EDISON

PharmaMar

Clinical update

Zepsyre misses in Ovarian, SCLC still promising

Pharma & biotech

PharmaMar recently announced that Zepsyre® failed to show a progression-free survival (PFS) benefit over Topotecan and pegylated liposomal doxorubicin (PLD) in the 443-patient CORAIL study in platinum-resistant ovarian cancer. Zepsyre is currently in a Phase III trial in small cell lung cancer (SCLC) patients with protocols for pivotal studies in endometrial and breast cancer being finalised.

Year end	Sales revenue (€m)	PBT* (€m)	EPS* (c)	DPS (c)	P/E (x)	Yield (%)
12/15	162.0	5.9	3.0	0.0	60.7	N/A
12/16	164.0	(24.7)	(10.8)	0.0	N/A	N/A
12/17e	171.2	(11.1)	(5.0)	0.0	N/A	N/A
12/18e	184.0	20.1	9.0	0.0	20.2	N/A

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

Phase III CORAIL study missed the primary endpoint

The 443-patient CORAIL study in platinum-resistant ovarian cancer missed the PFS primary endpoint. Details are scarce, although the company acknowledged that PFS for Zepsyre, Topotecan and PLD were the same (indicating that the drug does have single agent activity, just not enough to show a benefit over the standard of care). On a positive note, the company did disclose that Zepsyre demonstrated a better safety profile than the control arm, which is important for its programmes in other cancers.

Zepsyre continues to be promising in SCLC

PharmaMar presented promising Zepsyre data in SCLC patients at the European Society for Medical Oncology (ESMO). Importantly, in Cohort B, which has the same dose as that being used in the Phase III trial, PFS was 5.3 months, which is higher than the 3-4 months typically seen with Topotecan, the current standard of care. The 600-patient Phase III ATLANTIS study in relapsed SCLC patients is ongoing.

More Zepsyre pivotal studies coming

Beyond SCLC, PharmaMar is also about to embark on pivotal studies in endometrial and breast cancer, where protocols are being finalised. The 44% response rate seen in second-line endometrial cancer patients is especially noteworthy as these patients are typically chemo-resistant. We expect the Phase III in endometrial cancer to be initiated in H118.

Valuation: Decreased to €1.35bn or €6.06 per share

We are decreasing our valuation from €1.84bn or €8.28/share to €1.35bn or €6.06/share as we have removed Zepsyre in ovarian cancer from our model. We have also delayed our expected EU launch timeline for Aplidin to 2021 from 2018 and reduced the probability of success to 30% from 90% due to a negative CHMP recommendation in Europe and uncertainty regarding the product's future.

23 January 2018

Price	**€1.82**
Market cap	**€404m**
	$1.22/€
Net debt (€m) at end September 2017	66.4
Shares in issue	222.2m
Free float	80%
Code	PHM
Primary exchange	BME
Secondary exchange	N/A

Share price performance

%	1m	3m	12m
Abs	(27.0)	(41.3)	(35.7)
Rel (local)	(29.8)	(43.3)	(43.0)
52-week high/low		€4.2	€1.7

Business description

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

Next events

Final EMA decision on Aplidin	June/July 2018

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Zepsyre setback

PharmaMar recently announced that the 443-patient CORAIL study in platinum-resistant ovarian cancer missed the primary endpoint and Zepsyre showed no PFS benefit over Topotecan and PLD, which are the standard of care. Details are scarce as the company expects to present the full results at a scientific conference. However, the company acknowledged that PFS for Zepsyre, Topotecan and PLD were the same (indicating that the drug does have single agent activity, just not enough to show a benefit over the standard of care). This is a bit disappointing following the data from a previous Phase II trial comparing Zepsyre to Topotecan, in which the drug showed a statistically significant PFS benefit in platinum-resistant cancer patients (5.7 months versus 1.7 months, p=0.005) in the randomised-controlled stage of the trial.

So what happened? There were some important changes in the design of the Phase III trial compared to the Phase II, which may have affected the results. First, the comparator arm is different as patients could receive either Topotecan or PLD rather than just Topotecan. Initially, the Phase II trial was supposed to have PLD as a comparator but, due to a worldwide shortage at the time, it was switched to Topotecan. Additionally, in the Phase III, patients who received Topotecan only received the standard, five-day regimen rather than the weekly regimen. In the Phase II, patients could receive both and 21 of the 29 Topotecan patients were on the weekly regimen. In a previous trial comparing the two Topotecan regimens in platinum-resistant ovarian cancer patients, there were trends favouring the five-day regimen in both response rate (15% vs 4%) and PFS (4.3 months vs 3.0 months), although neither difference was significant.[1]

Another key change is that the company amended the Zepsyre dosing regimen. It was a flat dose of 7mg given every three weeks in the Phase II, but was based on body surface area in the Phase III. At a dose of 3.2mg/m^2 and an average body surface area of around 1.7 for women with ovarian cancer,[2] the average dose would be approximately 5.4mg, somewhat lower than the 7mg dose used in the Phase II. The main reason for the change was the high level of neutropenia found in the Phase II (85% grade 3/4, 64% grade 4), especially in those with low body surface area. Changes to the control arm likely benefited its performance, while changing the Zepsyre dosing regimen likely negatively affected its efficacy.

Zepsyre in SCLC

Despite the negative trial result in platinum-resistant ovarian cancer, we continue to be optimistic about the drug's potential in other cancers, especially SCLC. PharmaMar recently presented promising updated data on Zepsyre in SCLC patients at ESMO in Madrid. The new data include Cohort B, which had a body surface area-based dose of Zepsyre (2mg/m^2) in combination with 40mg/m^2 of doxorubicin (DOX), as well as a single agent arm with Zepsyre at a 3.2mg/m^2 body surface area-based dose. In both the new arms, the response rate is much higher than the response rate typically seen with Topotecan (13-24%[3]). Importantly, in Cohort B, which has the same dose as that being used in the Phase III trial, PFS was 5.3 months, which is higher than the 3-4 months typically seen with Topotecan. The PFS in Cohort B, which featured body surface area-based dosing, was also higher than the PFS seen in Cohort A, which featured fixed dosing for patients.

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1 Sehouli et al., Topotecan Weekly Versus Conventional 5-Day Schedule in Patients With Platinum-Resistant Ovarian Cancer. *Journal of Clinical Oncology* 29, no. 2 (January 2011) 242-248.

2 Sacco et al., The Average Body Surface Area of Adult Cancer Patients in the UK. *PLoS One*. 2010; 5(1): e8933.

3 Garst et al., Topotecan: An evolving option in the treatment of relapsed small cell lung cancer. Therapeutics and Clinical Risk Management 2007:3(6) 1087-1095.

Exhibit 1: Zepsyre in SCLC

	Lurbinectedin + DOX (q3wk)		Lurbinectedin + TAX (q3wk)	Lurbinectedin single agent (q3wk)
	Cohort A L 3-5mg FD D1 + DOX 50mg/m² D1 (n=21)	Cohort B L 2mg/m² D1 + DOX 40mg/m² D1 (n=27)	L 2.2mg/m² D1 + TAX 80mg/m² D1 & D8 (n=7)	L 3.2mg/m² D1 (n=36)
Complete response rate (%)	10%	4%	14%	0%
Partial response rate (%)	57%	33%	57%	36%
Objective response rate (%)	67%	37%	71%	36%
Stable disease (%)	14%	33%	0%	39%
Progressive disease (%)	19%	30%	29%	25%
Disease control rate (%)	81%	70%	71%	75%
Duration of response (months)	4.5	5.2	2.3	6.2+
Progression free survival (months) - patients with chemotherapy free interval of >30 days	4.7	5.3	3.9	3.1+
Progression free survival (months) - platinum sensitive patients	5.8	6.2	3.9	4.6+

Source: PharmaMar, ESMO 2017. Note: L = lurbinectedin, DOX = doxorubicin, TAX = paclitaxel.

In August 2016, PharmaMar initiated the ATLANTIS trial, which is a multicentre, open-label, randomised Phase III trial in 600 patients with relapsed (second-line) SCLC following platinum-containing therapy. The primary endpoint is progression free survival (PFS) comparing patients treated with the combination of Zepsyre and doxorubicin to the control arm where patients are treated with either Topotecan or the CAV regimen, a combination of cyclophosphamide, adriamycin (the brand name for doxorubicin) and vincristine. Data from the ATLANTIS trial are expected in 2019.

Promising recent endometrial cancer data

Other than SCLC, Zepsyre has had promising data in endometrial cancer (EC), which were recently presented at the ASCO meeting held in Chicago on 2-6 June 2017. The ASCO data included four cohorts of endometrial cancer patients from three separate studies, who were treated with Zepsyre as a single agent or in combination with chemotherapy drugs.

In Cohort B (which used the regimen that will be used in the upcoming Phase III trial: Zepsyre at 2mg/m^2, doxorubicin at 40mg/m^2) of the Zepsyre plus doxorubicin Phase Ib trial, there was 44% response rate (8/18) and acceptable toxicity. Only three of the 18 subjects experienced disease progression, so the disease control rate (DCR) was a high 83%.

In Cohort A where patients received a fixed dose of 3-5mg Zepsyre in combination with 50mg/m^2 of doxorubicin every three weeks, there was a 28% ORR (4/14), including two patients who had a complete response rate. However, there was also a high incidence of myelosuppression, including febrile neutropenia in 40% of subjects (3/14). In other cohorts, the toxicity was more tolerable, with only 16% of subjects experiencing febrile neutropenia in Cohort B and 3.6% in the Zepsyre-only arm. Patients in the Zepsyre/doxorubicin trials had been treated with up to two lines of prior chemotherapy for advanced disease (median one prior line).

The 44% response rate seen in Cohort B of the Zepsyre/doxorubicin combination trial is a very encouraging outcome for a study in which all of the subjects were undergoing second-line chemo treatment where EC is largely a chemo-resistant disease.[4] Also, the platinum-free interval (PFI) in these patients was just 4.3 months, an interval associated with a low rate of response (the average response rate for those with a PFI of less than six months is 25% compared to 65% for patients with a PFI of greater than 24 months[5]). The 13% single agent response rate was also promising as typical single agent chemotherapy response rates for patients who received platinum therapy

[4] Colombo et al., Endometrial cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Annals of Oncology* (2013) 24 (suppl_6): vi33-vi38.

[5] Nagao et al., Applicability of the concept of "platinum sensitivity" to recurrent endometrial cancer., *Gynecologic Oncology* 2013 Dec; 131(3):567-73.

previously range from 4-13.5%.[6] The 7.7- to 7.8-month PFS seen in the Zepsyre/doxorubicin combination trial was also encouraging as PFS is typically closer to 3.2 months in similar patients.[7]

Exhibit 2: Activity of Zepsyre (lurbinectedin, PM01183) as single agent and in combination in patients with endometrial cancer

	L+DOX (q3wk)		L+TAX (q3wk)	L alone (q3wk)
Response (evaluable patients)	Cohort A L 3-5mg FD D1 + DOX 50mg/m² D1 (n=14)	Cohort B L 2mg/m² D1 + DOX 40mg/m² D1 (n=18)	L 2.2mg/m² D1 + TAX 80mg/m² D1 & D8 (n=11)	L 3.2mg/m² D1 (n=40)
CR	2 (14%)	-	-	1 (3%)
PR	2 (14%)	8 (44%)	3 (27%)	4 (10%)
ORR	4 (28%)	8 (44%)	3 (27%)	5 (12.5%)
SD	8 (57%)	7 (39%)	2 (18%)	15 (38%)
PD	2 (14%)	3 (16%)	6 (55%)	20 (50%)
DCR	9 (85%)	15 (83%)	5 (45%)	20 (50%)
DOR (months)	19.5	6.8	6.1	4.3+
PFS (months)	7.8	7.7	1.9	2.5+

Source: PharmaMar 2017 ASCO abstract 5586. Note: L = lurbinectedin; CR = complete response; D = day; DCR = disease control rate; DOR = duration of response; DOX = doxorubicin; FD = flat dose; ORR = overall response rate; PD = progressive disease; PFS = progression-free survival; PM = PM1183; PR = partial response; q3wk = every three weeks; SD = stable disease; TAX = paclitaxel.

PharmaMar plans to initiate a Phase III study of Zepsyre in EC. While the design has not been finalised, it is expected to have 500 patients who will either receive 2.0mg/m^2 of Zepsyre plus 40mg/m^2 of doxorubicin or 60mg/m^2 of doxorubicin with a primary endpoint of overall survival. The trial is expected to begin in H118.

The company is also planning a registrational trial in 116 BRCA2 mutated, HR-positive, HER2-negative metastatic breast cancer patients, which will be a single arm study in which patients would receive 3.5mg/m^2 of Zepsyre. That protocol is currently being finalised.

Valuation

We are decreasing our valuation from €1.84bn or €8.28/share to €1.35bn or €6.06/share as we have removed Zepsyre in ovarian cancer from our model. We have also delayed our expected EU launch timeline for Aplidin to 2021 from 2018 and reduced the probability of success to 30% from 90% due to a negative CHMP recommendation in Europe, which the company is appealing (a final decision is expected in the June/July time frame) as well as uncertainty regarding the future of the product. Otherwise, we are keeping our valuation the same. We have also updated our financial estimates by removing Aplidin sales from 2018. We will make a more complete update of financials and the valuation following the Q417 results report.

[6] Fleming et al., Second-Line Therapy for Endometrial Cancer: The Need for Better Options. *Journal of Clinical Oncology* 33, no. 31 (November 2015) 3535-3540.

[7] Nagao et al., Applicability of the concept of "platinum sensitivity" to recurrent endometrial cancer., *Gynecologic Oncology* 2013 Dec; 131(3):567-73.

Exhibit 3: PharmaMar sum-of-the-parts DCF

Product	rNPV (€m)	rNPV/ share (€)	Assumptions
Chemicals business FCF	131.2	0.59	7.5% WACC, 3% growth rate from 2019 onwards, accounts for 45% of group capex.
Yondelis (Europe)	578.6	2.60	Second-line soft-tissue sarcoma (STS) peak sales of €87m with 40% penetration; third-line ovarian cancer peak sales of €37m with 8% penetration into addressable platinum sensitive market. First potential generics in 2024. 10% WACC.
Yondelis (US)	146.6	0.66	STS (second-line) peak sales of $130m, launched 2016; peak sales in platinum-sensitive ovarian cancer of $50m, 65% risk adjustment, 2020 launch; both assume 15% royalty from J&J.
Yondelis (Japan)	24.1	0.11	STS only: peak sales of €34m; 15% royalty from Taiho. 10% WACC.
Aplidin (multiple myeloma)	52.9	0.24	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; 30% success probability in Europe, 30% in the US; launch in 2021 in the US and EU; 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 regulatory milestones out of €30m total Chugai milestones. No milestones included for other territories at this stage.
Zepsyre (SCLC)	691.8	3.11	Peak sales of €680m; US and EU: 65% success probability, 2020 launch sold direct in Europe and US; Japan: 50% success probability, 2022 launch, 20% royalty.
Zepsyre (breast – BRCA2 mutated)	136.8	0.62	Peak sales of €250m; 45% success probability; US and EU: 2021 launch – sold direct in Europe and US; Japan: 50% success probability, 2023 launch, 20% royalty.
Zepsyre (endometrial cancer)	211.6	0.95	Peak sales of €198m; US and EU: 65% success probability, 2022 launch sold direct in Europe and US; Japan: 50% success probability, 2023 launch, 20% royalty.
Zepsyre upfront and milestones	47.7	0.21	Chugai upfront €30m, plus Chugai Japan development milestones assumed to be €35m of ~€70m total potential Chugai milestone payments (assumed to average €7m/year over 2017-21), risked at 50-90%; no Chugai sales-based milestones or milestones for other territories included in our forecasts at this stage.
Sylentis	7.0	0.03	Cumulative peak sales of $200m, with 20% probability of success, potential launch 2021, 10% royalty.
Genomica	57.7	0.26	Conservative 2% growth rate.
R&D	(354.2)	(1.59)	12.5% WACC.
SG&A	(302.2)	(1.36)	10% WACC.
Capex	(17.6)	(0.08)	55% of group capex for biopharma business.
Net cash/(debt)	(66.4)	(0.30)	At Q317
Total	**1,346**	**6.06**	

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

Exhibit 4: Financial summary

€'000s	2015	2016	2017e	2018e
Year end 31 December	IFRS	IFRS	IFRS	IFRS
PROFIT & LOSS				
Revenue	161,992	164,035	171,235	184,043
Cost of Sales	(45,705)	(43,971)	(47,461)	(49,518)
Gross Profit	116,287	120,064	123,774	134,526
R&D Expenses (gross)	(63,549)	(79,780)	(76,797)	(78,615)
Capitalised in-house R&D	3,258	1,357	1,753	1,800
Sales, General and Administrative Expenses	(74,067)	(71,550)	(64,346)	(60,320)
Other (milestones and royalties)	31,825	16,913	22,563	41,210
EBITDA	17,578	(11,463)	924	32,517
Operating Profit (before amort. and except.)	11,297	(18,706)	(6,536)	24,833
Depreciation & Amortisation	(6,281)	(7,243)	(7,460)	(7,684)
Exceptionals	0	0	0	0
Operating Profit	11,297	(18,706)	(6,536)	24,833
Net Interest	(5,388)	(5,993)	(4,576)	(4,734)
Other	0	0	0	0
Profit Before Tax (norm)	5,909	(24,699)	(11,112)	20,099
Profit Before Tax (as reported)	5,909	(24,699)	(11,112)	20,099
Tax	654	592	0	0
Deferred tax	0	0	0	0
Profit After Tax (norm)	6,563	(24,107)	(11,112)	20,099
Profit After Tax (FRS 3)	6,563	(24,107)	(11,112)	20,099
Minority interests	25	25	0	0
Discontinued operations	0	0	(48)	0
Net income (normalised)	6,588	(24,082)	(11,112)	20,099
Net income (FRS3)	6,588	(24,082)	(11,160)	20,099
Average Number of Shares Outstanding (m)	222.2	222.2	222.2	222.2
EPS - normalised (c)	3.0	(10.8)	(5.0)	9.0
EPS - FRS 3 (c)	0.03	(10.8)	(5.0)	9.0
Dividend per share (c)	0.00	0.00	0.00	0.00
Gross Margin (%)	71.8%	73.2%	72.3%	73.1%
EBITDA Margin (%)	10.9%	-7.0%	0.5%	17.7%
Operating Margin (before GW and except.) (%)	7.0%	-11.4%	-3.8%	13.5%
BALANCE SHEET				
Fixed Assets	99,804	100,145	98,411	96,024
Intangible Assets	29,377	27,448	25,691	27,491
Tangible Assets	30,624	31,141	30,978	26,791
Other	39,803	41,556	41,742	41,742
Current Assets	112,135	120,992	108,114	115,240
Stocks	22,990	22,158	23,144	27,133
Debtors	40,200	62,652	44,259	42,859
Cash and current financial assets	45,625	32,367	35,357	39,894
Other	3,320	3,815	5,354	5,354
Current Liabilities	(70,623)	(87,164)	(84,697)	(79,883)
Creditors	(41,994)	(59,258)	(57,444)	(52,630)
Short term borrowings	(28,629)	(27,906)	(27,253)	(27,253)
Long Term Liabilities	(68,280)	(85,478)	(82,783)	(72,493)
Long term borrowings	(64,973)	(67,583)	(71,678)	(71,678)
Other long term liabilities	(3,307)	(17,895)	(11,105)	(815)
Net Assets	73,036	48,495	39,045	58,887
CASH FLOW				
Operating Cash Flow	10,195	(3,040)	11,562	14,568
Net Interest	252	(5,000)	(4,576)	(4,734)
Tax	654	(374)	0	0
Capex	(9,221)	(6,093)	(6,193)	(5,297)
Acquisitions/disposals	0	129	0	0
Financing	6,169	(632)	(979)	0
Other	0	0	0	0
Net Cash Flow	8,049	(15,010)	(187)	4,537
Opening net debt/(cash)	54,886	46,910	61,984	62,550
Exchange rate movements	0	0	0	0
Other	(73)	-64	-379	0
Closing net debt/(cash)	46,910	61,984	62,550	58,013

Source: PharmaMar accounts, Edison Investment Research

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