survival	0.55	<0.0001	4.2	1.5
Time to progression	0.52	<0.0001	4.2	1.5
Overall response rate	N/A	0.33	9.9%	6.9%
Duration of response	0.47	0.14	6.5	4.2
Primary endpoint interim analysis				
Overall survival	0.87	0.37	12.4	12.9
Additional analysis not listed as secondary endpoint				
Clinical benefit rate (CR+PR+SD≥18wks)	N/A	0.0002	34.2%	18.5%

Source: Demetri et al ASCO abstract June 2015, Edison Investment Research. Note: CR = complete response; PR = partial response; SD≥18wks = stable disease for at least 18 weeks.

PM01183 – ovarian cancer Phase III underway, lung next

PM01183 is effectively a second-generation compound of Yondelis, with activity in similar (ovarian cancer) and new indications (SCLC, NSCLC, breast cancer). The compound has been optimised to improve the PK profile, such that PM01183 can be given at 4x the tolerated dose level of Yondelis and offers administration advantages. PM01183 can be administered in a one-hour infusion using a peripheral intravenous catheter, compared to a 24-hour infusion with Yondelis via a central catheter.

On 29 June, Zeltia initiated a Phase III trial of PM01183 as a monotherapy in platinum-resistant ovarian cancer, compared to a control arm with topotecan or liposomal doxorubicin. The randomised open-label trial will enrol 420 women with unresectable platinum resistant ovarian cancer, and will assess whether PM01183 can improve PFS as the primary endpoint. This pivotal study follows encouraging PFS and OS rates in a Phase IIb trial.

Zeltia is currently finalising the design of a pivotal Phase III study in small cell lung cancer (SCLC) after positive data from a Phase Ib study. The proposed Phase III will be a head-to-head study comparing the combination of PM01183 and doxorubicin against topotecan, in relapsed (second-line) SCLC patients. Preliminary results from the Phase Ib study showed that 67% of SCLC patients responded to PM01183 plus doxorubicin, compared to response rates of 20-25% typically seen with standard-of-care drug Topotecan.

Aplidin – ADMYRE fully recruited, results in Q116

Recruitment in the 255-patient Phase III ADMYRE trial of Aplidin in relapsed/refractory multiple myeloma was completed in June. The trial is comparing the effectiveness of the combination of Aplidin plus dexamethasone vs dexamethasone alone. PFS is the primary endpoint (estimated average of five months); an interim analysis in December 2012 reported that at that stage Aplidin was on track to meet the efficacy target of a 60% improvement in PFS. OS (estimated average of nine months) will also be assessed as a secondary endpoint. Results are expected in Q116; if the results are positive, Zeltia plans to file for marketing approval in Europe in 2016.

Zeltia licensed Aplidin marketing rights in certain EU country rights (France, Germany, the UK, Benelux, Ireland, Austria) to Chugai in July 2014; Taiwan rights to TTY Biopharm in July 2015; and Australia and New Zealand rights to Specialised Therapeutics Australia in August 2015. Zeltia retains commercialisation rights in several key European territories, including Spain, Italy and Northern Europe, where we assume it will market Aplidin using its existing sales force. We expect Zeltia to also seek a partner in the US, where the initial approval may be for the ultra-orphan indication immunoblastic T-cell lymphoma (which accounts for 2% of non-Hodgkin's lymphomas).

Valuation

Our sum-of-the-parts DCF model (project-based rNPV for the biopharma business; FCF for the chemicals division to 2025) is unchanged at €1.03bn or €4.65/share (Exhibit 2), with some minor increases in forecast costs offset by the roll forward of the DCF model. We have not made any changes to product development timelines or likelihoods of success.

Notable changes include:

- forecast R&D expenditure increased by 16% in FY16 and 25% in FY17, in light of the Phase III trial of PM01183 in breast cancer having started in Q215, and another Phase III in lung cancer expected to begin before the end of the year; and
- increasing capex in line with the higher run-rate in H115.

Exhibit 2: Zeltia sum-of-the-parts DCF

Product	rNPV (€m)	rNPV/ share (€)	Assumptions
Chemicals business FCF	57.7	0.26	7.5% WACC, 2% growth rate, accounts for 25% of group capex and depreciation and amortisation.
Yondelis (Europe)	752.1	3.38	Second-line STS peak sales of €80m with 35% penetration; third-line ovarian cancer peak sales of €100m with 22% penetration into addressable platinum sensitive market. First potential generics in 2022. 10% WACC
Yondelis (US)	71.0	0.32	STS (second-line) peak sales of $130m with 90% probability and 2016 launch; peak sales in platinum-sensitive ovarian cancer of $150m, 65% risk adjustment, 2020 launch; both assume 15% royalty from J&J.
Yondelis (Japan)	49.1	0.22	STS only: peak sales of €130m; 90% success probability; launch 2016; 15% royalty from Taiho.
Yondelis (milestones)	12.0	0.05	Known milestones for H215 only – Janssen: $10m in for US approval; Taiho: Japan approval. Risk-weighting applied; assumes $/€ FX rate of 1.10.
Aplidin (multiple myeloma)	140.7	0.63	Global peak sales of $300m assuming 40% of MM patients ultimately receive fourth-line therapy and 25% penetration; pricing of $25k in EU with 25% US premium; 65% success probability; launch 2018; sold by Chugai in eight European territories (assume effective royalty of 25%) and direct in other EU regions, assume 25% royalty in US; includes €20m of near-term regulatory milestones out of €30m total. No milestones included for other territories at this stage.
PM01183 (ovarian cancer)	286.8	1.29	Third-line platinum-resistant ovarian cancer: peak sales of €492m with 65% success probability, 2019 launch; sold direct in Europe with 25% royalty in US (post Phase III).
PM01183 (SCLC)	51.9	0.23	Peak sales of $200m; 50% success probability; launch 2019; 25% royalty (post Phase III).
PM01183 (breast/NSCLC)	32.6	0.15	Combined peak sales of $500m; 15% success probability; launch 2020; 25% royalty (post Phase III).
Sylentis	5.7	0.03	Cumulative peak sales of $250m, with 25% probability of success, potential launch 2019, 10% royalty.
Genomica	26.9	0.12	Conservative 2% growth rate.
R&D	(165.2)	(0.74)	12.5% WACC.
SG&A	(180.3)	(0.81)	10% WACC.
Unallocated central costs	(36.1)	(0.16)	10% WACC.
Capex	(9.9)	(0.04)	75% of group capex for biopharma business.
Net cash/(debt)	(61.7)	(0.28)	At end-Q215.
Total	**1,033.3**	**4.65**	

Source: Edison Investment Research. Note: WACC of 12.5% used except where indicated otherwise.

With regard to PM01183 and Aplidin, we note that we have maintained our previous assumptions that these products will be out-licensed at some stage. However, we acknowledge that with the new corporate structure, US IPO plans and resulting opportunity to establish a US commercial business, PM01183 (and possibly also Aplidin) could be retained by PharmaMar for self-commercialisation. This would typically provide greater economic returns on these products (even after the extra investment required), so confirmation of a go-it-alone strategy in the US (and across Europe) would add upside.

Sensitivities

PharmaMar is subject to various sensitivities common to speciality pharmaceutical companies, including potential clinical or regulatory failure or delay, manufacturing and commercialisation risks (launch, uptake, pricing, reimbursement and competition), and reliance on partners for ex-Europe markets. The chemical business is predominantly exposed to economic factors, although raw material costs, environmental/regulatory requirements and external weather conditions may also affect sales or margins.

Key stock-specific sensitivities for the core oncology business include, but are not limited to:

- **Yondelis**: European sales growth; outcome of ongoing US clinical trials; outcome of FDA and Japanese approval decisions in 2015; timing of milestones from partners and sales achieved.
- **Aplidin**: outcome of the ADMYRE trial; development progress in T-cell lymphoma; timing and economics of any additional licensing deal(s).
- **PM01183**: development progress in various indications; deal timing and economics.

Financials

Zeltia's H115 net revenues of €84.4m were up 8% on H114 (€78.2m), with the 12% growth in biopharmaceuticals (FY14: €82.3m vs FY13: €79.1m) much stronger than Consumer Chemicals (up 3%; H115: €37.1m vs H114: €36.1m). H115 net sales of Yondelis (mainly in Europe, reported within biopharma) rose 11.4% to €43.6m, including €3.3m from the sale of raw materials to Janssen; commercial sales of Yondelis (excluding raw materials) rose by 3%. Gross margin in H115 was 71.8% (vs 72.7% in H114). Other revenues of €11.7m were 41% lower than H114 (€19.8m), reflecting the smaller $10m (€8.8m) Yondelis milestone received from Janssen, compared with US$25m (€18.3m) in H114. Yondelis approval in the US and Japan could trigger a further ~$20m (€18m) in milestone payments in H215.

R&D spending, which is predominantly focused on the oncology business, rose 29% to €30.6m (€22.1m in H114). The increase in R&D spending was mainly due to the pivotal registration trial of PM1183 in platinum-resistant ovarian cancer. We forecast R&D spending to total €55m in FY15e and €47m in FY16e. Note that a proportion of this R&D is capitalised (we assume c 10%). Total SG&A expenses were €33.0m in H115 (vs €31.0m in FY13); we forecast SG&A to total €64.3m in FY15 and €66.6m in FY16. EBITDA for the group in H115 was €9.5m, 57% below the €22.1m reported in H114, again reflecting the smaller $10m Yondelis milestone in the current period; we forecast ~$20m Yondelis approval milestones in H215e to lead to 5% EBITDA growth to €27.0m in FY15e.

At December 2014 the company had €26m net deferred tax assets, plus additional unrecognised or unallocated deferred tax assets totalling €96m. In view of this, we now forecast a continuing minimal tax charge into FY17 compared with our previous assumption of a 21% tax rate in that year. Slight reductions to forecast earnings and cash flow reflect the R&D expenditure increasing by 16% in FY16 and 25% in FY17 due to PM01183 Phase III clinical trials.

Exhibit 3: Financial summary

€000s	2012	2013	2014	2015e	2016e	2017e
Year-end 31 December	IFRS	IFRS	IFRS	IFRS	IFRS	IFRS
PROFIT & LOSS						
Revenue	138,229	141,824	149,652	163,083	198,233	224,015
Cost of Sales	(39,793)	(37,900)	(40,765)	(44,878)	(47,454)	(50,363)
Gross Profit	98,436	103,924	108,887	118,205	150,779	173,653
R&D Expenses (net of capitalised in-house work)	(36,996)	(38,335)	(46,477)	(55,050)	(48,500)	(46,550)
Sales, General and Administrative Expenses	(62,467)	(61,489)	(60,831)	(64,253)	(66,598)	(69,270)
EBITDA	20,473	23,817	25,704	27,044	47,702	84,716
Operating Profit (before GW and except.)	15,985	20,735	22,096	20,360	41,013	78,682
Intangible Amortisation	(1,418)	(1,779)	(1,859)	(1,092)	(2,119)	(1,950)
Other (milestones and royalties)	23,549	22,858	28,408	30,310	13,258	29,044
Exceptionals	0	0	0	0	0	0
Operating Profit	14,567	18,956	20,237	19,267	38,894	76,732
Net Interest	(5,056)	(5,690)	(5,762)	(5,132)	(5,154)	(5,008)
Other	(85)	535	0	0	0	0
Profit Before Tax (norm)	10,844	15,580	16,334	15,228	35,859	73,673
Profit Before Tax (FRS 3)	9,426	13,801	14,475	14,135	33,740	71,724
Tax	5,048	(1,960)	(1,304)	(1,030)	(1,784)	(2,016)
Deferred tax	0	0	0	0	0	0
Profit After Tax (norm)	15,892	13,620	15,030	14,197	34,075	71,657
Profit After Tax (FRS 3)	14,474	11,841	13,171	13,105	31,956	69,708
Minority interests	2,868	189	20	0	0	0
Discontinued operations	(10,749)	(708)	(76)	0	0	0
Net income (normalised)	18,760	13,809	15,050	14,197	34,075	71,657
Net income (FRS3)	6,593	11,322	13,115	13,105	31,956	69,708
Average Number of Shares Outstanding (m)	220.8	220.2	222.2	222.2	222.2	222.2
EPS - normalised (€)	0.08	0.06	0.07	0.06	0.15	0.32
EPS - FRS 3 (€)	0.03	0.05	0.06	0.06	0.14	0.31
Dividend per share (€)	0.00	0.00	0.00	0.00	0.00	0.00
Gross Margin (%)	71.2%	73.3%	72.8%	72.5%	76.1%	77.5%
EBITDA Margin (%)	14.8%	16.8%	17.2%	16.6%	24.1%	37.8%
Operating Margin (before GW and except.) (%)	11.6%	14.6%	14.8%	12.5%	20.7%	35.1%
BALANCE SHEET						
Fixed Assets	90,614	92,627	98,401	97,385	92,542	89,038
Intangible Assets	22,292	25,138	28,836	29,040	26,920	24,971
Tangible Assets	29,794	27,959	29,218	27,869	25,145	23,590
Other	38,528	39,530	40,347	40,477	40,477	40,477
Current Assets	106,431	95,895	101,916	137,666	176,818	252,326
Stocks	23,502	22,232	24,404	24,591	26,002	27,596
Debtors	41,956	38,630	36,989	40,212	48,879	55,237
Cash	34,428	28,835	35,511	67,004	96,078	163,634
Other	6,545	6,198	5,012	5,859	5,859	5,859
Current Liabilities	(87,355)	(74,058)	(82,626)	(71,138)	(72,482)	(73,970)
Creditors	(32,621)	(32,731)	(38,160)	(30,737)	(32,081)	(33,569)
Short term borrowings	(54,734)	(41,327)	(44,466)	(40,401)	(40,401)	(40,401)
Long Term Liabilities	(73,749)	(65,877)	(58,694)	(81,737)	(82,496)	(83,053)
Long term borrowings	(62,016)	(52,941)	(47,003)	(70,171)	(70,171)	(70,171)
Other long term liabilities	(11,733)	(12,936)	(11,691)	(11,566)	(12,325)	(12,882)
Net Assets	35,941	48,587	58,997	82,176	114,382	184,340
CASH FLOW						
Operating Cash Flow	5,751	15,489	23,475	13,034	39,976	79,061
Net Interest	876	1,057	(1,000)	(2,419)	(5,154)	(5,008)
Tax	(308)	(201)	(366)	(1,030)	(1,784)	(2,016)
Capex	(2,029)	(2,095)	(10,179)	(6,541)	(3,965)	(4,480)
Acquisitions/disposals	0	447	4	0	0	0
Financing	1,368	0	0	9,050	0	0
Other	0	0	0	0	0	0
Net Cash Flow	5,658	14,697	11,934	12,094	29,074	67,556
Opening net debt/(cash)	84,259	79,537	64,585	54,886	42,488	13,414
Exchange rate movements	0	0	0	0	0	0
Other	(936)	255	(2,235)	304	0	0
Closing net debt/(cash)	79,537	64,585	54,886	42,488	13,414	(54,142)

Source: Edison Investment Research, company accounts. Note: Discontinued operations/minority interest relate to CNS subsidiary Noscira, which was wound up in 2014.

Frankfurt +49 (0)69 78 8076 960
Schumannstrasse 34b
60325 Frankfurt
Germany

London +44 (0)20 3077 5700
280 High Holborn
London, WC1V 7EE
United Kingdom

New York +1 646 653 7026
245 Park Avenue, 39th Floor
10167, New York
US

Sydney +61 (0)2 9258 1161
Level 25, Aurora Place
88 Phillip St, Sydney
NSW 2000, Australia

Wellington +64 (0)48 948 555
Level 15, 171 Featherston St
Wellington 6011
New Zealand