Topotarget

Restructuring and outlook for belinostat

Edison investment research

Time for BELIEF

Pharma & biotech

Data from the BELIEF study on Topotarget's key asset belinostat due in Q412 could transform the company's prospects. Positive data could lead to substantial milestones being received in H213 from its partner Spectrum Pharmaceuticals, belinostat being launched in the US in 2014 and the product potentially being partnered in Europe and Asia Pacific. Recent data from a Phase II study in cancer of unknown primary (CUP) was mixed, but still indicated that belinostat has anti-tumour activity. We value Topotarget at DKK909m and the BELIEF data could lead to a re-rating of the shares.

Year end	Revenue (DKKm)	PBT* (DKKm)	EPS* (DKK)	DPS (DKK)	P/E (x)	Yield (%)
12/10	107.8	(6.7)	1.01	0.0	1.1	N/A
12/11	65.6	(31.4)	(0.22)	0.0	N/A	N/A
12/12e	4.2	(82.5)	(0.62)	0.0	N/A	N/A
12/13e	3.8	(40.3)	(0.30)	0.0	N/A	N/A

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

Pivotal BELIEF data due in Q412

Topotarget expects to report data from the pivotal BELIEF study in peripheral T-cell lymphoma (PTCL) in Q412. This could result in Topotarget receiving a c $10m milestone and 1m Spectrum shares in H213 and the US launch of belinostat in 2014. There is a delay to the expected filing of belinostat by Spectrum, which seems to have been caused by Spectrum's acquisition of Allos Therapeutics rather than the progress of the BELIEF trial.

Phase II CUP data mixed but still shows promise

The Phase II trial in CUP failed to show that belinostat in combination with carboplatin and paclitaxel increased progression free survival, but clinical activity was indicated by a doubling of overall response rate (statistically significant) and a trend towards improved overall survival. There were only 89 patients in the trial and CUP is very heterogeneous. In total, the data indicates that belinostat has activity in solid tumours.

Strategic review to assess all options for Topotarget

Topotarget has asked ABG Sundal Collier, the Nordic investment bank, to conduct a strategic review to assess licensing and M&A options. The results will be presented in Q412. The decision by the board to conduct the review led to the resignation of Francois Martelet as CEO and the promotion of Anders Vadsholt from CFO. The resignation of CMDO, Axel Mescheder, is unrelated and due to personal reasons.

Valuation: DCF valuation of DKK909m

We have reduced our valuation by DKK111m to DKK909m, because of the mixed data from the Phase II CUP data. However, the current market cap is DKK142m and the shares could undergo a major re-rating in Q412 if data from the BELIEF trial are positive. The company has sufficient capital to operate into 2014, by which time it might have received the substantial milestone payments from Spectrum.

Topotarget is a research client of Edison Investment Research Limited

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Price	DKK1.07
Market cap	DKK142m

Shares in issue	132.7m
Free float	88%
Code	TOPO
Primary exchange	Copenhagen
Other exchanges	N/A

Share price performance

%	1m	3m	12m
Abs	(2.7)	(68.4)	(37.4)
Rel (local)	(3.1)	(72.1)	(56.4)
52-week high/low	DKK3.7	DKK1.0	

Business description

Topotarget is a Danish drug development company in the field of oncology. It is focused on developing belinostat with its partner Spectrum Pharmaceuticals.

Next events

BELIEF study data	Q412
Q312 results	21 November 2012

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Investment summary: Time for BELIEF

Company description: Danish oncology company

TopoTarget is a drug development and marketing company focused on oncology. It was founded in 2000 and listed on the Copenhagen Stock Exchange (now OMX) in 2005. Its headquarters are in Copenhagen and it has operations in the UK with c 17 employees. To date it has raised a total of DKK1.06bn in equity. It has taken one drug to market, called Totect in the US and Savene in Europe, which prevents tissue damage caused by anthracycline extravasation (leakage of blood vessels) following chemotherapy; Totect has since been sold to Apricus Biosciences and Savene to SpePharm Holding. It is now solely focused on developing belinostat, a histone deacetylase inhibitor (HDACi), which is in a pivotal Phase II (BELIEF) study in PTCL and has potential in other haematological cancers and solid tumours. The North American and Indian rights to the drug were out-licensed to Spectrum Pharmaceuticals in a deal worth c $350m in February 2010.

Valuation

We have reduced our valuation from DKK1,020m to DKK909m because of the mixed data from the Phase II study in CUP as we have reduced the probability of success to 40%. In comparison, the current market cap is DKK142m and the shares have fallen by over 70% since the announcement of the CUP data. Although there was no change in PFS between the belinostat and placebo arms, there were differences in ORR and OS, indicating that belinostat did enhance the activity of paclitaxel and chemotherapy, and CUP is a highly heterogeneous indication. Also, our view on the likely outcome of the pivotal BELIEF study is unchanged, as other HDACi, which do not have significant anti-tumour activity in solid tumours have been shown to be efficacious as monotherapy in PTCL and other haematological cancers.

Positive results from the pivotal BELIEF trial in PTCL in Q412 should act as a major catalyst and enable belinostat to be approved in 2013.

Sensitivities

The prospects of the company are linked to that of its lead drug, belinostat, and in the short term they are very sensitive to the results of the pivotal BELIEF study in PTCL. Positive results should lead to a major re-rating of the shares, a milestone payment of c $10m in H213 and the potential launch of belinostat in the US in 2014. They could also help Topotarget out-license the European/Asia Pacific rights to the product. Alternatively, the company will be dependent on Spectrum or another company believing in belinostat's potential in solid tumours despite the recent mixed data.

Financials

Topotarget had a net cash position of DKK70.8m at H112. Following the completion of the CUP study and the restructuring programme that is underway, we forecast that both R&D and administrative costs will be reduced significantly so that Topotarget should be able to operate beyond 2013. The company should receive a $2m (c DKK12m) milestone from Apricus for the technology transfer to a new manufacturer of Totect following the sale of the product in December 2011. If the data from the BELIEF study is positive, Topotarget could receive $10m in cash and 1m shares in Spectrum (currently worth c $12m) if the FDA accepts the NDA for belinostat and Topotarget might be able to out-license the European/Asia Pacific rights to belinostat.

Outlook: Time for BELIEF with belinostat

Topotarget's sole product, belinostat, is approaching a critical time in its development as data from the pivotal BELIEF clinical trial in PTCL is due in Q412. These results could lead to Topotarget receiving significant milestones in H213 and belinostat being launched in 2014. The Phase II trial in CUP did not meet its primary endpoint of progression free survival (PFS), but still indicated that belinostat has significant activity, so we remain optimistic about the outcome of the BELIEF study. Topotarget has also commissioned a strategic review to ensure all options for maximising the value of belinostat are considered. This led to the resignation of Francois Martelet as CEO, but reassuringly with the BELIEF data imminent Anders Vadsholt has stepped up from CFO to CEO. We value Topotarget at DKK909m and the BELIEF results could result in a major re-rating of the shares.

Options for belinostat are under review

Topotarget is carrying out a strategic review to explore alternative methods of maximising the value of the company. This process will include assessing out-licensing options for its key product belinostat in territories outside North America and India (Spectrum Pharmaceuticals licensed belinostat in these markets in a deal worth c $350m), M&A and potential sale of the company. ABG Sundal Collier, the Nordic investment bank, will be conducting the review and the results should be reported in Q412.

A potential catalyst for belinostat being out-licensed in Europe/Asia Pacific is data from the BELIEF study in PTCL in Q412. However, this trial is unlikely to be sufficient for approval in Europe as it is not placebo controlled. Companies could also be interested in the product's potential to treat solid tumours in combination with chemotherapy, despite the disappointing PFS data from the Phase II study in cancer of unknown primary (see below). A complication to any deal could be the licensing deal with Spectrum as a joint development plan would have to be agreed and Spectrum could not afford to pay for an extensive Phase III programme.

If Topotarget is able to out-license the European/Asia Pacific rights to belinostat, it would leave the company with a significant cash pile and potential royalty revenue streams. The company might then decide to invest this money in purchasing other oncology assets to develop or return the proceeds to investors.

Topotarget could look to be acquired by Spectrum or another company. If Spectrum bought Topotarget, it would gain full control of belinostat and be relieved of the potential obligation to pay Topotarget up to $313m and 1m shares in milestone payments and estimated royalties of c18%. Alternatively, another company might be willing to pay more for Topotarget to gain the European/Asia Pacific rights (possibly with a view to obtaining the North American rights from Spectrum).

We believe these are the main options that ABG Sundal Collier will consider. It could advise Topotarget to commercialise belinostat itself in Europe, but this is unlikely given the funds that would need to be raised to conduct Phase III trials in various solid tumours.

Following the board's decision to implement the strategic review, Francois Martelet's position as CEO became untenable and he resigned. Separate to this decision, Axel Mescheder is resigning as CMDO for personal reasons and because he will leave Topotarget once the work for the potential filing of belinostat in PTCL has essentially been completed. Anders Vadsholt has stepped up to CEO from CFO, but will retain his previous responsibilities, which suggests that he continues to be optimistic about the prospects for Topotarget and belinostat (including the open-label BELIEF study).

Exhibit 1: HDAC competitive summary

Drug / Company	Development stage	Notes
Vorinostat/ SAHA/ Zolinza **Merck & Co**	Approved (CTCL)	Main indications: CTCL (approved in US and Japan), MM (soon to be filed) Other indications: Lymphoma (only three active trials conducted by Merck & Co) Efficacy: CTCL: ORR 30% (n=74, mono), ORR 31% (n=33, mono); MM: median PFS 7.6 vs 6.8 mths, HR 0.774 (n=637, with bortezomib), ORR 26% SD 53% (n=34, comb); Renal: ORR 18%, SD 67% (n=32, comb); CRC: ORR 5%, SD 52% (n=21, comb); NSCLC: ORR 47% SD 42% (n=19, comb); prostate: no efficacy shown because of toxicities; MDS: no OS survival benefit, HR 0.98 (n=660, mono) Tolerability: Nausea, fatigue, thrombocytopenia, anaemia, no QT prolongation Approval date: 2006 (CTCL)
Depsipeptide/ romidepsin/ Istodax **Celgene**	Approved (CTCL, PTCL)	Main indications: CTCL (approved in US), PTCL (approved in US), MM Other indications: Melanoma, bladder, head & neck, GI, leukaemia (15 active trials) Efficacy: CTCL: ORR 35% (n=96+71, mono); PTCL :ORR 25% (n=130, mono); solid tumours: ORR 3%, SD 36% (n=33, comb); prostate: ORR 3% SD 6% (n=31, mono) Tolerability: Nausea, vomiting, fatigue and haematological AE (neutropenia, thrombocytopenia, anaemia), no QT prolongation observed Approval date: November 2009 (CTCL) Other: Obtained via acquisition of Gloucester Pharma. for $340m + $300m (milestones)
Panobinostat/ LBH589 **Novartis**	Phase III	Main indications: MM, HL (received a refusal to file received from FDA in January 2011) Other indications: CTCL, CML, B-cell lymphoma, (16 active trials sponsored by only Novartis) Efficacy: CTCL: ORR 16% (n=63, mono), prostate ORR 19% (n=16, comb), breast: ORR 11% (n=18, comb), ORR 7%, SD 27% (n=15, comb); MM: ORR 57% SD 23% (n=30, comb); SCLC: ORR 11% (n=19, mono) Tolerability: dyspnea, thrombocytopenia, nausea, QT prolongation Potential launch date: 2014
Belinostat / PXD101 **TopoTarget/ Spectrum**	Pivotal Phase II	Main indications: PTCL (SPA, FTA, orphan status), CUP, NSCLC Other indications: Thymic, bladder, ovarian, STS, MDS, AML, and others (17 active trials) Efficacy: PTCL: ORR 32% (n=19, mono); ovarian: ORR 54% (n=35, comb.); bladder cancer: ORR 27%, SD 67% (n=16, comb); thymic ORR 54% (n=13, comb), solid tumours: ORR 9%, SD 64% (n=23, comb) and ORR 0%, SD 64% (n=92, mono); lymphoma: ORR 7%, SD 72% (n=28, mono) MDS: ORR 5% (n=21, mono), AML/MDS: ORR 32% (n=56, comb) Tolerability: Nausea, vomiting and fatigue with limited haematological AE; can be taken at recommended dose in combination with chemotherapy Potential launch date: 2014 for PTCL Other: North American and Indian rights acquired by Spectrum in $350m deal + royalties
Entinostat/ MS-245 **Syndax**	Phase II	Main indications: HL Other indications: Breast, NSCLC, Efficacy: NSCLC: ORR 10% SD 20% (n=10, comb); breast: ORR 4%, SD 4% (n=27, comb) Tolerability: Nausea, fatigue, diarrhoea, cytopenias Potential launch date: 2016 Other: Acquired from Bayer Schering Pharma AG in April 2007
Resminostat/ 4SC-201 **4SC**	Phase II	Main indications: Hodgkin's lymphoma (monotherapy), HCC (with sorafinib) Other indications: CRC (with FOLFIRI) Efficacy: HL: ORR 33.3%; HCC (with sorafinib): median PFS 4.7mths vs c two mths in historic trials Tolerability: Nausea, vomiting, fatigue, well tolerated (Phase I, n=19) Potential launch date: 2017
Mocetinostat/ MGCD0103 Methylgene/ **Taiho**	Phase II	Main indications: HL, CLL, AML, MDS Other indications: - Efficacy: HL: ORR+SD 35% (n=23, mono), AML: ORR 29% (n=24, comb) Tolerability: Fatigue, diarrhoea, nausea, thrombocytopenia, neutropenia, anaemia, pericardial SAE Potential launch date: 2017
Abexinostat/ PCI-24781 **Pharmacyclics/ Servier**	Phase I/II	Main indications: Sarcoma, B-cell lymphoma Other indications: solid tumours (4 active trials) Efficacy: Lymphoma: ORR 31% SD 44% (n=16, mono) Tolerability: Fatigue, nausea, few incidence of thrombocytopenia and anaemia Potential launch date: 2017 Other: Partnership with Servier for ex-US development worth $39m in payments
CHR-2845 **Chroma Therapeutics**	Phase I	Main indications: Haematological tumours (Phase I completed) Potential launch date: 2018
CHR-3996 **Chroma Therapeutics**	Phase I	Main indications: Solid tumours (Phase I completed) Potential launch date: 2018

Source: Edison Investment Research; Note: Active trials are the clinical trials that are active according to clinicaltrials.gov.

Belinostat

Topotarget is solely focused on developing belinostat, which has commercial potential as a treatment of both haematological cancers and solid tumours. Data from the pivotal BELIEF study in PTCL due in Q412 could lead to an NDA being filed with the FDA and belinostat being launched in 2014. If there is a positive outcome to the BELIEF study, the product will probably be developed for other haematological cancers and the solid tumour programme could be expanded.

Belinostat is believed to have an anti-tumour effect via several mechanisms of action. It is a pan HDACi, meaning that it inhibits the activity of several HDAC enzymes (there are four classes of HDACs and at least 11 different HDACs – excluding the sirtuins, Class III HDACs). Thus belinostat's effect on tumour cells is probably because of its effect on:

- the organisation of DNA (via histones);
- the stability of microtubules (via α-tubulin); and
- the activity of many other proteins, including P53 and HSP90.

Through each of these mechanisms the drug could have a direct effect on cancer cells or make them more sensitive to the activity of other chemotherapy agents.

There are c 10 HDACi in clinical development or on the market (Exhibit 1). The most advanced drugs in this class are Celgene's romidepsin (Istodax, approved in cutaneous T-cell lymphoma [CTCL] and PTCL), Merck & Co's vorinostat (Zolinza, approved in CTCL) and Novartis's panobinostat (Phase III studies for multiple myeloma, CTCL and Hodgkin's lymphoma). Belinostat is being targeted at a haematological cancer initially, as these other HDACi have demonstrated their potential in these indications. It also has potential in combination with chemotherapy to treat solid tumours, unlike these other drugs, as it appears to have a better safety profile. However, other HDACi in development, such as 4SCs resminostat, have potential in solid tumours.

The composition of matter patents for belinostat are valid until 2021, but there are formulation and manufacturing patent applications pending that could provide additional protection.

PTCL and other haematological cancers

Data from the pivotal open-label BELIEF clinical trial in PTCL should be reported in Q412 (Exhibit 2). The study needs to demonstrate an overall response rate (ORR) of >20% (as agreed in a Special Protocol Assessment or SPA); there is no active comparator in the trial. An ORR of 31.6% was observed in the CLN-6 Phase II trial (n=19). If this is achieved, Spectrum should start submitting a rolling NDA in Q412/Q113, which should be completed in H113. There has been an approximate six-month delay to the filing of belinostat caused by the acquisition of Allos Therapeutics by Spectrum. However, belinostat could still be approved for the treatment of PTCL in H114.

If belinostat is approved, it will probably face most competition from romidepsin as they are both HDACi (other treatments for PTCL include gemcitabine, pralatrexate – Folotyn – and various combination therapies such as CHOP, HyperCVAD, DHAP, ESHAP, GDP and GemOx). Romidepsin will benefit from the marketing power of Celgene and from being on the market before belinostat, but if belinostat has a better safety profile and shows comparable efficacy, it could gain market share.

However, the potential positioning of belinostat will be affected by Spectrum's acquisition of Allos Therapeutics, whose only marketed product is pralatrexate (Folotyn). Spectrum has stated that it is still committed to belinostat, if this remains the case both products will probably be marketed as alternative treatments and it might be investigated if the two drugs can be used as a combination therapy. We currently estimate that belinostat could achieve sales of $72m in PTCL.

Exhibit 2: Ongoing and selected completed clinical trials of belinostat in haematological cancers

Trial	Indication	Comments
BELIEF, CLN-19 (Pivotal Phase II)	Relapsed or refractory PTCL (monotherapy)	Ongoing (n=120), results expected H212. 1,000mg/m^2 by 30min iv infusion on days 1-5 of 21-day cycle. Primary endpoint is overall response rate of 20% in 100 evaluable pts. No active comparator. Started December 2008. Spectrum expected to start rolling NDA Q412/Q113 (Fast-track designation). Funded by Spectrum.
NCI 7285 Phase I/II	AML/MDS (+azacitidine)	Ongoing (n=56). Dose escalation study with iv belinostat in combination with azacitidine. Primary endpoint to identify MTD with tumour response a secondary endpoint, started June 2006. Preliminary results: 1,000mg/m^2 well tolerated with no MTD identified, 6 CR, 2 marrow CR, 1 PR, 8 haematological improvement. Carried out in collaboration with NCI.
Virginia Group/ MCC-12517 Phase I	Relapsed and refractory acute leukaemia and MDS (+bortezomib)	Ongoing (n=24), results expected H113. Dose escalation study. IV over 30 min on days 1-5 and 8-12 and bortezomib IV on days 1, 4, 8 and 11 on 21-day cycle for up to 12 cycles in the absence of disease progression or unacceptable toxicity, started June 2010. Primary objective to identify dose for Phase II together with safety and tolerance. Carried out in collaboration with Virginia Commonwealth University and MD Anderson.
TT30 Phase I	Haematological neoplasia (monotherapy)	Completed (n=16). Dosing of 600, 900 and 1,000mg/m^2 iv over 30 min on days 1-5 of 21-day cycle. Nausea, vomiting and fatigue were the most common AE, two Grade 4 AE of renal failure in two pts with MM, 1 haematological Grade 3 AE (lymphopenia), no cardiac AE. 0 CR; 0 PR; 6 SD and 2 achieved disease stabilisation during 5 and 9 cycles. Funded by Topotarget.
301-G Phase II	Advanced myeloma (± dexamethasone)	Completed (n=25). Open-label, non-randomised study in patients who had failed two previous therapies, non-responders to monotherapy were given dexamethasone. 9 SD on monotherapy, 10 patients on combination therapy of which 2 PR and 2 MR. Funded by Topotarget.
CLN-6 Phase II	Recurrent/ refractory CTCL/PTCL (monotherapy)	Completed (n=53; evaluable patients: CTCL n=28; PTCL n=19). Open-label, non-randomised study, 1,000mg/m^2 iv over 30min on days 1-5 of 21 day cycle. Nausea, vomiting, diarrhoea and fatigue most common AE, 1 Grade 3/4 AE of thrombocytopenia. CTCL efficacy: 2 CR; 2 PR; 18 SD (n=28). PTCL efficacy: 2 CR; 4 PR; 4 SD (n=19). Funded by Topotarget.
NCI 7258 Phase II	MDS (monotherapy)	Completed (n=21). Dosing of 1,000mg/m^2 iv over 30 min on days 1-5 of 21-day cycle for 4 cycles. Grade 3/4 AE possibly related to belinostat: neutropenia (10 pts); thrombocytopenia (9 pts); anaemia (5 pts). ORR 5% (1 pt). Trial not extended by 29 pts as ORR <3 pts. Carried out with NCI.

Source: Edison Investment Research; Note: There are also Phase I trials with warfarin, with an oral version of belinostat in solid tumours and lymphomas and one in patients with hepatic dysfunction (Exhibit 6).

Belinostat also has the potential to treat a wide range of haematological cancers, but clinical trial and commercial considerations will probably limit the indications that Topotarget and Spectrum will choose to pursue. For example, there are c 10 products in Phase III trials for multiple myeloma (c 20,000 new cases in the US pa), of which two are HDACi (panobinostat and vorinostat); this competition contributed to Topotarget terminating two clinical trials in this indication (CLN-5, CLN-16) because of difficulty recruiting patients.

Belinostat has a better safety profile than most HDACi and could be developed to be taken in combination with standard-of-care chemotherapy regimens to treat various haematological cancers. However, Topotarget and its partner will probably only target a limited number of these indications due to the reasons mentioned above and the fragmented nature of the haematological oncology market.

Topotarget has indicated that it might target myelodysplastic syndromes (MDS) and acute myeloid leukaemia (c 13,000 new cases in the US pa in both indications). It could pursue these indications with belinostat as a monotherapy or in combination with standard-of-care chemotherapy regimens (eg cytarabine/fludarabine ± daunorubicin/idarubicin or azacitidine). But the further development of belinostat in other haematological indications is probably dependant on positive data from the BELIEF study in PTCL.

Solid tumours

The commercial potential of belinostat is greater in solid tumours than it is in haematological cancers. There is less potential competition from other HDACi in these indications as their anti-tumour effects appear to be limited by the dose at which they can be tolerated, either as monotherapy or in

combination with other chemotherapy regimens. These cancers also affect many more people (c 190,000 new cases of non-small cell lung cancer pa in the US). Belinostat has the potential to become an important adjuvant treatment for many solid tumours, sensitising tumour cells to other chemotherapy drugs and has already been shown to have activity in many tumour types (Exhibit 7).

However, Topotarget recently reported mixed results from the Phase II study in CUP in combination with carboplatin and paclitaxel. But CUP is a highly heterogeneous indication and the size of the trial means that it should only be viewed as an exploratory trial. No difference was seen in PFS, the primary endpoint, despite a doubling in ORR in the belinostat arm (statistically significant, p=0.025) and the duration of response being the same between the two arms (Exhibits 3-5). There was an increase in median overall survival of 2.6 months, (the difference is not significant but the trial was not powered to detect one) and there is a clear separation of the Kaplan-Meier for overall survival after c nine months. Also there was a non-significant increase in time to progression or change of therapy of 2.2 months in the belinostat arm. Overall, the data supports the hypothesis that belinostat enhances the activity of carboplatin and paclitaxel in CUP, even though the primary endpoint of PFS was not met.

Exhibit 3: Results of the Phase II study in CUP (intent-to-treat population)

Efficacy measure	Trial objective	BelCaP (Arm A) (N=44)	CaP (Arm B) (N=45)	p-value	Hazard ratio
Median PFS, month	Primary	5.4	5.3	0.553	1.034
Median OS, months	Secondary	11.5	9.1	0.291	0.861
Objective Response Rate, n (%)	Secondary	19 (43%)	10 (22%)	0.025	2.850
Complete Response		3 (6.8%)	3 (6.7%)	-	-
Partial Response		16 (36%)	7 (16%)	-	-

Exhibit 4: PFS in Phase II study in CUP (ITT population)

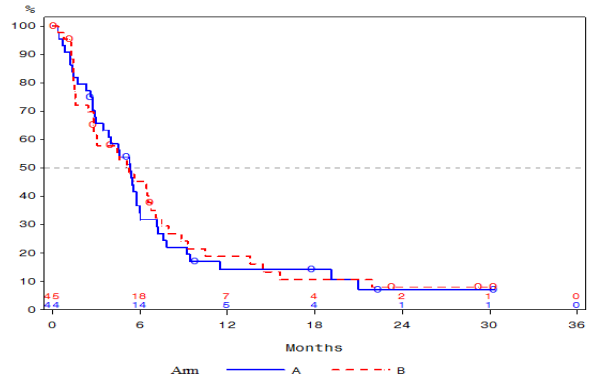
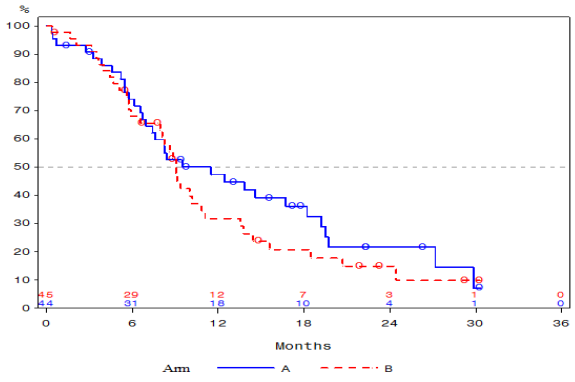


Exhibit 5: OS in Phase II study in CUP (ITT population)



Source: Topotarget; Note: BelCaP is belinostat, carboplatin and paclitaxel combination therapy; CaP is carboplatin and paclitaxel therapy; ITT population is intent-to-treat population.

If Topotarget and Spectrum decide to continue with the development of belinostat in CUP, the product could have considerable commercial potential as there are no approved therapies in this indication, and the prognosis for patients with this disease is poor. Also a large number of people are diagnosed with CUP each year (30,000-90,000 new cases pa in the US), although this is expected to fall as molecular diagnostics improve, allowing better classification of tumour origin. We estimate that it could achieve peak sales of $540m in this indication. However, two large Phase III studies might be required to demonstrate that belinostat in combination with paclitaxel and carboplatin does significantly improve survival in CUP because of the heterogeneity of the disease.

Exhibit 6: Ongoing and selected completed clinical trials of belinostat in solid tumours

Trial	Indication	Funding	Comments
CLN-14 Phase I/II trial	Solid tumours/ STS (+doxorubicin)	30% Topotarget 70% Spectrum	Ongoing (n=65), results from Phase I stage expected shortly. Phase I dose escalation trial with iv belinostat with doxorubicin (completed), followed by Phase II trial with iv belinostat being given to 40 pts at MTD to assess tumour response.
SPI-1014-Bel Phase I/II trial	NSCLC (+carboplatin +paclitaxel)	30% Topotarget 70% Spectrum	Ongoing (n=15), estimated completion date in H113. MTD study, followed by efficacy and tolerability trial (n=20); iv belinostat on days 1-5 of 21-day cycle with carboplatin and paclitaxel on day 3; during Phase II stage, pts will be treated at MTD to assess PFS and ORR. Trial began March 2011.
NCI 8174 Phase II trial	Thymoma/ thymic carcinoma (monotherapy)	Collaboration with NCI	Ongoing (n=41), estimated completion date is June 13. Belinostat 1,000mg/m^2 iv delivered over 30 min on days 1-5 of 21-day cycle for 12 courses, patients had recurrent or metastatic tumours. No active comparator. Preliminary results report that belinostat was well tolerated and that 2 PR and 25 SD were observed.
CLN-20 Phase I	Solid/ haem-atological cancers (+warfarin)	Co-sponsored (Topotarget/ Spectrum)	Ongoing (n=24), data expected in H113. Trial to study PK and PD of belinostat in combination with warfarin to support filing activities. Safety and efficacy of belinostat will also be evaluated.
NCI 8602 Phase I/II trial	Thymoma/thymic carcinoma (+cisplatin+cyclo -phosphamide +doxorubicin)	Collaboration with NCI	Ongoing, estimated completion date February 2013. 1st line treatment of advanced or recurrent thymoma/thymic carcinoma (n=58). Phase I dose escalation study, Phase II study (n=37) at MTD. Primary endpoint of Phase I part to determine MTD; primary endpoint of Phase II part is clinical response. Preliminary results: 54% ORR (n=13). Trial began March 2010.
NCI 8238 Phase I	SCLC/other cancers (+cisplatin +etoposide)	Collaboration with NCI	Ongoing, expected completion date is December 2013. Dose escalation study with iv belinostat in combination with cisplatin and etoposide, 44 pts. Primary endpoint to identify a safe and tolerable dose. Started June 2009.
NCI 7251 Phase I	Advanced solid tumours (+isotretinoin)	Collaboration with NCI	Ongoing, estimated completion date is December 2012. Trial (n=36) to identify safety and tolerability of belinotstat in combination with isotretinoin and MTD.
NCI 8846 Phase I	Solid tumours/ lymphomas	Collaboration with NCI	Ongoing study in patients with hepatic dysfunction (n=80), estimated completion date is December 2012. Primary endpoint to identify a safe and tolerable dose in patients with hepatic dysfunction.
CLN-17 Phase II trial	CUP (+carboplatin +paclitaxel)	100% Topotarget	Recruitment completed (n=89). Open-label, two-arm, randomised trial with iv and oral belinostat. Fatigue and nausea most common AEs and there was higher incidence of thromboembolic events (not significant) in BelCaP arm. Median PFS was 5.4 vs 5.3 mths, median OS was 11.5 vs 9.1 months (non-significant) and ORR was 43% vs 22% (p=0.025) in BelCaP and CaP arms respectively.
CLN-9 Phase I	Solid tumours/ lymphomas (monotherapy, oral formulation)	30% Topotarget 70% Spectrum	Completed (n=120; 92 pts with solid tumours and 28 with lymphoma). Fatigue, nausea, anorexia, diarrhea and vomiting most common AEs. One sepsis (fatal) and one Grade 4 embolic stroke assessed as related to belinostat. Solid tumour efficacy: 59 (64%) SD. Lymphoma efficacy: 1 CR; 1 PR; 20 (72%) SD.
NCI 7237 Phase I/II trial	Hepatocellular cancer (monotherapy)	Collaboration with NCI	Completed (n=66. Phase I dose escalation study (n=24) with iv belinostat in 24 pts showed that 1,400mg/m^2 was the MTD. Preliminary results from Phase II study (n=42) at MTD showed PFS of 2.64mths, OS of 6.60mths and belinostat was generally well tolerated although 2 pt experienced prolonged QTc.
CLN-8/040 Phase I/II trial	Advanced cancer/ ovarian/ bladder cancer (+carboplatin +/- paclitaxel)	Topotarget	Completed (n=85). Open-label, non-randomised study. In Phase I dose escalation (n=27) belinostat tolerated up to 1,000mg/m^2 day 1-5. In Phase II (ovarian [n=35], bladder [n=16], and refractory solid tumours [n=7]), belinostat generally well tolerated, but 3 pts discontinued (2 cardiac ischemia, 1 abnormal liver parameters). Ovarian cancer: ORR 54% (3 CR, 16 PR), 9 SD; 48% PFS at 6 month. 6 month PFS was 62% in patients sensitive to most recent platinum treatment vs 40% for platinum resistant patients. Bladder cancer: ORR 27% (1 CR, 3 PR), 10 SD.
NSCLC Phase I/II trial	+erlotinib	Herlev Hospital, Copenhagan	Terminated, MTD reached (gastrointestinal side effects), Phase I dose escalation (3+3 trial design) in 58 pts. Primary endpoint: safety and establishment of MTD.
HCH003 Phase I/II trial	NSCLC (+carboplatin +paclitaxel +bevacizumab)	Collaboration with Holy Cross Hospital, Florida	Terminated, principal investigator left institution. It was a Phase I dose escalation study to establish MTD, which would have been used during Phase II of trial (n=28).
GOG/ NCI 0126T Phase II trial	Pt- resistant ovarian cancer (+carboplatin)	Collaboration with GOG/NCI	Terminated. Single arm, Simon's two-stage design, 51 pts. Insufficient activity observed during first stage of trial, leading to termination of study.

Source: Edison Investment Research

Alternatively, Topotarget and Spectrum might decide to target other solid tumours in which it should be easier to demonstrate the efficacy of belinostat as they are more homogeneous. They will also probably focus on cancers which are routinely treated with carboplatin and paclitaxel (Exhibit 7). Such cancers include NSCLC, ovarian and bladder cancer. There is already a Phase I/II trial (SPI-1014-Bel) ongoing in NSCLC to investigate the maximum tolerated dose in this indication and CLN-8/040 indicated that belinostat enhances the activity of carboplatin and paclitaxel in both ovarian and bladder cancer. The GOG/NCI 0126T Phase II trial in platinum-resistant ovarian cancer failed to demonstrate sufficient activity to be completed, but this trial did not include paclitaxel.

Exhibit 7: Main chemotherapy regimens for various oncology indications

Cancer	Line of care	Treatment
Bladder	First	Gemcitabine/cisplatin (preferred)
	First	MVAC (methotrexate, vinblastine, doxorubicin and cisplatin)
	First	Carboplatin
	Others	Include carboplatin/paclitaxel; fluorouracil/cisplatin; pemetrexed; doxorubicin (vinflunine)
Colorectal	First	FOLFOX (leucovorin/fluorouracil/oxaliplatin)
	First	FOLFIRI (leucovorin/fluorouracil/irinotecan)
	First	Capecitabine
	Others	Include oxaliplatin/capecitabine, leucovorin/fluorouracil; oxaliplatin/irinotecan
CUP	(adenocarcinoma)	Paclitaxel/carboplatin ± etoposide
	(adenocarcinoma)	Docetaxel/carboplatin
	(adenocarcinoma)	Gemcitabine/cisplatin
	(adenocarcinoma)	Gemcitabine/docetaxel
	(squamous cell carcinoma)	Fluorouracil/cisplatin + paclitaxel or docetaxel
Ovarian	First	Paclitaxel/cisplatin
	First	Docetaxel/carboplatin
	Others	Include paclitaxel/carboplatin; gemcitabine/carboplatin; carboplatin/doxorubicin
NSCLC	First	Paclitaxel/carboplatin (most common in US)
	First	Gemcitabine/cisplatin (most common in Europe)
	First	Gemcitabine/paclitaxel
	First	Pemetrexed/cisplatin
	First	Docetaxel/cisplatin
	Second	Docetaxel, erlotinib
	Others	Include paclitaxel/cisplatin; cisplatin/vinorelbine; cisplatin/etopiside, pemetrexed
Pancreatic	First	Gemcitabine ± erlotinib
	Others	Include gemcitabine/capecitabine, gemcitabine/cisplatin, FOLFIRINOX

Source: Edison Investment Research. Note: Many targeted therapies are used to treat various cancers, eg bevacizumab is approved for the treatment of colorectal cancer, non-squamous NSCLC, glioblastoma and renal cell carcinoma.

The further development of belinostat in solid tumours is probably dependent on the results of the BELIEF study in PTCL and Topotarget finding a European/Asia Pacific partner. The latter is needed because of the funding requirements to carry out the necessary clinical trials, as Topotarget's cash resources are not currently sufficient to fund more clinical trials, let alone a significant Phase III programme. Thus Topotarget ideally needs to out-license the European/Asia Pacific rights to belinostat (possibly with a co-promotion option) to a major pharmaceutical company. This is made more challenging because Spectrum has the North American rights, unless it is willing to enter a sub-licensing agreement with Topotarget's potential European/Asia Pacific partner, since Spectrum would only be able to make a very limited contribution to the kind of Phase III programme that a major pharmaceutical company would like to conduct with belinostat. This is particularly the case, if Spectrum wanted to investigate the efficacy of belinostat across different cancers in combination with various chemotherapy regimens, other than only carboplatin and paclitaxel (Exhibit 7).

Sensitivities

The key sensitivity for Topotarget is the data from the BELIEF study in PTCL. If the ORR is greater than 20%, the shares should undergo a major re-rating, Spectrum will probably submit an NDA for the approval of belinostat, which could result in a significant milestone payment being received (c $10m) in H213. Alternatively, if the ORR is less than 20%, Topotarget's prospects are dependent on Spectrum or another company believing in the potential of belinostat to treat solid tumours, despite the recent mixed data from the CUP Phase II trial.

Other issues that will affect the company are its ability to partner the European rights to belinostat, its development programme in other cancers, pricing of belinostat (romidepsin costs c $23,000 per month and vorinostat c $10,000 per month) and changes in the competitive landscape for HDACi.

Valuation

Our DCF valuation has been decreased from DKK1,020m to DKK909m, mainly because of changing the risk adjustment for belinostat in CUP from 50% to 40%, and delaying the potential launch dates for the product in PTCL and CUP by a year. The main assumptions for our valuation are shown in Exhibit 8 and we continue to forecast peak sales of $1.2bn for belinostat.

Exhibit 8: Main assumptions for valuation of TopoTarget

Product	Launch date	Peak sales	Risk adjustment	Market penetration	Royalty
Belinostat in PTCL	2014	$72m	60%	15%	18%
Belinostat in CUP	2016	$540m	40%	15%	18%
Belinostat in NSCLC	2017	$560m	40%	5%	18%

Source: Edison Investment Research; Note: WACC of 12.5% used.

The shares fell by c 65% following the announcement that the Phase II trial in CUP had failed to increase PFS, although overall there was a promising efficacy signal after taking into account the size of the trial and heterogeneity of CUP. They have since drifted further to DKK142m. The catalyst for a major re-rating of the shares is data from the BELIEF study in PTCL.

Financials

Topotarget should have sufficient cash to operate into FY14, by which time it might have received a milestone of c $10m and 1m Spectrum shares currently worth c $12m from Spectrum on acceptance of the NDA filing. This assumes that R&D and administrative costs are reduced by 78% to DKK10m and 18% to DKK33m respectively in FY13. We also expect Topotarget to receive $2m (c DKK12m) in H113 from Apricus on completion of technology transfer to a new manufacturer of Totect (Apricus acquired Totect in December 2011). Changes to our forecasts are shown in Exhibit 9. The reduction in R&D spending should not affect the potential of belinostat as Spectrum is mainly responsible for costs.

Exhibit 9: Summary of changes to estimates

	Sales			PBT			EPS		
	Old	New	% chg.	Old	New	% chg.	Old	New	% chg.
2012e	2.4	4.2	73.7	(82.8)	(82.5)	N/A	(0.62)	(0.62)	N/A
2013e	2.2	3.8	73.7	(78.0)	(40.3)	N/A	(0.59)	(0.30)	N/A

Source: Edison Investment Research; Note: Revenues relate to work reimbursed by Spectrum. Figures in DKKm except per share data.

Exhibit 10: Financial summary

DKK'000s	2009	2010	2011	2012e	2013e
Year end 31 December	IFRS	IFRS	IFRS	IFRS	IFRS
PROFIT & LOSS					
Revenue	**43,979**	**107,826**	**65,598**	**4,231**	**3,808**
Cost of Sales	(10,125)	(5,442)	(1,840)	(1,179)	(952)
Gross Profit	33,854	102,384	63,758	3,052	2,856
EBITDA	**(106,756)**	**(3,810)**	**(28,041)**	**(81,262)**	**(38,680)**
Operating Profit (before GW and except.)	**(132,491)**	**(8,002)**	**(31,352)**	**(83,557)**	**(40,662)**
Intangible Amortisation	0	0	0	0	0
Exceptionals	0	(189,541)	0	0	0
Operating Profit	**(132,491)**	**(197,543)**	**(31,352)**	**(83,557)**	**(40,662)**
Net Interest	978	1,288	(13)	1,102	358
Other financial income	(11,229)	67,485	1,100	0	0
Profit Before Tax (norm)	**(131,513)**	**(6,714)**	**(31,365)**	**(82,455)**	**(40,304)**
Profit Before Tax (FRS 3)	**(142,742)**	**(128,770)**	**(30,265)**	**(82,455)**	**(40,304)**
Tax	2,277	43,985	1,253	0	0
Discontinued operations	0	29,096	(3,999)	0	12,000
Profit After Tax (norm)	**(140,465)**	**133,852**	**(29,012)**	**(82,455)**	**(40,304)**
Profit After Tax (FRS 3)	**(140,465)**	**(55,689)**	**(33,011)**	**(82,455)**	**(28,304)**
Average Number of Shares Outstanding (m)	99.5	132.6	132.7	132.7	132.7
EPS - normalised (DKK)	(1.41)	1.01	(0.22)	(0.62)	(0.30)
EPS - FRS 3 (DKK)	(1.41)	(0.42)	(0.25)	(0.62)	(0.21)
Dividend per share (DKK)	0.00	0.00	0.00	0.00	0.00
Gross Margin (%)	77.0	N/A	N/A	N/A	N/A
EBITDA Margin (%)	N/A	N/A	N/A	N/A	N/A
Operating Margin (before GW and except.) (%)	N/A	N/A	N/A	N/A	N/A
BALANCE SHEET					
Fixed Assets	**440,300**	**242,680**	**235,197**	**234,124**	**234,163**
Intangible Assets	431,885	235,717	229,626	229,549	229,549
Tangible Assets	7,044	5,991	4,963	3,949	3,988
Other	1,371	972	608	626	626
Current Assets	**145,113**	**223,143**	**135,279**	**43,598**	**17,093**
Stocks	1,944	1,625	0	0	0
Debtors	6,758	15,537	11,209	9,273	8,346
Cash	130,145	205,068	124,070	34,325	8,747
Other	6,266	913	0	0	0
Current Liabilities	**(58,920)**	**(91,489)**	**(26,163)**	**(23,741)**	**(23,119)**
Creditors	(37,299)	(16,868)	(16,274)	(3,230)	(2,608)
Short term borrowings	0	0	0	0	0
Other	(21,621)	(74,621)	(9,889)	(20,511)	(20,511)
Long Term Liabilities	**(114,695)**	**(14,116)**	**(13,585)**	**(3,248)**	**(3,248)**
Long term borrowings	0	0	0	0	0
Other long term liabilities	(114,695)	(14,116)	(13,585)	(3,248)	(3,248)
Net Assets	**411,798**	**360,218**	**330,728**	**250,733**	**224,889**
CASH FLOW					
Operating Cash Flow	**(104,807)**	**27,602**	**(92,435)**	**(80,854)**	**(23,915)**
Net Interest	1,231	12,500	2,335	2,141	358
Tax	4,377	0	1,253	0	0
Capex	2,016	(1,633)	(2,283)	(1,264)	(2,021)
Acquisitions/disposals	0	35,920	0	0	0
Financing	119,095	138	0	0	0
Dividends	0	0	0	0	0
Other	550	399	364	0	0
Net Cash Flow	22,462	74,926	(90,766)	(79,977)	(25,578)
Opening net debt/(cash)	**(107,998)**	**(130,145)**	**(205,068)**	**(124,070)**	**(34,325)**
HP finance leases initiated	0	0	0	0	0
Other	(315)	(3)	9,768	(9,768)	0
Closing net debt/(cash)	**(130,145)**	**(205,068)**	**(124,070)**	**(34,325)**	**(8,747)**

Source: Edison Investment Research

Contact details	Revenue by geography
Symbion Science Park Fruebjergvej 3 2100 Copenhagen 0, Denmark +45 39 17 83 92 www.topotarget.com	N/A

CAGR metrics		Profitability metrics		Balance sheet metrics		Sensitivities evaluation	
EPS 09-13e	N/A	ROCE 12e	N/A	Gearing 12e	N/A	Litigation/regulatory	●
EPS 11-13e	N/A	Avg ROCE 09-13e	N/A	Interest cover 12e	N/A	Pensions	○
EBITDA 09-13e	N/A	ROE 12e	N/A	CA/CL 12e	N/A	Currency	◖
EBITDA 11-13e	N/A	Gross margin 12e	N/A	Stock turn 12e	N/A	Stock overhang	○
Sales 09-13e	N/A	Operating margin 12e	N/A	Debtor days 12e	N/A	Interest rates	○
Sales 11-13e	N/A	Gr mgn / Op mgn 12e	N/A	Creditor days 12e	N/A	Oil/commodity prices	○

Management team

CEO: Anders Fink Vadsholt	Chairman: Bo Jesper Hansen
Joined as CFO in April 2010 and became CEO in August 2012. He worked at BankInvest Biomedical Venture, a shareholder of TopoTarget (2005-10) and has been the CFO of many smaller companies as well as an investment banker.	Joined the board in 2009. From 1998-2010, he was CEO and president of Swedish Orphan International (SOI). SOI was acquired by Biovitrum AB for SEK3.5bn in January 2010 and Mr Hanson is now the chairman for Swedish Orphan Biovitrum. He is also a medical doctor.
VP business development: Inge Holm Lauritzen	**Director of pharmaceutical operations: Elisabeth Carstensen**
Joined in December 2010. Previously, she was Director, biopharma partnering at Novozymes and has also worked at H. Lundbeck and Boehringer Mannheim.	Joined in 2000 and has held a number of positions at Topotarget. She has a PhD in chemical engineering from Technical University of Denmark.

Principal shareholders	(%)
Avanza Bank Holding AB	6.4
HealthCap AB	5.5

Companies named in this report

4SC (VSC), Celgene (CELG), Chroma Therapeutics, Merck & Co (MRK), Methylgene (MYLGF), Novartis (NOVN), Pharmacyclics (PCYC), Servier, Spectrum Pharmaceuticals (SPPI)