EDISON

Zeltia

Initiation of coverage

Deep sea treasures

Pharma & biotech

Zeltia is a holding company that is increasingly focused on the potentially high-growth marine oncology activities of PharmaMar. This subsidiary has a unique business model and has built a pipeline of first-in-class cancer drugs for development with strategic partners. Yondelis, its first product, sold in Europe since 2007, is approaching regulatory catalysts in the US and Japan. Other catalysts include Phase III Aplidin data (expected in 2015) and deal potential for PM01183 (shortly to begin pivotal trials). Approval(s), data and/or deal news should increase our €904m valuation.

Year end	Revenue (€m)	PBT* (€m)	EPS* (€)	DPS (€)	P/E (x)	Yield (%)
12/12	138.2	10.8	0.08	0.0	34.6	N/A
12/13	141.8	15.6	0.06	0.0	46.9	N/A
12/14e	158.9	23.3	0.10	0.0	29.4	N/A
12/15e	173.8	36.3	0.16	0.0	18.8	N/A

Note: *PBT and EPS are normalised, excluding intangible amortisation, exceptional items and share-based payments.

Yondelis: A foundation for profitability

Net Yondelis sales of €73m in FY13 underpin profitability, with potential for growth in Europe and beyond. Filings in soft tissue sarcoma in Japan (H214) and in the US around mid-2015 could lead to approvals in 2015/16, significantly boosting revenue through royalties from partners and near-term milestones. Japan approval would trigger a Taiho milestone, with up to $20m potentially due from Janssen.

Hidden potential: Aplidin and PM01183

Aplidin has secured a strong haem-oncology partner in Chugai (ahead of Phase III multiple myeloma data in 2015), which should enable higher penetration in the eight EU countries covered, without needing additional investment from Zeltia. Updates from ongoing PM01183 trials (and pivotal trial start in ovarian, endometrial and small cell lung cancers) may catalyse a lucrative ex-Europe deal.

Financials: Focused investment and reducing debt

Revenue growth teamed with stable operating expenditure (ex-R&D) should enable Zeltia to grow its bottom line; we forecast EBITDA improvement from €23.8m in FY13 to €35.2m in FY14. R&D spending for FY14/15 will increase with investment in pivotal trials (Aplidin and PM01183) and the Sylentis glaucoma study. Increased operating cash flow should result in a continuing reduction in net debt.

Valuation: €904m SOTP, PM01183 prospects ignored

Our €904m (€4.07/share) valuation is based on a sum-of-the-parts DCF to 2025 (rNPV for the biopharma business; DCF for the chemicals division). It suggests the current market cap is largely supported by Yondelis, with limited value ascribed to earlier-stage assets, such as PM01183, which could drive significant value as part of a life cycle management strategy. Japan/US approval decisions for Yondelis in STS represent near-term upside as would Aplidin data or a PM01183 partnership.

30 July 2014

Price	**€2.94**
Market cap	**€653m**
Net debt (€m) at end-June 2014	62.53
Shares in issue	222.2m
Free float	63.7%
Code	ZEL
Primary exchange	Madrid
Secondary exchange	N/A

Share price performance

%	1m	3m	12m
Abs	1.9	5.1	(2.2)
Rel (local)	1.4	9.5	27.3

52-week high/low	€3.08	€2.21

Business description

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

Next events

Yondelis: Japan filing in STS	H214
Yondelis: US STS data and filing	H214-H115
PM01183: start of pivotal trials	H214-H115
Partnering: PM01183	Undisclosed

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Edison profile page

Investment summary

Company description: A marine biotech core focused on cancer

Zeltia is a Madrid-based holding company with two business divisions: biopharmaceuticals (based in the Madrid region) and consumer chemicals (based in Galicia). It is primarily focused on the development and commercialisation of marine-derived oncology drugs, with non-core operations in consumer chemicals, molecular diagnostics and RNAi technology. It consists of five wholly owned independent operating subsidiaries (Exhibit 1), and its lead product, Yondelis, was developed and is marketed by the most important, PharmaMar. Zeltia was founded in 1939 and has been listed on the Madrid Stock Exchange since 1963. It has 628 employees, 340 of whom are at PharmaMar.

Exhibit 1: Zeltia SA subsidiaries and main business lines

Division	Subsidiary	Primary focus (founded)	Key product(s)
Biopharma	**PharmaMar**	Discovery and development of novel marine-derived oncology drugs. (1986)	Yondelis: approved for soft tissue sarcoma (EU + 42 additional countries) and relapsed ovarian cancer (EU, 31 additional countries + Brazil); Phase III (US); registration imminent (Japan). Three other priority compounds in clinical development.
	Genomica	Molecular diagnostics. (1990)	Development of *in vitro* molecular diagnostics for infectious diseases, oncology and personalised medicine for partners. DNA profiling/genetic fingerprinting.
	Sylentis	Discovery and development of RNA interference drugs. (2006)	Ophthalmology: two ongoing Phase II programmes for glaucoma (US Phase IIb to start in June) and ocular discomfort associated with dry eye syndrome.
Consumer chemicals	**Zenova**	Marketing/manufacture of domestic and industrial chemicals. (1991 in present form)	Insecticides, air fresheners, cleaners and disinfectants. Brands include: Casa & Jardín, Kill-Paff, ZZ Paff, Coopermatic, Baldosinin and Hechicera.
	Xylazel	Marketing/manufacture of wood/metal paint and varnish. (1975)	Xylazel (wood protectors) and Oxirite (metal protectors).

Source: Edison Investment Research; company data

Valuation: €904m suggests market overlooks PM01183

Our Zeltia valuation of €904m, or €4.07/share, is based on a sum-of-the-parts DCF to 2025. We use an rNPV method to discount future cash flows for the biopharma business (12.5% WACC) and have applied a standard DCF model for the chemicals division (7.5% WACC). Cash flows are taxed at a 25% corporate tax rate from 2020, tapering up from a lower rate to reflect accumulated tax losses. Our model suggests that Zeltia's current market cap of c €653m is largely underpinned by Yondelis, with limited value ascribed to earlier-stage development assets, in particular PM01183, which we believe has the potential to drive significant future value, given partnering potential and the commitment to start three Phase III trials in the near term.

Sensitivities: Yondelis insulates downside and drives upside

Zeltia's biopharma division is subject to typical sensitivities including potential clinical/regulatory failure/delay, manufacturing and commercialisation risks and reliance on partners. The chemical business is predominantly exposed to economic factors. Specific sensitivities for the core oncology business relate to Yondelis (outcome of US trials, regulatory decisions and sales trajectory), clinical data (Aplidin) and deal progress (for PM01183). PharmaMar's sample library, technology platforms and discovery capabilities could represent unappreciated upside.

Financials: Focused on growing the bottom line

Zeltia's revenues are recovering from the impact of the Caelyx shortage on Yondelis sales. In 2015, milestones are expected and should be replaced by recurring royalties from 2016. R&D spend is largely in the biopharma business (€38m in FY13 net of capitalised R&D), and will increase to c €41m (net) in FY14 with investment in pivotal trials (Aplidin and PM01183) and the Sylentis glaucoma study. SG&A of c €60m per year does not include c €8m of unallocated central costs. Growing revenues coupled with stable operating expenditure (ex-R&D) should enable Zeltia to grow its bottom line; we forecast EBITDA improvement from €23.8m in FY13 to €35.2m in FY14. Increased operating cash flow should further reduce net debt (FY13: €65.4m to FY14: €52.3m).

Outlook: Deep sea treasures

Zeltia is approaching a period of acceleration in profitability, driven by its world-leading marine-derived oncology therapeutics business, PharmaMar. PharmaMar is the core business, and the major growth driver, of the group. Since the first EMA approval of its marketed drug Yondelis, in 2007, PharmaMar has been a fully integrated speciality pharmaceutical company. It uses the sea as a source of first-in-class cancer drugs and has a diverse library of 150k marine samples. It has active discovery and preclinical programmes (with the aim of regularly advancing a new product to the clinic), a prioritised clinical development programme of three marine-derived synthetic compounds targeting multiple cancer indications, and a European sales infrastructure for Yondelis.

Anticipated regulatory filings for Yondelis for soft tissue sarcoma (STS) in Japan (by partner Taiho Pharmaceuticals) this year and also in the US (by Janssen) around mid-2015 are key catalysts, although the latter is contingent on positive results from Janssen's fully recruited Phase III study in L-sarcoma. Potential Yondelis approvals in 2015 and 2016 would significantly boost Zeltia's revenue – and profitability – through royalty receipts from partners and near-term milestones. Japanese approval would trigger an approval milestone from Taiho, and $20m is potentially due from Janssen ($10m development; $10m on approval). Additionally, Yondelis approval by the FDA may have positive knock-on effects on European sales[1] in STS.

Newsflow from the two most advanced pipeline programmes, including PM01183, a second-generation product related to Yondelis, represents further important inflection points over the next two years. Exhibit 2 summarises these upcoming catalysts.

Exhibit 2: Pipeline newsflow

Product	Indication	Next news	Timing
Yondelis	STS	NDA filing in Japan by partner Taiho Pharmaceuticals (milestone on approval in 2015)	H214
		Results of Phase III L-sarcoma study and US filing (Janssen)	Q414/H215
	Ovarian cancer	Read out of 670-pt US Phase III trial; preceded by event driven interim OS analysis (308 deaths)	H218
PM01183	Ovarian cancer	Start of Phase III in platinum-resistant ovarian cancer vs investigator choice. SPA pending	H214
	Endometrial cancer	Start of pivotal Phase III trial in <500-pts planned	H214
	SCLC	Start of pivotal Phase III trial in 250 pts planned	H115
	NSCLC	Read out of 120-pt Phase II trial in second-line NSCLC	Late 2015/early 2016
	All	Ex-Europe partnering deal	Undisclosed
Aplidin	Multiple myeloma	Completion of recruitment into ADMYRE trial	Q414
		PFS and OS trend analysis for ADMYRE	Q115
		Final results/EMA filing (potential Chugai milestone)	Q415
	Lymphoma	Start of US Phase II trial in angioimmunoblastic T-cell lymphoma	Undisclosed
		US partnering deal	Undisclosed

Source: Edison Investment Research, company data

The read out of two key trials – the Phase III study of Aplidin in multiple myeloma and the Phase III relapsed/refractory ovarian cancer trial of PM01183 – are also major near-term value drivers that could catalyse lucrative licensing deals or development/commercialisation partnerships for non-European territories. Assuming both drugs reach the market, PharmaMar intends to sell these through its existing European sales infrastructure, in the regions where it retains rights (Aplidin is licensed to Chugai for eight EU territories), with only modest future expansion. It is also seeking to license third-party solid tumour oncology products for select countries to leverage the sales force in the interim. An example of this is the recent exclusive distribution agreement with GP Pharma for prostate cancer drug Politrate in Italy, effective from October.

We value Zeltia at €904m, or €4.07/share. Our model suggests the current c €653m market cap is largely underpinned by Yondelis, with limited value ascribed to earlier-stage development assets, in particular PM01183, which we believe has the potential to drive significant future value.

[1] Two oncology drugs have received EMA approval prior to FDA approval: Eloxatin (EU approved 1999 and US approved 2002) and Zevalin (EU: 2004 and US: 2007). In both cases, European sales received a 20-40% boost to growth following US approval.

Yondelis: Approaching a next wave of filings

Yondelis (trabectedin) is a synthetic marine-derived intravenous anti-tumour drug originally isolated from the colonial tunicate *Ecteinascidia turbinate*. It has a novel mechanism of action, binding to the minor groove of DNA, and interfering with cell division, gene transcription and DNA repair mechanisms causing apoptosis. It is approved in over 75 countries for advanced soft tissue sarcoma (STS) after failure of first-line treatment or in patients who are unsuitable for the indicated first-line regimen (doxorubicin or ifosfamide), and for relapsed platinum sensitive ovarian cancer (OC) in combination with pegylated liposomal doxorubicin[2] (PLD, Doxil [US]/Caelyx [Europe], Janssen). Its first approval in the EU was for STS in 2007, with EMA approval in OC following in 2009.

PharmaMar's net sales of Yondelis were €72.9m in 2013, with a record quarterly sales figure of €19.7m in Q114 (an 18% increase on the prior period), indicating a strong recovery in sales growth following the negative impact on sales for use in ovarian cancer due to supply issues with Caelyx (Q311 to Q213). Continued growth is expected in the markets where Yondelis is already approved, with much of this likely to be driven by use in ovarian cancer (the indication in which Edison expects it to have the greater sales potential). Yondelis is sold by PharmaMar in Europe[3] and is subject to partnerships with Janssen and Taiho Pharmaceuticals in the US/ROW and Japan respectively (deal structures are outlined in Exhibit 3). Upcoming NDA filings by both partners in STS followed by potential Japan and US approvals in 2015/16 could be financially transformative for Zeltia.

Exhibit 3: Yondelis partnership deals

Partner	Structure	Economics
Janssen (formerly Ortho Biotech products)	**August 2001**: joint development and commercialisation licence agreement. Marketing rights to Europe (including Eastern Europe) retained by PharmaMar; rest of world rights obtained by Janssen (Japan rights returned July 2008).	**Milestones**: $20m upfront plus undisclosed milestones **Royalties**: escalating double-digit depending on sales
	December 2011: revised framework agreement for US with $110m of supplementary milestones. Janssen committed to complete two Phase III trials (one in relapsed ovarian cancer and one in L-Sarcomas).	**Development milestones**: totalling $110m in 2011-15 (split $25m in each of 2011, 2012, 2013 and 2014 – all received – and $10m in 2015)
Taiho Pharmaceuticals	**March 2009**: development/commercialisation licence agreement for Japan.	**Upfront payment**: ¥1bn (c $10m) **Milestones**: includes approval milestone **Royalties**: double-digit

Source: Edison Investment Research, company data. Note: PharmaMar has exclusive manufacturing rights (supply on cost-plus basis).

Our valuation of Zeltia is underpinned by Yondelis sales in Europe, where we forecast peak sales of €80m in second-line STS and €100m in third line platinum-sensitive resistant ovarian cancer based on a price of c €25,000 per course of treatment and 35% market penetration in STS and 22% penetration in OC. European IP extends to 2021 although given the complexity of the Yondelis manufacturing process and the niche markets in which it is approved, generic entry may be later. Following ex-Europe approvals, we forecast peak sales in Japan of €120m in STS and assume a 15% royalty, with US peak sales of $160m for second line STS and $190m for third line platinum-sensitive resistant OC ovarian and a 15% royalty. We assume premium pricing in Japan (40% higher than Europe) and in the US (50% higher). In both these markets, Yondelis will enjoy orphan drug market exclusivity post-launch (for seven years in the US and 10 years in Japan).

Taiho's intention to file an NDA in Japan in H214 is supported by the compelling data from the pivotal randomised Phase II STS trial that was presented at ASCO in June. This showed a significant improvement in the clinically meaningful endpoint of progression free survival (PFS) of 5.6 months for Yondelis vs 0.9 months for best supportive care ($p<0.0001$).

[2] This was developed to prevent doxorubicin accumulation in the skin as the original formulation causes hand-foot syndrome (palmar plantar erythrodysesthesia).

[3] The 65 rep infrastructure in Western Europe (88% of the European market) is split between PharmaMar (Spain, Italy, Germany and France) and a dedicated Innovex (Quintiles) resource (UK, Belgium, Netherlands, Switzerland, Portugal) which may become internalised under a timeline to be determined by PharmaMar. Distributors are used in other regions: SOBI for Scandinavia and Eastern Europe, and Genesis Pharma for Greece, Cyprus and the Balkans. PharmaMar additionally employs seven medical liaisons.

Janssen has two ongoing pivotal Phase III clinical trials. The first trial, comparing Yondelis with dacarbazine in L-sarcoma, is powered to detect a 30% improvement in overall survival; data should become available in H214. If positive, an FDA filing will be made for this indication in mid-2015. The 670-patient study in relapsed platinum sensitive ovarian cancer is an event-driven trial (the final overall survival, OS, analysis will occur after 514 deaths) and is not expected to render final results until late 2018, although an interim analysis for futility/efficacy is planned (after 308 deaths). This latter trial has been prospectively stratified by platinum-free interval (PFI, a key prognostic factor for ovarian cancer) and BRCA mutation status to further explore the findings of the earlier OVA-301 trial, which, in a retrospective subgroup analysis by PFI showed an overall survival benefit for patients with a PFI of six to 12 months (ie partially platinum sensitive patients). PFS data (the primary endpoint) from OVA-301 supported the approval of Yondelis in Europe, Canada and other regions, but was the subject of a negative FDA Oncologic Drugs AdCom vote in 2009; this explains the delay between commercialisation in Europe and potentially in the US. We note that the FDA AdCom took place before full overall survival data had matured and PFI subpopulations were analysed. We discuss this further below Exhibit 4, which reviews the current clinical and regulatory status of Yondelis. A number of additional small investigator-sponsored trials are also ongoing.

Exhibit 4: Yondelis (trabectedin) development status

Indication	Stage	Notes
Platinum-sensitive relapsed ovarian cancer	Marketed	**Europe**: approved November 2009 in combination with Doxil/Caelyx (liposomal doxorubicin); sold by PharmaMar. Orphan drug status. **RoW** (ex-US, ex-Japan): marketed by Janssen in 32 additional countries. Approved on the basis of improvement in PFS and ORR in the pivotal 672-pt OVA-301 trial (primary endpoint: PFS; secondary endpoint: OS). **Clinical Data**: OVA-301 trial showed 6 wk improvement in PFS for the combination (7.3 vs 5.8 mths, HR = 0.79, p=0.019) and a median survival benefit of 3.2 mths for Yondelis+Caelyx vs Caelyx alone for all pts (multivariate analysis: 18% risk reduction of death, p=0.0285), with the largest benefit (35% risk reduction of death, p=0.0056) in PPS (partially platinum-sensitive) ovarian cancer.
	Phase III (US)	670-pt pivotal Phase III trial of Doxil ± Yondelis ongoing in third-line advanced relapsed epithelial ovarian, primary peritoneal or fallopian cancer (study overview at ASCO 2014; results: H218). Primary endpoint: OS. Secondary endpoints: PFS, ORR, safety. Interim OS analysis after 308 deaths; final OS analysis after ≥514 deaths. Orphan drug status. **Regulatory history:** NDA submitted (Nov 2008). FDA AdCom panel voted 14-1 against a favourable risk-benefit profile due to increased liver enzyme levels despite improved PFS in the OVA-301 study (July 2009). FDA Complete Response Letter against approval (Sept 2009) requested additional information including OVA-301 OS data (secondary endpoint, which had not yet matured) and additional clinical data. NDA withdrawn by Janssen (April 2011). Janssen committed to completing a second Phase III trial under a revised framework agreement (Dec 2011).
	Phase II + bevacizumab	74-pt Phase II trial of bevacizumab and Yondeils ± carboplatin in epithelial ovarian cancer at first recurrence 6-12 months after the end of the first platinum-containing regimen. PFS primary endpoint (results: H115).
Soft tissue sarcoma (STS): 2nd/3rd line	Marketed	**Europe**: approved September 2007 for advanced or metastatic STS after failure of anthracyclines and ifosfamide; sold by PharmaMar. Orphan drug status. **RoW** (ex-US, ex-Japan): marketed by Janssen in 42 additional countries. China bridging study ongoing. Approval based on 266-pt Phase II trial in advanced/metastatic liposarcoma or leiomyosarcoma. **Clinical data**: Protocol specified final TTP showed 26.6% reduction in relative risk of progression for pts receiving 1.5mg/m^2 Yondelis every 3 weeks (HR =0.734), with median TTP of 3.7 mths. Median OS was 13.9 mths with 60.2% pts alive at one year. Also 903-pts assessed under an expanded access programme demonstrated median survival of 11.9 mths (18.1 months for liposarcoma, 16.2 mths for leiomyosarcoma and 8.4 mths for other sarcoma types).
	Phase III (US)	570-pt Phase III trial in locally advanced metastatic L-sarcoma of Yondelis vs dacarbazine after prior treatment with anthracyclines and ifosfamide fully recruited (results: H214). Primary endpoint of overall survival. 3,000-pt expanded access programme ongoing (ET743-SAR- 3002). FDA orphan drug status. NDA filing with FDA expected late-2014/early 2015.
	Pivotal/ registration Phase II (Japan)	76-pt randomised placebo controlled Phase II in malignant translocation-related sarcomas (TRS) of Yondelis vs best supportive care (BSC). PFS primary endpoint met and results presented at ASCO 2014: median PFS for Yondelis of 5.6 months vs 0.9 months for BSC (p<0.0001, HR = 0.07, 90% CI 0.03-0.14). Median OS (95% CI) was not reached (NR) (12.8-NR) for Yondelis arm and was 8.0 months (7.0-NR) for the BSC arm respectively (p=0.025; HR=0.38, 95% CI: 0.16-0.91). Japan NDA submission expected H214.
Soft tissue sarcoma (STS): 1st line	Phase II	TR1US and GEIS investigator led trials exploring efficacy of different doses of Yondelis + doxorubicin and prognostic biomarkers in advanced/metastatic STS.
Breast cancer	Phase II	100-pt Phase II in advanced breast cancer patients who are carriers of the BRCA1 and BRCA2 mutations and BRCAness phenotype recruitment complete; data analysis ongoing. Primary endpoint: objective response.

Source: Edison Investment Research, company data, clinicialtrials.gov. Notes: PFS = progression free survival; ORR = overall response rate; OS= overall survival; HR = hazard ratio; TTP = time to progression.

The FDA AdCom vote (14-1 against a favourable risk-benefit profile) and subsequent FDA Complete Response Letter (CRL) in September 2009 requesting additional information, including overall survival data (a secondary endpoint) from the OVA-301 study and additional clinical data to better assess the risk-benefit profile, slowed its progress to market in the US. The AdCom accepted that Yondelis plus doxorubicin increased PFS by a statistically significant six weeks (7.3 months vs 5.8 months for doxorubicin alone, HR of 0.79) but focused on the adverse event profile of Yondelis

in combination with doxorubicin. The combination showed more toxicities than doxorubicin alone (in particular, grade 3-4 neutropaenia 63% vs 22%; grade 3-4 thrombocytopaenia 18% vs 3%; raised liver enzyme levels 31% vs 1%), although it was noted that these adverse events were neither clinically important nor had a detriment to quality of life, and the liver enzyme elevations were reversible. The panel assessment of Yondelis's risk-benefit profile was more cautious than the EMA, which concentrated on Yondelis's clinically relevant efficacy and the significant unmet need in relapsed/refractory ovarian cancer. Notably, the CRL also did not raise concerns about Yondelis's safety profile, rather it requested additional data, in particular, on overall survival, which was at that time 18 months from maturity.

There was limited progress on the FDA filing until PharmaMar and Janssen agreed on and executed a revised framework agreement in December 2011 as US Yondelis rights were held by Janssen, which withdrew the NDA in April 2011. Under this new agreement, PharmaMar became eligible for an additional $110m of milestones and Janssen committed to completing two Phase III trials (one in relapsed ovarian cancer and one in L-Sarcomas, ie leiomyosarcoma and liposarcoma, two of the most common soft tissue sarcoma subtypes). The latter trial is fully recruited, with results expected during H214 and filing anticipated mid-2015. The ovarian cancer trial has begun recruitment, with 11 patients enrolled as of end-January; results are not expected until 2018 and thus we do not anticipate launch until 2020.

An overview of soft tissue sarcoma and ovarian cancer and the competitive landscape in these indications is provided in Exhibits 5 and 6.

Exhibit 5: Soft tissue sarcoma (STS) overview

What is STS?	Soft tissue sarcomas are malignant cancers of connective tissue, arising from mesenchymal cells, which normally produce various soft tissues (muscle, fat, cartilage, tendons, nerves and blood vessels). STS can occur anywhere in the body including the limbs (c 40%), trunk (c 40%), and head/neck (c 20%). There are >50 different STS subtypes. The most common are leiomyosarcoma (smooth muscle, 20-25%) and liposarcoma (fat, c 15%). In early stage disease, 5-year OS rates of approximately 90% are reached, while patients with inoperable, locally advanced or metastatic disease at initial diagnosis have a 5-year survival rate of only 20-50%.
Incidence/prevalence	STS is rare, accounting for c 1% of all cancers and 2% of cancer-related mortality. Median age of diagnosis is 50 yrs, with global incidence rates ranging from 2-5 cases per 100,000 per year. In the US, an estimated 12,020 new STS were diagnosed in 2014, with c 4,700 deaths. There are c 23,400 new cases per year in the EU27 countries.
Treatment outline	Initial treatment for STS includes surgical resection of the primary tumour and adjuvant radiotherapy. While this achieves local control and is potentially curative, up to 40% of patients experience local recurrence or metastatic disease. These patients are treated with sequential chemotherapies with the goal of palliation. Advanced STS patients face a poor prognosis, with median survival around 12 months and two-year survival rates approaching 30%. Chemotherapy remains the backbone of therapy for advanced STS. Approved treatments include first-line doxorubicin (cytotoxic chemotherapy) and second-line pazopanib (GSK's Votrient), although imatinib (Novartis's Gleevec) is indicated for specific STS subtypes (GIST and dermatofibrosarcoma).
Front-line chemotherapy for advanced STS	Single-agent doxorubicin is the gold standard therapy, despite offering modest improvements in response rates (13-25%), PFS (4-5 mths) and median OS (c 12 mths). Moreover, doxorubicin is associated with significant side effects including haematological toxicity (35-50% grade 3 or 4 neutropenia) and dose-dependent cardiotoxicity. Combining doxorubicin with other agents (usually ifosfamide) shows higher tumour responses and PFS than monotherapy, but no OS improvement and greater toxicity. This was confirmed by the EORTC 62012 study, where combination therapy (doxorubicin + ifosfamide) improved PFS vs doxorubicin (7.4 vs 4.6 months; p=0.002) but showed no OS benefit (two-year OS: 31% vs 28%, p=0.06). Moreover, combo therapy had more adverse events (neutropenia: 46% vs 14%, anaemia: 14% vs 5%).
Second-line chemotherapy for advanced STS	**GSK's Votrient (pazopanib):** FDA and EMA approval for second-line STS (2012). Data from the 369-pt Phase III PALETTE study showed modest improvements in response rates (4% vs 0%) and PFS (4.6 vs 1.6 mths) vs placebo but no significant impact on OS (12.6 vs 10.7 mths). Moreover, side effects caused dose interruption in 58% of patients and dose reduction in 39%, with 14% discontinuing therapy. **Yondelis (trabectedin):** EMA approval for second-line STS (2007), based on a 27% reduction in the risk of disease progression for advanced patients dosed every three weeks (time to progression 3.8 mths) vs weekly (TTP 2.1 months). Median OS with q3 weekly dosing was 13.9 mths. However, most patients experienced side effects (liver enzyme elevations and haematological effects) and c 10% had serious adverse events.
Late-stage development pipeline	**Aldoxorubicin (Cytrx)** is a tumour-targeted doxorubicin conjugate being studied in a 400-pt Phase III trial in second-line STS (results: H216). The 105-pt Phase IIb in first-line STS reported top-line results showing that aldoxorubicin was superior to doxorubicin on various measures: reported PFS was 8.4 mths vs 4.7 mths (investigator assessed, or IA, p=0.0002); Hazard ratio (HR) of 0.37 (p=0.0004); 5.7 mths vs 2.8 mths (central lab review, or CLR, p=0.018), HR of 0.59 (p=0.034). Six-month PFS 67.1% vs 36.1% (p=0.005, IA) and 46.8% vs 23.7% (p=0.038, CLR). Final ORR was 25.4% vs 5.4% (IA) and 23% vs 0% (CLR). Top-line results from the 450-pt Phase III trial of **Halaven (eribulin, Eisai)** vs dacarbazine should be available in H115, with regulatory submission targeted in 2015. **TH-302 (Threshold Pharmaceuticals/Merck KGaA)** is in a pivotal, 620-pt Phase III first-line STS comparator trial in combination with doxorubicin vs doxorubicin alone (results: H115). Phase II trial results showed median PFS of 6.7 months, median OS of 21.5 months, one-year survival of 73%, and two-year survival of 44%.

Source: Edison Investment Research, company data, clinicaltrials.gov

Exhibit 6: Ovarian cancer overview

What is ovarian cancer?	Ovarian cancer forms in the tissues of the ovary; the most common type, epithelial ovarian cancer, accounts for about 90% of primary ovarian tumours. Approximately 60-70% of cases are diagnosed at an advanced stage (III or IV).
Incidence/prevalence	Ovarian cancer is the seventh most common cancer among women globally, with c 240,000 new cases diagnosed in 2012. In the US and Europe it accounts for 4% of all cancers among women. Median age of diagnosis is 60 yrs, and incidence increases with age, although it may occur in younger women with a family history of the disease (5-10% are familial). The global incidence rate ranges from 4-19 cases per 100,000 women per year. In the US, an estimated 21,980 new OC were diagnosed in 2014, with c 14,300 deaths. There are c 44,150 new cases per year in the EU27 countries. Nearly 70% of women with epithelial OC are not diagnosed until the disease is advanced.
Treatment outline	Initial treatment for OC includes surgical resection of the primary tumour (including hysterectomy) and adjuvant chemotherapy (often of a combination); however, up 70% of patients experience recurrence or metastatic disease. Median survival for recurrent OC patients ranges from 12-24 months, with a 5-year survival rate for Stage III/IV disease of 15-20%. Platinum-based chemotherapy is the backbone of therapy for advanced OC, although c 80% of patients relapse after first-line platinum-based and taxane-based chemotherapy.
Front-line chemotherapy	Gold standard therapy is a platinum-based chemotherapy regimen, often combining carboplatin or cisplatin (although the latter has greater side-effects) with a taxane, such as Taxol (paclitaxel) or Taxotere (docetaxel). Platinum plus paclitaxel vs single agent carboplatin has shown improved PFS (HR=0.76; p=0.004) and OS (HR=0.82; p=0.023).
Second-line chemotherapy	First-line chemotherapy fails to produce a remission in more than 70% of patients, and of those that do achieve remission, 40-50% experience a cancer recurrence within three years. Patients who have failed first-line chemotherapy are categorised into three broad groups: (1) persistent OC (which typically continue with standard chemotherapy or second-line therapy), (2) recurrent OC or (3) refractory OC. Of the latter two categories, 15% are platinum refractory and for the remainder further treatment depends on whether the OC is platinum-sensitive (relapse occurs 12 months or more after platinum-based therapy – in 70% of cases – of which a third are partially platinum sensitive ie have a platinum-free interval [PFI] of between six and 12 months) or platinum-resistant (relapse within six months of therapy, 15%). For platinum-sensitive OC, re-treatment with single agent platinum, or a platinum combination is standard therapy with an expected tumour response rate of 22-59% depending on PFI; other options include Yondelis in combination with Caelyx/Doxil. Platinum-resistant and platinum refractory patients are treated with monotherapy with liposomal doxorubicin (Caelyx/Doxil – 20-25% RR), topotecan (Hycamtin – ORR of 13-16%), or gemcitabine (Gemzar) in combination with carboplatin (ORR of 46%). Third-line options typically include inclusion in clinical trials.
Late-stage development pipeline	**Platinum-sensitive:** **Olaparib (Astra Zeneca)** – FDA AdCom delivered an 11 to 2 vote that current evidence from clinical studies does not support an accelerated approval for use of olaparib as a maintenance treatment for platinum-sensitive relapsed OC patients with a BRCA mutation, who are in complete or partial response to platinum-based chemotherapy. PDUFA date of 3 October 2014. **Niraparib (Tesaro/Merck & Co)** – 360-pt Phase III NOVA trial ongoing in high grade serous, platinum sensitive relapsed OC, which is stratifying patients based on germline BRCA mutation status. PFS primary endpoint. Results: H216. **Rucaparib (Clovis/Pfizer)** – 540-pt Phase III ARIEL3 study ongoing in high-grade serous platinum-sensitive relapsed OC. PFS primary endpoint. Results: H216. **Platinum- resistant:** **Avastin (Roche)** – positive recommendation from the EMA's CHMP based on the 361-pt AURELIA Phase III trial in recurrent platinum-resistant OC, which showed that adding Avastin to chemotherapy doubled median PFS to 6.7 mths from 3.4 mths, with an ORR of 30.9% vs 12.6% with chemotherapy alone. The final EMA decision is pending. **Trebananib (Amgen)** – 900-pt Phase III TRINOVA-1 trial of trebananib plus paclitaxel in recurrent partially platinum-sensitive or platinum-resistant OC met its primary endpoint of PFS with a 34% reduction of risk of disease progression or death (HR=0.66, p<0.001) with a median PFS of 7.2 mths vs 5.4 mths for control. Two other Phase III OC trials ongoing: TRINOVA-2 evaluating whether trebananib plus pegylated liposomal doxorubicin is superior to placebo plus PLD and TRINOVA-3 is evaluating trebananib or placebo in combination with paclitaxel and carboplatin in the first-line treatment of epithelial ovarian, primary peritoneal or fallopian tube cancer.

Source: Edison Investment Research, company data, clinicaltrials.gov

Development pipeline, beyond Yondelis

The clinical pipeline includes three additional drugs that have been prioritised for development (Exhibit 7). Final data from the Phase III Aplidin multiple myeloma study in 2015, and further updates from ongoing trials of PM01183, are major near-term value drivers that may catalyse a partnership for non-European territories.

Aplidin: Courting ADMYRE-ing glances from partners

The 250-patient ADMYRE Phase III study in fourth-line relapsed/refractory multiple myeloma (MM) is on track for recruitment by year end. ADMYRE is powered to detect a 60% progression free survival benefit (primary endpoint) between Aplidin in combination with dexamethasone (a mainstay of MM therapy) randomised 2:1 vs dexamethasone alone. An interim futility analysis of 79 patients in December 2012 received a positive recommendation from the IDMC; Aplidin was well-tolerated, and had demonstrated a response rate of over 30%. Assuming recruitment is achieved this year, data will be available in 2015, potentially facilitating an EMA filing in Q415. A possible CHMP approval recommendation around end-2016 would suggest launch in 2017.

Exhibit 7: Non-Yondelis PharmaMar R&D pipeline

Programme	Indication	Stage	Notes
Aplidin (plitidepsin)	Relapsed/refractory multiple myeloma (r/r MM)	Phase III	250-pt Phase III (ADMYRE) pf dexamethasone ± Aplidin in r/r MM (after three but no more than six lines of chemotherapy) ongoing. Primary endpoint: 60% increase in PFS in Aplidin arm; IDMC recommendation to continue following interim analysis after 79-pts, which showed ≥30% response rate (Dec 2012). 128-pts recruited (Jan-2014); full recruitment expected H214. Orphan drug designation (EMA and FDA). Combination potential for life cycle management: synergistic mechanism of action with Velcade. 30-pt Phase I bortezomib + dexamethasone combo trial in r/r MM underway to determine dosing: expansion cohort planned to assess efficacy (results: March 2016). Commercialisation rights in eight European countries licensed to Chugai Pharma Marketing.
	Relapsed/refractory T-cell lymphoma	Pivotal Phase II (pending)	Single-arm 60-pt pivotal trial in angioimmunoblastic T-cell lymphoma (a PTCL subtype) planned to start in 2014. FDA acceptance of proposal for Aplidin production process. US partner sought.
PM01183 (lurbinectedin)	Platinum resistant/ refractory ovarian cancer (PRROC)	Phase II	Two-part Phase IIb monotherapy trial vs topotecan in topotecan-naïve pts with <3 prior lines of chemo. First stage met primary endpoint of ≥2 responses in 22-pts: initial results at ESMO 2012 indicated 6 responses for 27% ORR with 1 radiological CR and 4 month median PFS. Only six patients (27%) had progressed. 58-pts randomised 1:1 to PM01183 or topotecan into second-stage open-label phase (ORR primary endpoint; PFS and OS secondary endpoints). Overall results presented at ASCO 2014. ORR for PM01183 of 21% vs 0% for topotecan (p=0.006), which rose to 30% in the platinum resistant subgroup (p=0.002). Overall PFS was 3.9 mths with PM01183 vs 2 mths with topotecan (p=0.003) and overall OS was 10.6 mths with PM01183 vs 5.7 mths with topotecan (p=0.029). Orphan drug status (FDA, with positive opinion issued by EMA COMP). Phase III in platinum-resistant OC planned in 2014.
	BRCA 1/2 associated breast cancer (BC)	Phase II	117-pt two part Phase IIb trial in BRCA1/2-associated or unselected metastatic BC ongoing (results: March 2015). Stage one: 20-pts with mut-BRCA1/2 mutation (targeting ≥4 pts with ORR) and 30-pts with unknown status (targeting ≥3pts with ORR), leading into second stage with 33-pts in each arm if positive. Second stage ongoing. Primary endpoint of ORR.
	Non-small cell lung cancer (NSCLC)	Phase II	120-pt three-arm Phase II of PM01183 ± gemcitabine vs docetaxel in 2nd line unresectable NSCLC (results: Dec 2015). Primary endpoint: PFS at 4 months. Secondary endpoints: ORR, PFS/OS, histology. Phase I study + gemcitabine resulted in 1 CR, 4 PR and 7 SD in 19 evaluable NSCLC pts.
	Endometrial cancer (EC)	Phase I/ pivotal trial pending	73-pt Phase I + doxorubicin undergoing cohort expansion in select tumour types including endometrial adenocarcinomas. Activity seen in initial three EC patients (CR, PR and SD) with good duration of response: targeting enrolment/evaluation of additional 12 EC patients. Pivotal trial in <500-pts planned.
	Small cell lung cancer (SCLC)	Phase I/ pivotal trial pending	73-pt Phase I + doxorubicin undergoing cohort expansion in select tumour types including SCLC. 12 SCLC pts so far evaluated: activity seen in 6 of 8 second-line pts with 5 PR and 1 SD (no third-line responders). Targeting enrolment of additional 12 second-line pts to evaluate duration of response. Pivotal trial in 250 pts planned.
PM060184	Solid tumours/combo studies	Phase I	Two Phase I dose-finding/safety studies ongoing in US, Spain and France, also evaluating pharmacokinetic profile and preliminary anti-tumour activity. Strong in vitro and in vivo anti-tumour activity and a favourable safety profile shown in preclinical toxicology studies.

Source: Edison Investment Research, clinicaltrials.gov. Note: PFS = progression free survival; IDMC = independent data monitoring committee; PTCL = peripheral T-cell lymphoma; ORR = overall response rate; CR = complete response; PR = partial response; SD = stable disease.

In July 2014, PharmaMar entered into an exclusive European licensing and commercialisation agreement with Chugai Pharma Marketing covering eight countries (France, Germany, UK, Belgium, Netherlands, Luxembourg, Ireland and Austria) in which Chugai has an established haematological oncology sales force (which currently markets RoActemra [tocilizumab], Granocyte [lenograstim] and Antepsin [sucralfate]). Under this deal PharmaMar receives a €5m upfront payment and is eligible for in excess of €30m in regulatory, development and sales milestones from Chugai. PharmaMar also retains production rights and will supply Aplidin to Chugai for sale in the above regions (as a benchmark, similarly structured deals have generated an effective royalty of 20-30%) and 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 infrastructure.

The Chugai deal is significant for PharmaMar on a number of fronts in addition to the features outlined above. Its closure prior to ADMYRE read out removes potential uncertainty around timing, and gaining a partner with an established European specialist haem-oncology sales force suggests potential higher market penetration from day one without the need for additional investment in commercialisation by PharmaMar in these regions. Consequently, this deal structure should prove to be more profitable for PharmaMar over the long term.

There is potential for further licensing news flow with Aplidin as the regulatory dossier for European approval will also be valid for over 40 additional ex-EU countries. Licensing opportunities for these territories are being explored, and a partnership for the US, where a different development strategy is being pursued, is sought. PharmaMar's strategy for the US market is to target an ultra-orphan

subtype of peripheral T-cell lymphoma (PTCL), angioimmunoblastic T-cell lymphoma (lymphoma, which accounts for 2% of non-Hodgkin's lymphomas), as its first indication. The route to market is likely to be more rapid – although trial recruitment could be challenging – and there is potential for premium pricing, which should be an attractive proposition for a US partner. A pivotal Phase II trial in 60 patients is planned to begin enrolment in 2014.

We forecast global peak sales for Aplidin of $300m assuming that 40% of multiple myeloma patients ultimately receive fourth line therapy and 25% penetration. Our pricing assumptions are for pricing of $25,000 per treatment course in the EU with 25% US pricing premium; we believe that this is conservative given Revlimid (indicated as a second line therapy) is priced at c $74,000 per year and Velcade, a first-line therapy approved 2008 in the US and 2013 in Europe, costs $26,000-$35,000. We err on the side of conservatism as we believe that Aplidin could be moved into earlier lines of therapy as part of a combination regimen, increasing the market opportunity and also the combined price, although additional trials will need to be run. Aplidin has non-cumulative toxicity and a manageable safety profile (myalgia being the most common adverse effect) with a mechanism of action[4] that has been shown to be synergistic in preclinical models with other MM therapies, eg as proteasome inhibitors (Velcade, bortezomib) and immunomodulators (Revlimid, lenalidomide), which are used as induction and second-line therapy respectively. This is being studied further in an ongoing Phase I combination trial with Velcade designed to determine efficacy and dosing.

PM01183: Second-generation Yondelis with broad potential

At ASCO 2014, compelling PFS and OS data for PM01183 as a single-agent was presented from a Phase II study in platinum-resistant/refractory ovarian cancer (OC). The ORR for PM01183 was 21% vs 0% for topotecan[5] (p=0.006), which rose to 30% in the platinum-resistant subgroup (p=0.002). Other efficacy measures were also improved on PM01183 vs topotecan, including overall PFS of 3.9 months (vs 2 months, p=0.003) and overall OS of 10.6 months (vs 5.7 months, p=0.029). Consequently, a pivotal Phase III study in platinum-resistant OC is planned to start this year. This is an indication where the competitive landscape has recently moved in PharmaMar's favour with the DSMB recommendation that the PROCEED Phase III trial of Endocyte's vintafolide be stopped following an interim analysis for futility. Competing developmental-stage therapies in this indication are outlined in Exhibit 6.

PM01183's activity as a combination agent in other solid tumours, including endometrial and small-cell lung cancers, is also being explored in an expanded Phase I/II trial (data reported to date are presented in Exhibit 8), which should inform the merit in and design of additional pivotal trials planned for 2014-15. These indications have been selected on the basis of the promising data seen in a limited number of patients coupled to the unmet need in both endometrial cancer (where there are no approved drugs,[6] and platinum or taxane-based chemotherapy is common) and SCLC (five-year survival rates for metastatic disease is less than 5%). This could result in potentially favourable competitive dynamics, market access and pricing if PM01183 is launched in either of these indications, ahead of ovarian cancer.

We forecast global peak sales of €492m in third-line platinum-resistant ovarian cancer, with an assumption that PM01183 is priced at a 50% premium to Yondelis (for reasons we elaborate on below) and that PharmaMar is responsible for European sales and receives a 15% royalty in the US. For SCLC and endometrial cancer, we forecast combined peak sales of $525m but expect to

[4] Aplidin targets the eukaryotic elongation factor eEF1A protein in tumour cells, resulting in oxidative stress and apoptosis.

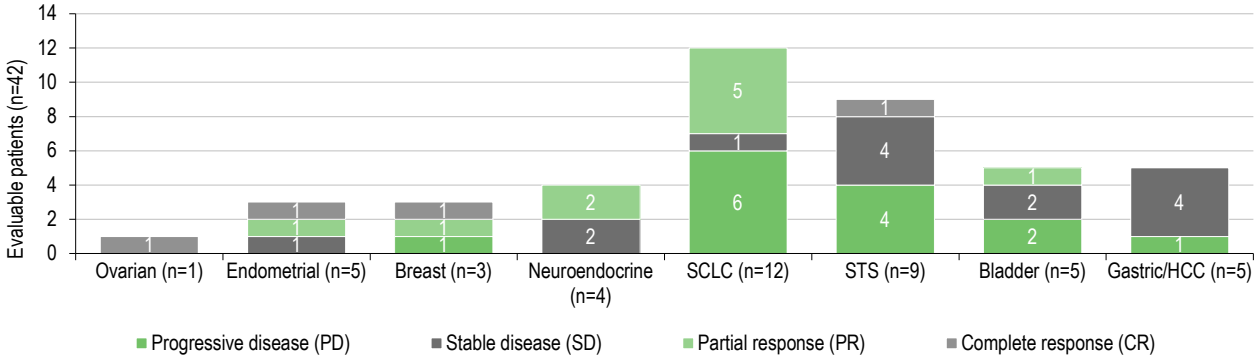
[5] Topotecan was used as the active comparator rather than Caelyx due to shortage issues with the latter when the trial started.

[6] Two programmes are currently in Phase III studies: Aeterna-Zentaris' zoptarelin doxorubicin and Bristol Myers Squibb's ixabepilone.

refine this following additional data on PM01183's clinical profile in these indications. At this stage we only estimate peak sales in indications where there is a clear plan to advance PM01183 but it has potential in other cancers.

PharmaMar has the resources to fund the pivotal trials but could seek non-dilutive funding from a cooperative group; however, a PM01183 partnership prior to the start of Phase III trials would be preferred in order to accelerate profitability. PharmaMar intends to retain production and European commercial rights while partnering in the rest of the world. A number of parties have expressed an interest in the programme, and it is expected that any licensing deal would cover all indications. Edison believes that PharmaMar's strategy should be attractive to a potential partner and that Yondelis provides commercial validation for the company's approach.

Exhibit 8: PM01183 Phase I doxorubicin combination data (RECIST criteria)



Source: Calvo *et al* ESMO 2013. Note: Chronic tolerance demonstrated with 6+ cycles in 34% of patients.

PM01183 is a second-generation synthetic analogue of Yondelis with the same mechanism of action and a more tolerable safety profile (haematological toxicity is most common) with no cumulative toxicity, but has a number of key advantages including linear dosing (a 7mg capped dose uncorrelated with body surface area), an improved therapeutic index (allowing dosing through a one-hour peripheral infusion each 21 days vs 24 hour [STS]/three hour [OC] infusions every 21 days via central catheter for Yondelis) and long IP (composition of matter patents extend to 2030 with potential extensions).

Given these similarities and advantages, PM01183 is likely to have utility in the same indications as those in which Yondelis is marketed/seeking approval and thus could form part of a life cycle management strategy if these are pursued at a later stage. Consequently, we would expect PharmaMar, at least in Europe (and potentially in the rest of the world, depending on who PM01183 is partnered with) to seek to transition sales in platinum-sensitive resistant/refractory ovarian cancer to PM01183 once Yondelis reaches patent expiry, assuming that the necessary approvals have been granted. This would significantly increase the potential value of PM01183. In addition, PM01183's shared mechanism of action suggests that it may also be effective in STS, although there is as yet no clinical evidence for this, and potentially many other tumour types.

Discovery platform and IP

Exploring the biodiversity of the sea as a source of potential new anti-tumour compounds with differentiated mechanisms means PharmaMar's drug discovery process is unique. Through annual diving expeditions around the globe, the company has built an extensive library of c 150,000 marine samples that form the basis of its cancer research activities. Exhibit 9 outlines the key activities in the discovery process; once a lead candidate is selected, it enters standard preclinical and clinical development. PharmaMar' synthetic chemistry capabilities have three major benefits: (1) ensuring drug supply for clinical trials/commercial use does not rely on natural sources; (2) potential for

discovery and synthesis of more potent derivatives; and (3) a strong IP position and barriers to entry, particularly as the underlying molecules are complex (eg Yondelis has an 18-step manufacturing process).

Exhibit 9: Key steps in the PharmaMar discovery process

Stage	Aim	Process
Expeditions	Discovery of new marine-derived compounds with anti-tumour properties and new mechanisms of action	Diving expeditions into different regions to collect samples of marine invertebrates (sponges, molluscs, crustaceans) and algae, which form the basis of its extensive library of 150,000 marine samples (both macro-organisms and micro-organisms).
Sample preparation and storage	To ensure traceability of origin and preservation	Biological samples are freeze-dried and bagged immediately after collection and labelled with necessary information regarding their collection (location, time etc) and identification (species). This information is logged in the proprietary PharmaMar database and samples are moved into long-term storage at -40°C.
Screening	Identification of samples with anti-tumour activity	Extracts prepared from small quantities of samples are screened against a panel of tumour cells to determine activity. Chromatographic fractionation of those demonstrating promising anti-tumour activity enables isolation of active compounds/molecules of interest and elucidation of their chemical structure.
Medicinal chemistry	To achieve security of supply through chemical synthesis, more potent derivatives and formulation development	Compounds of interest are purified and characterised to enable chemical synthesis to produce sufficient quantities to pursue further development. Analogues with potentially improved pharmacological properties are also synthesised and screened to identify lead candidates. Potential formulations are also considered for in vivo evaluation to study anti-tumour activity and toxicity profile.

Source: Edison Investment Research, company data

The sample library and IP estate (over 1,200 granted patents and 600 pending patents in 100 families) represents a significant barrier to entry. Patents cover composition of matter (including of analogues), use (including in combination), formulation and manufacturing, with the company also benefiting from significant know-how and marketing exclusivities. Edison also notes the significant potential value in the sample library outside oncology as it is likely to contain novel compounds with utility in other disease areas (eg anti-infectives) that could be exploited through potential future IP licensing deals. However, this is not a priority for management, which instead is exploring the potential for antibody-drug conjugate (ADC) partnership in oncology. PharmaMar's screening process has identified novel compounds with high potency that have not been further developed due to their toxicity profile; these could have significant potential as part of an ADC approach.

Non-core operations

Zeltia's operating subsidiaries are independently managed, allowing the respective management teams to concentrate on their line of activity. Zenova and Xylazel (consumer chemicals) are leaders in their market segments, which are, like molecular diagnostics company Genomica, self-sustaining profitable businesses requiring little external investment. Historically, the rationale for the holding company structure and the seemingly disparate activities was that the cash generative consumer chemicals division provided funding for the biopharmaceuticals business and access to banking debt. However, consumer chemicals could now be considered non-core legacy businesses, and as Zeltia's business focus evolves and shifts increasingly toward oncology drug development, there may be future potential for the sale or spin-off of this division to create a pure-play biopharma company. The timing of such a move may be opportunistic rather than being actively sought by management as the priority is on growing the marine oncology franchise, and consumer chemicals continues to help bridge a potential funding gap until further products are launched.

We note that since 2010, around 40% (€62-73m) of Zeltia's total sales at the group level have been generated by the consumer chemicals division. This business has a gross margin of 45-50% although given the diversity of products and the exposure to economic factors it is difficult to assess the growth prospects of this division and a potential sales price. Our conservative discounted cash flow valuation, assuming a 7.5% WACC and a 2% sales growth rate, suggests a c €42m valuation.

The remaining biopharmaceuticals subsidiaries have both complementary (Genomica) and distinct (Sylentis) activities to marine oncology. Genomica develops and commercialises in vitro diagnostic kits with its CLART platform (launched in 2006) and performs DNA identification analysis. The company is currently diversifying strategically into cancer molecular diagnostics with the launch of a

new line of products (CLART CMA) based on the detection of genetic DNA mutations in genes associated with cancer. The two CMA products already commercialised are CMA KRAS BRAF PI3K and CMA NRAS. The implementation of new technologies like RT-PCR (reverse transcription polymerase chain reaction) and NGS (next-generation sequencing) has increased the synergy and collaboration with PharmaMar in the area of mutational analysis of in-house clinical tumour cell line samples.

Zeltia is approaching an inflection point with Sylentis. It has committed to funding and completing a Phase IIb glaucoma study, with the expectation that further positive data will be sufficient to secure a near-term licensing/M&A deal for this project/subsidiary so that Zeltia is able benefit from any future upside in Sylentis without further financial commitment. Ongoing R&D is shown in Exhibit 10.

Exhibit 10: Sylentis R&D pipeline

Programme	Indication	Stage	Notes
SYL040012 (bamosiran)	Glaucoma	Phase II	84-pt Phase IIa trial completed in patients with ocular hypertension and glaucoma: one dose of three tested showed a statistically significant effect in reducing intraocular pressure (IPO) in patients with high IPO and/or glaucoma. 180-pt Phase IIb five-arm parallel randomised, blinded trial (SYLAG) to determine dose and efficacy of bamosiran vs active control (timolol) to start in H214 following grant of first country authorisation (Estonia) to begin patient recruitment.
SYL1001	Ocular pain in dry eye syndrome	Phase I/II	60-pt Phase I/II pilot trial ongoing to compare the analgesic effect of SYL1001 vs placebo in patients with ocular discomfort associated with dry eye syndrome.

Source: Edison Investment Research, company data

Valuation

Our Zeltia valuation of €904m or €4.07 per share is based on a sum-of-the-parts DCF to 2025. We use a risk-adjusted net present value (rNPV) method to discount future cash flows for the biopharmaceuticals business and have applied a standard DCF model for the chemicals division. Our valuation breakdown and key assumptions are shown in Exhibit 11. We use a 7.5% WACC for the chemicals division, 10% for central costs and the commercial segment of the biopharma business (ie Yondelis European and RoW revenues, and the associated sales and marketing infrastructure) and 12.5% for the rest of the biopharma business, which is our standard discount rate assumption for development-stage therapeutics companies. Cash flows are taxed at a 25% Spanish corporate tax rate from 2020 (reflecting the new bill, yet to be implemented, lowering the current 30% corporate tax rate from 2016), tapering up from a lower rate of 21% from 2014 onwards reflecting accumulated tax losses.

Our model suggests that Zeltia's current market cap of c €653m is largely underpinned by Yondelis, with limited value ascribed to earlier-stage programmes, principally PM01183. At present our PM01183 valuation is based on conservative assumptions, and we only estimate peak sales in indications where there is a clear plan to advance PM01183, although it has potential in other cancers. We believe PM01183 could be worth considerably more as the development programme progresses (eg in NSCLC) and expands (eg into breast cancer, platinum-sensitive OC or STS), particularly as part of a Yondelis life cycle management strategy. On confirmation of further development plans and additional data on PM01183's clinical profile, we will refine our assumptions and potentially include additional indications. We will also take a similar approach with Aplidin, where our current valuation assessment focuses only on the fourth-line multiple myeloma opportunity; future line extensions (including as a combination therapy) would represent upside.

Exhibit 11: Zeltia sum-of-the-parts DCF

Product	rNPV (€m)	NPV/share (€)	Assumptions
FCF of chemicals business	42.22	0.19	7.5% WACC, 2% growth rate, accounts for 25% of group capex and depreciation and amortisation
Yondelis (Europe)	809.77	3.64	10% WACC. STS (second line): peak sales of €80m with 35% penetration; ovarian cancer (third-line platinum sensitive): peak sales of €100m with 22% penetration. First generics in 2022.
Yondelis (US)	63.51	0.29	STS (second line): peak sales of $160m with 80% success probability, 2016 launch; ovarian cancer (third-line platinum sensitive) peak sales of $190m, 65% risk adjustment, 2020 launch; both assume 15% royalty
Yondelis (Japan)	43.07	0.19	STS only: peak sales of €120m; 90% success probability; launch 2016; 15% royalty
Yondelis (milestones)	11.75	0.05	Known milestones for 2015 only – Janssen: $20m in aggregate for development and US approval; Taiho: Japan approval. Risk-weighting applied; assumes $/€ FX rate of 1.35.
Aplidin (multiple myeloma)	102.28	0.46	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 15% royalty in US; includes Chugai milestones of €5m on deal signing in 2014 and €20m of near-term regulatory milestones out of €30m total. No milestones included for other territories at this stage.
PM01183 (ovarian cancer)	282.38	1.27	Ovarian cancer (third-line platinum-resistant): peak sales of €492m with 65% success probability, 2019 launch; sold direct in Europe with 15% royalty in US
PM01183 (SCLC and endometrial cancer)	15.82	0.07	Combined peak sales of $525m; 15% success probability; launch 2020; 15% royalty
PM01183 (milestones)	9.31	0.04	Only assumes receipt of €25m signing milestone in 2014 (50% risk weighted)
Sylentis	4.13	0.02	Cumulative peak sales of $250m; 25% probability of success; potential launch 2019; 10% royalty
Genomica	34.02	0.15	Conservative 2% growth rate
R&D	(127.75)	(0.57)	Approximate split 35% discovery and preclinical: 65% clinical development
SG&A	(244.61)	(1.10)	10% WACC. Expenses relate to biopharma infrastructure and Yondelis sales force
Unallocated central costs	(67.98)	(0.31)	10% WACC
Capex	(11.00)	(0.05)	75% of group capex for biopharma business
Net cash	(62.53)	(0.28)	At end-Q214
Total	904.38	4.07	

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

Near-term sources of potential upside include Japan and US regulatory decisions on Yondelis in STS and receipt of associated milestones (which would result in an unwinding of the risk adjustment and a €922m valuation), Phase III data for Aplidin (increasing the probability of success) and confirmation of a licensing deal for PM01183 as while our model does include upfront payments (but not clinical/regulatory or sales milestones) from a potential deal, these have been risk-adjusted. Additionally, we also do not ascribe an explicit value to the sample library, technology platforms and discovery capabilities, which could represent unappreciated upside and potential for diversification.

Sensitivities

Zeltia's biopharma division 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 company's chemical business is predominantly exposed to economic factors, although raw material costs, environmental/regulatory requirements and external weather conditions may also have an impact on sales or margins.

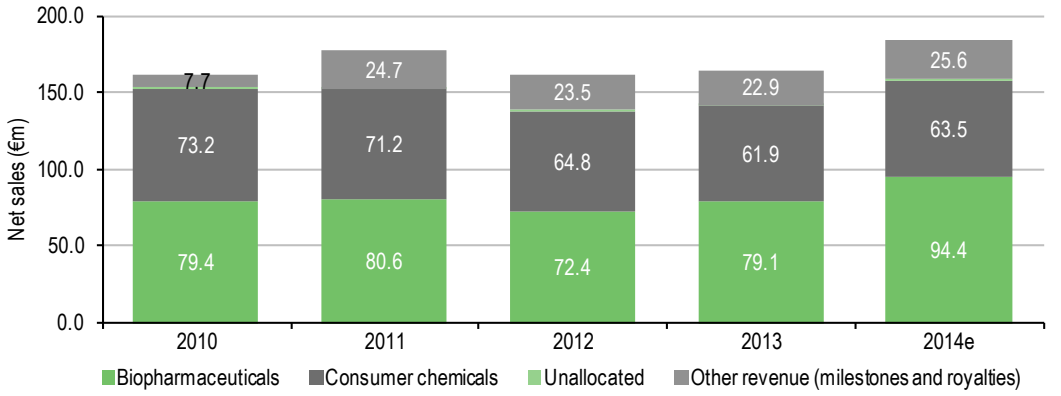
Key stock-specific sensitivities for the core oncology business include, but are not limited to:

- **Yondelis**: European sales growth; outcome of ongoing US clinical trials; outcome of FDA and Japanese MHRW approval decisions; 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.
- **Discovery**: new NCEs to come from marine discovery capability; potential collaborations.

Financials

Zeltia's improving revenue trend (Exhibit 12) indicates the company is recovering from the setback to Yondelis sales caused by the Caelyx shortage (Q311-Q213) and that Yondelis-associated milestone revenues make a recurring contribution, which will continue into 2015, being replaced by recurring royalties from 2016. Net revenue increased across both business segments in H114: biopharma sales grew 10% year-on-year to €41.8m (of which €39.2m related to Yondelis) with consumer chemicals also up 10% to €36.1m.

Exhibit 12: Zeltia Group total revenue breakdown



Source: Edison Investment Research, company accounts

R&D spending is predominantly focused on the biopharma business (€38m in FY13, net of €4.4m of capitalised R&D), with this expected to grow further to c €41m in FY14 (net of €4m in capitalised R&D) with the pivotal trials for Aplidin and PM01183 and more modest investment into the Sylentis glaucoma study. A proportion of R&D is capitalised (we assume c10%). SG&A of c €60m per year does not include c €8m of unallocated central costs (which are classed as other expenses in the P&L), and we note the potential to leverage the existing biopharma sales force to market additional cancer drugs.

Growing revenues coupled with stable operating expenditure (ex-R&D) should enable Zeltia to grow its bottom line, and we forecast EBITDA improvement from €23.8m in FY13 to €35.2m in FY14.

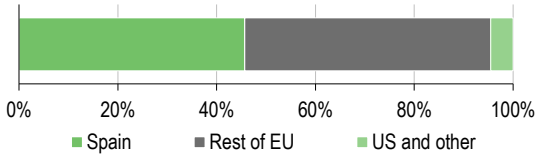
Increased operating cash flow is likely to result in a continuing reduction in net debt (FY13: €65.4m to FY14: €52.3m). The debt structure consists of a €26.5m RCF (c €12m undrawn) and a €50m ECB loan to 2016, with a number of smaller banking facilities to accommodate funding requirements post-2016. Last reported net debt stood at €62.5m at end-June 2014 (cash and equivalents of €36.3m offsetting total debt of €98.8m).

Exhibit 13: Financial summary

€000s	2011	2012	2013	2014e	2015e
Year end 31 December	IFRS	IFRS	IFRS	IFRS	IFRS
PROFIT & LOSS					
Revenue	152,486	138,229	141,824	158,887	173,785
Cost of Sales	(42,955)	(39,793)	(37,900)	(43,607)	(45,018)
Gross Profit	109,531	98,436	103,924	115,280	128,767
EBITDA	29,675	20,473	23,817	35,248	49,224
Operating Profit (before GW and except.)	24,848	15,985	20,735	29,374	43,906
Intangible Amortisation	(997)	(1,418)	(1,779)	(932)	(1,755)
Other (milestones and royalties)	24,712	23,549	22,858	25,661	28,258
Exceptionals	0	0	0	0	0
Operating Profit	23,851	14,567	18,956	28,442	42,152
Net Interest	(5,724)	(5,056)	(5,690)	(6,039)	(7,626)
Other	(159)	(85)	535	0	0
Profit Before Tax (norm)	18,965	10,844	15,580	23,335	36,280
Profit Before Tax (FRS 3)	17,968	9,426	13,801	22,403	34,526
Tax	(2,511)	5,048	(1,960)	(1,141)	(1,564)
Deferred tax	0	0	0	0	0
Profit After Tax (norm)	16,454	15,892	13,620	22,194	34,716
Profit After Tax (FRS 3)	15,457	14,474	11,841	21,262	32,962
Minority interests	6,114	2,868	189	45	0
Discontinued operations	(16,830)	(10,749)	(708)	(168)	0
Net income (normalised)	22,568	18,760	13,809	22,239	34,716
Net income (FRS3)	4,741	6,593	11,322	21,139	32,962
Average Number of Shares Outstanding (m)	220.6	220.8	220.2	222.2	222.2
EPS - normalised (€)	0.10	0.08	0.06	0.10	0.16
EPS - FRS 3 (€)	0.02	0.03	0.05	0.10	0.15
Dividend per share (€)	0.00	0.00	0.00	0.00	0.00
Gross Margin (%)	71.8	71.2	73.3	72.6	74.1
EBITDA Margin (%)	19.5	14.8	16.8	22.2	28.3
Operating Margin (before GW and except.) (%)	16.3	11.6	14.6	18.5	25.3
BALANCE SHEET					
Fixed Assets	88,285	93,399	93,475	92,997	85,056
Intangible Assets	19,873	22,292	25,138	25,151	23,396
Tangible Assets	33,862	29,794	27,959	24,605	18,418
Other	34,550	41,313	40,378	43,241	43,241
Current Assets	159,726	106,431	95,895	118,428	131,330
Stocks	25,309	23,502	22,232	23,894	24,667
Debtors	80,636	41,956	38,630	39,178	42,851
Cash	49,325	34,428	28,835	46,511	54,966
Other	4,456	6,545	6,198	8,846	8,846
Current Liabilities	(89,367)	(87,355)	(74,058)	(82,969)	(83,926)
Creditors	(36,681)	(32,621)	(32,731)	(30,738)	(31,695)
Short term borrowings	(52,686)	(54,734)	(41,327)	(52,231)	(52,231)
Long Term Liabilities	(93,947)	(73,749)	(65,877)	(62,443)	(61,243)
Long term borrowings	(83,060)	(62,016)	(52,941)	(46,564)	(46,564)
Other long term liabilities	(10,887)	(11,733)	(12,936)	(15,879)	(14,679)
Net Assets	64,697	38,726	49,435	66,013	71,217
CASH FLOW					
Operating Cash Flow	(4,589)	5,751	15,489	19,379	16,578
Net Interest	565	876	1,057	(3,839)	(7,626)
Tax	(258)	(308)	(201)	(603)	(1,366)
Capex	(3,055)	(2,029)	(2,095)	(1,310)	869
Acquisitions/disposals	0	0	447	4	0
Financing	125	1,368	0	0	0
Dividends	0	0	0	0	0
Other	2,405	(3,824)	5,760	(8,402)	0
Net Cash Flow	(4,807)	1,834	20,457	5,229	8,455
Opening net debt/(cash)	81,618	86,421	82,322	65,433	52,284
HP finance leases initiated	0	0	0	0	0
Exchange rate movements	0	0	0	0	0
Other	4	2265	(3,568)	7920	0
Closing net debt/(cash)	86,421	82,322	65,433	52,284	43,829

Source: Edison Investment Research, company accounts. Note: Discontinued operations and minority interest relate to Noscira, Zeltia's CNS subsidiary, which is in the process of being wound up.

EDISON

Contact details	Revenue by geography (2013)
Plaza del Descubridor Diego de Ordás, 3, planta 5 28003, Madrid Spain +34 91 444 45 00 www.zeltia.com	

CAGR metrics		Profitability metrics		Balance sheet metrics		Sensitivities evaluation	
EPS 2011-15e	11.2%	ROCE 14e	22.5%	Gearing 14e	79.2%	Litigation/regulatory	●
EPS 2013-15e	57.9%	Avg ROCE 2011-15e	20.5%	Interest cover 14e	4.9x	Pensions	○
EBITDA 2011-15e	13.5%	ROE 14e	31.8%	CA/CL 14e	1.4x	Currency	◖
EBITDA 2013-15e	43.8%	Gross margin 14e	72.6%	Stock days 14e	54.9	Stock overhang	○
Sales 2011-15e	3.3%	Operating margin 14e	18.5%	Debtor days 14e	90.0	Interest rates	◖
Sales 2013-15e	10.7%	Gr mgn / Op mgn 14e	3.9x	Creditor days 14e	49.4	Oil/commodity prices	○

Management team

Chairman, Zeltia and PharmaMar: José Maria Fernández Sousa-Faro

Dr Sousa-Faro has been chairman of Zeltia since 1985 (having been a director since 1971) and PharmaMar (which he founded) since 1986. He has over 25 years of experience in pharmaceutical and chemical companies, including ICI-Farma, Antibióticos, Zeltia and PharmaMar, and has held board positions at Antibióticos, Penibérica, Biolys, ICI-Farma, Pescanova, Transfesa, Cooper–Zeltia, ICI-Zeltia and Banco Guipuzcoano. He is professor of biochemistry at the Complutense University of Madrid and the University of Santiago de Compostela. He holds a degree in business administration from IESE and a doctorate in biochemistry from Complutense University of Madrid.

Managing Director, PharmaMar: Luis Mora

Mr Mora has been managing director since 2007, having joined PharmaMar in 2000 as chief financial officer. Previously he was financial controller with the Antibióticos Group (Montedison) (1995-2000), having held prior positions as head of finance at Zambón Portugal and financial controller for Zambon SA and Pharmazam SA. He has 25 years of experience in the pharmaceutical industry and holds a degree in business administration and an MBA from the University of Barcelona.

Chief Financial Officer, Zeltia: Maria Luisa De Francia Caballero

Ms De Francia Caballero was appointed CFO in 2000, having worked in the Zeltia Group in various companies of the group, in several different positions over the past 25 years.

Principal shareholders	(%)
Fernández family	24.0
Rosp Corunna Participciones Empreseriales SL	5.0
Norges Bank	2.3
Kutxabank	2.0
Other board members and employees	2.0

Companies named in this report

Chugai, Genomica, Janssen (Johnson & Johnson), PharmaMar, Sylentis, Taiho Pharma, Xylacel, Zenova

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