

Company update

United Kingdom

# Antisoma

Well-funded, late-stage M&amp;A target

Pharmaceuticals

06/03/09

24.25p

**At present funding issues in biotech prevail. Antisoma, however, has sufficient cash to reach key phase III inflexion points over the next 24 months. Success of its lead product would, in our view, result in acquisition. BUY.**

**Cash injection.** Likely near-term proceeds from the disposal of FDA-approved chemotherapy drug, oral fludarabine, should swell Antisoma's cash position by at least £20m, extending the cash runway to mid-2011. This would carry Antisoma beyond its expected phase III data inflexion points.

**Blockbuster potential.** We see blockbuster potential for lead drug ASA404 in multiple indications, supported by a lucrative partnership with Novartis. Plans for development in breast cancer will be communicated later this year, which we expect will drive the stock. Together with lung cancer, peak sales of c.US\$1.4bn pa are achievable, we estimate.

**Vastly undervalued.** Antisoma shares are, we believe, vastly undervalued despite our heavy risk adjustments on ASA404 and the company's other phase III candidate, AS1413. Beyond our NPV valuation, we see Antisoma as a likely M&A target for Novartis if the latter gains further confidence in ASA404. Its failure in phase III remains the key risk.

#### Forecasts and ratios (£m)

Yr to Jun	2008	2009F	2010F	2011F
Turnover	39.5	5.5	22.9	63.2
EBITDA	12.0	(33.1)	(31.6)	(11.3)
Net profit	12.3	(26.5)	(32.8)	(12.0)

Source: Company data, ING estimates

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Maintained

## Buy

9 March 2009

Target price (12 mth): Previously 54p

62p

Reuters

ASM.L

#### 12-month forecast returns (%)

Share price	156.8
Dividend	0.0
12m f'cst total return	156.8

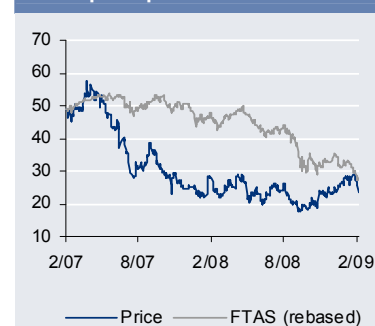
#### Key ratios (%)

	2008	2009F
Turnover growth	396.2	19.2
EBITDA margin	N/A	N/A
Operating margin	N/A	N/A
Net debt/equity	N/A	N/A
ROACE	N/A	N/A

#### Share data

No. of shares (m)	613.5
Daily turnover (shares)	1,985,620
Free float (%)	85.9
Enterprise value (£m)	96.1
Market cap (£m)	148.8

#### Share price performance



Source: ING

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# Investment case

## An impressive 2008 drives differentiation

2008 was a year of major maturation for Antisoma. Its lead product, ASA404, entered phase III trials in lung cancer, and the acquisition of Boston-based Xanthus added two additional phase III products to its specialist oncology pipeline: AS1413 for secondary acute myeloid leukaemia (sAML), and a chemotherapy (oral fludarabine), which subsequently gained FDA approval. In our view, Antisoma has differentiated itself during testing financial market conditions with its first product approval and a healthy cash position. The company has gained critical mass with seven products in clinical development, and is supported by a lucrative partnership with Novartis.

## Blockbuster potential

In 2009, Antisoma continues to perform, recently announcing that Novartis will expand the development of its lead product, ASA404, into metastatic breast cancer, a highly lucrative (US\$650m pa) opportunity. Together with lung cancer, we predict ASA404 could achieve peak sales of US\$1.4bn pa. Clinical success would entitle Antisoma to receive further milestones (and ultimately sales-based royalties) from its collaboration with Novartis (the headline value of which was announced at US\$890m).

## Solid cash position

Antisoma's strong cash position (£53m on 31 December 2008) affords the company near immunity from the financial markets and an opportunity to make further acquisitions in cancer. The company has sufficient cash to achieve its strategic objectives out to mid 2010, extendable to at least mid 2011 with the successful divestment of oral fludarabine adding c.£20m to the cash pile, according to our estimates.

## Unique label opportunity adds value

We see additional potential in AS1413, which could be the first product ever to gain specific approval for sAML. We believe sAML patients have a poorer prognosis than those with *de novo* AML as a result of multi-drug resistance. The candidate is currently in phase III, and we expect launch in 2011.

## Valuation adjustments

We have made numerous adjustments to our valuation, the net effect of which has been to increase our target price by some 15%, from 54p/share to 62p/share. The overriding factor has been the positive currency effect of sterling weakness, given that the US and Eurozone are likely to represent the major markets for oncology drugs.

## Value driving catalysts

**End June 2009:** Oral fludarabine divestment; **Mid 2009:** AS1409 phase I data; **2H09:** initial phase II renal data on AS1411; **2009:** ASA404 clinical trial programme communication; further IP oncology acquisition(s); **2010:** ASA404 interim data in lung cancer; and final data on AS1411 in renal cancer; **Late 2010/early 2011:** Next clinical data point on AS1413; phase III data on ASA404 in NSCLC, and regulatory filing (US).

# Key value drivers

## Pipeline overview

In recent years, investor interest in Antisoma has focused almost exclusively on its lead drug, the vascular disrupting agent (VDA) ASA404, rights to which were handed back by Roche in 2006 before it was later partnered with Novartis in April 2007. With development of this drug passed to Novartis' R&D organisation, Antisoma has focused on moving forward its next novel oncology opportunity, AS1411, and on expanding its pipeline. The latter ambition was achieved in June 2008 via the acquisition of the Boston, USA-based oncology specialist, Xanthus Pharmaceuticals, for £27m (US\$55m), a deal that was accompanied by an additional £21m equity fund-raising. Xanthus' two key late-stage assets are AS1413 (formerly called Xanafide), a product for secondary acute myeloid leukaemia (AML), and an oral formulation of the standard chemotherapy fludarabine, which is used in the treatment of chronic lymphocytic leukaemia (CLL).

**Fig 1 Antisoma product pipeline**

Product	Cancer type	Phase I	Phase II	Phase III	Registration/ Approved
Oral fludarabine	CLL	[Progress bar]			
ASA404	Lung*	[Progress bar]			
AS1413	Secondary AML	[Progress bar]			
AS1411	AML, renal	[Progress bar]			
AS1402	Breast	[Progress bar]			
AS1409	Renal, melanoma	[Progress bar]			
P2045	Lung	[Progress bar]			

Note: CLL, chronic lymphocytic leukaemia; AML, acute myeloid leukaemia

\*Development plans in metastatic breast cancer to be announced in 2009

Source: Company data, ING estimates

## Oral fludarabine a source of cash?

Although ASA404 and, to a much lesser degree, AS1413 and AS1411, are crucial to our investment thesis, the disposal of oral fludarabine would represent a near-term cash opportunity at least sufficient for an extra year's cash runway.

Fludarabine is a standard treatment option in CLL and is frequently used in combination with Rituxan and cyclophosphamide ('FCR'). Antisoma has US rights to an oral formulation of the drug (it is sold elsewhere by Bayer-Schering), which was filed with the FDA for use in second-line CLL in November 2007, and approved in December 2008. The drug will benefit from Orphan Drug status, gaining seven years of market exclusivity.

Oral fludarabine offers a modest sales opportunity (it will compete with generic fludarabine, total US sales of which were US\$54m in 2007). Rather than build a costly US commercial infrastructure for this niche product two years ahead of the potential launch of ASA404 and AS1413, Antisoma has decided that 'the best way to realise the value of oral fludarabine is through a commercialisation deal with a partner that has an established marketing infrastructure in the US'.

All options are being considered, including out-licensing and divestment: 'We have been in talks with a number of companies and expect to conclude a divestment or partnering deal by the end of June [2009]. We understand that outright divestment would be the preferred option (possibly with a small royalty should the bidding become competitive), although substantial proceeds are unlikely in view of the limited commercial opportunity. Indeed, we believe that the product accounts for less than half of the value of the intangible assets (ie, c.£27m) in Antisoma's balance sheet, albeit this is likely to be a conservative valuation. Nevertheless, were Antisoma to raise, say, £20m or so from divestment of this product, we calculate this would extend its cash 'runway' to mid 2011.

## ASA404 remains the key

Over half of our Antisoma valuation is based on ASA404, which is the most advanced VDA in clinical development (see Appendix 1 for more information) and which was partnered in a US\$890m deal with Novartis in 2007 (see panel). ASA404 is being developed in phase III for lung cancer, and the plan is for further development in metastatic breast cancer. In its investor presentations, Novartis describes ASA404 as a potential 'blockbuster'. We calculate that the present value of Novartis' milestone and royalty obligations on this drug, should it be successful in clinical trials, vastly outweighs Antisoma's current capitalisation – by nearly 10x.

### Recap on Novartis partnership deal

In return for global rights to ASA404, Novartis agreed to pay US\$75m upfront to Antisoma plus US\$25m once the drug enters a phase III study in lung cancer. In addition, Novartis agreed to pay up to US\$355m in regulatory and development milestones across five indications (four oncology, one non-oncology) and US\$325m in sales-linked milestones, plus royalties on sales (we assume 25%). A further US\$110m could become payable on commercialisation of a follow-on compound. Lastly, Novartis granted an option for Antisoma to co-launch the drug in the US and agreed to part-finance Antisoma setting up a US sales force.

The key clinical data-set that persuaded Novartis to in-license ASA404 was the striking five-month survival advantage over standard chemotherapy (14.0 versus 8.8 months) seen in a phase II study in lung cancer. Retrospective analysis suggested that the benefit was similar across both major types of lung cancer, ie, squamous and non-squamous.

**Fig 2 Summarised phase II results in non-small cell lung cancer (NSCLC)**

	Median survival in months (change vs control*)	Median TTP in months	Response rate (%)
Chemotherapy	8.8 (N/A)	4.5	22
ASA404 1,200 mg/m <sup>2</sup> + chemotherapy	14.0 (+5.2)	5.4	31
ASA404 1,800 mg/m <sup>2</sup> + chemotherapy	14.9 (+6.1)	5.5	38
Squamous (pooled ASA404 doses)	10.2 (+4.7)	5.6	40
Non-squamous (pooled ASA404 doses)	14.9 (+3.9)	5.5	32

Note: \* higher dose did not have a control arm (comparison is against control arm of low-dose phase)

Source: Company data

Not only did the apparent survival benefit exceed that seen in other clinical studies (including with Avastin) but ASA404 did not appear to add to the toxicity burden of the taxane-based chemotherapy with which it is used in combination.

**Fig 3 Treatment-emergent serious adverse events (SAEs) in ASA404 phase II trials**

SAEs	Lung		Ovarian		Prostate		Combined	
	ASA404 (n=37)	Chemo (n=36)	ASA404 (n=39)	Chemo (n=38)	ASA404 (n=34)	Chemo (n=40)	ASA404 (n=112)	Chemo (n=114)
Blood and lymphatic	1	3	3	0	2	3	6	6
Cardiac	4	1	0	0	3	1	7	2
Gastrointestinal	3	3	6	4	3	3	12	10
General and admin site	4	4	1	0	1	1	6	5
Immune system	0	2	3	2	1	0	4	4
Infection	7	2	0	0	1	2	8	4
Injury, poisoning, procedural	0	1	1	0	0	0	1	1
Metabolism and nutrition	1	1	0	0	0	0	1	1
Renal and urinary	0	2	0	0	0	2	0	4
Respiratory, thoracic, mediastinal	2	4	1	0	0	0	3	4
Vascular	1	1	1	0	1	1	3	2
Investigations	0	0	1	0	0	0	1	0
Nervous system, psychiatry	0	0	2	0	1	1	3	1
Musculoskeletal, connective	0	0	0	0	0	1	0	1
Neoplasms	0	0	0	0	1	3	1	3
<b>Total patients with ≥1 SAE</b>	<b>16</b>	<b>17</b>	<b>16</b>	<b>6</b>	<b>10</b>	<b>9</b>	<b>42</b>	<b>32</b>

Source: Company data

In April 2008, Antisoma and Novartis confirmed that the pivotal phase III trial of ASA404 in non-small cell lung cancer (NSCLC) had begun, thereby triggering the expected US\$25m milestone payment. The study, known as ATTRACT-1, will include 1,200 newly-diagnosed patients with NSCLC of both squamous and non-squamous origin (whereas Avastin is only approved for use in non-squamous patients), making it the largest study in NSCLC that we are aware of. Patients will be randomised 1:1 to receive ASA404 plus standard taxane-based chemotherapy (carboplatin/placlitaxel) or placebo plus standard chemotherapy. The study will use the highest dose of ASA404 that was employed during the phase II studies (1,800 mg/m<sup>2</sup>), underscoring the favourable safety profile seen thus far, and will include up to six cycles of treatment, each cycle being given every three weeks. The primary endpoint will be overall survival, while secondary endpoints will include overall survival in the two patient sub-groups (ie, squamous and non-squamous) plus other standard clinical oncology measures (eg, progression-free survival, quality of life etc). The study is designed so that there may be a single interim 'look' at the data in 2H09 (after 300 events, out of the 950 events required to trigger the primary endpoint) and is targeted to finish in late-2010 or 2011, leading to regulatory filings in 2011 and launch in 2012, we estimate. We understand from the company that the termination criteria at the interim stage are quite extreme (ie, high demonstration of treatment futility or benefit) and so it is very unlikely that this will result in the trial being curtailed early (nor, if the conclusion is that the trial should continue, will it provide any real clue as to how ASA404 is performing in the study either). Thus the first meaningful data for investors is likely to be the results in late 2010/early 2011.

Underscoring its confidence in ASA404, Novartis announced plans in July 2008 for a second pivotal phase III trial, this time in second-line NSCLC, and in January 2009, Antisoma announced that this study, ATTRACT-2 was underway. The ATTRACT-2 study will enrol 900 patients and will examine the potential survival benefit of adding ASA404 1,800 mg/m<sup>2</sup> to docetaxel (the first drug to be approved in second-line lung cancer). The lower patient number and reduced survival in this sicker population (typically only 6-8 months) suggest that results may be obtained not long after those in

first-line NSCLC, likely in 2011. As with ATTRACT-1 there will be an interim 'look' focused mainly on safety, probably in 2010.

We currently assign a peak sales forecast to ASA404 in first-line lung cancer of US\$800m pa. Approval in second-line patients could add around a quarter (US\$200m) to this sales forecast (not currently in our model), we estimate, given that close to half of patients tend to receive second-line therapy. In forecasting the sales potential for ASA404 in NSCLC we make a number of key assumptions. We assume an annual cost per patient of US\$25,000 in the US and US\$20,000 in Europe. This represents a small proportion of the c.US\$100,000 cost of Avastin in NSCLC, albeit ASA404 is a small molecule drug and therefore dramatically cheaper to manufacture. We also assume that the drug is used in all forms of NSCLC, unlike Avastin, as: (1) phase II results showed very little difference observed in response between patients with squamous and non-squamous histologies; and (2) no safety issue was uncovered in patients with squamous histologies where Avastin (bevacizumab) is contraindicated, and known to be associated with fatal pulmonary haemorrhage. Ultimately, we believe the area of opportunity for Novartis and Antisoma is in squamous cell NSCLC, ie, c.30% of NSCLC patients, where competition from Avastin is absent.

**Fig 4 ASA404 sales model in NSCLC**

	2012F	2013F	2014F	2015F	2016F
NSCLC patients ('000)	475	475	475	475	475
Eligible patients ('000)	156	156	156	156	156
Blended price (US\$)	22,174	22,174	22,174	22,174	22,174
Price (£)	15,615	15,615	15,615	15,615	15,615
Penetration (%)	2	9	16	21	23
Sales (US\$m)	81	323	566	728	809
Sales (£m)	57	228	399	512	569

Source: ING estimates

Novartis' plans for ASA404 outside lung cancer are less well developed. The Novartis deal commits to paying milestones on four cancer indications and one non-cancer indication, though it does not limit the candidate's development to just five indications. In addition to NSCLC, ASA404 has been trialled in ovarian cancer and prostate cancer. Although the drug did not appear to show activity in ovarian cancer, the phase II data was more persuasive in prostate cancer. They were not, however, completely clear-cut (see panel).

The addition of ASA404 to docetaxel chemotherapy did not benefit *median* survival in patients with hormone-refractory prostate cancer (17.0 versus 17.2 months), but it did cut the overall probability of death during the study by 20% (ie, the survival hazard ratio was 0.80) and increased two-year survival (33% versus 23%). In terms of surrogate efficacy measures, the phase II data showed that the addition of ASA404 was associated with a higher tumour response rate (23% versus 9%) and a higher PSA response rate (59% versus 37%). (NB. PSA is a protein produced by the prostate gland that is frequently elevated in the presence of prostate cancer. It is thought that PSA reductions of over 50% correlate with increased survival in prostate cancer, although the regulators do not accept this as an endpoint).

Given the totality of the aforementioned data, and the fact that the primary endpoint in the two phase III lung cancer trials is survival hazard ratio, not median survival

(supporting a positive interpretation of the phase II prostate data), we had previously assumed that ASA404 would enter phase III in prostate cancer in 2H09 (FY10) triggering a US\$25m milestone payment from Novartis. However, following the recent (February 2009) announcement that Novartis would be evaluating the candidate as a treatment for HER 2-negative metastatic breast cancer, and would be prioritising this indication ahead of prostate cancer, we are now more sceptical of the status of prostate cancer development. We will have to wait until *'later on in the year'* for Novartis and Antisoma to communicate a more detailed clinical trial programme for ASA404. As it is, some six months have elapsed since the phase II prostate data was reported in August 2008, with no public comment from Novartis. This appears to have raised questions as to whether Novartis is having second thoughts about beginning a costly phase III programme in this second major indication, with some commentators speculating that the company may be contemplating further phase II studies with a higher dose. Pending further details on the clinical programme for ASA404, we have removed the prostate cancer indication from our valuation, including associated milestones.

ASA404's mechanism of action points to its broad applicability in solid tumour settings. We believe targeting metastatic breast cancer represents a sound strategy both clinically and commercially. While no pre-clinical or clinical data exists for ASA404 in breast cancer, we understand that Novartis selected the indication for four reasons: (1). Existing phase II data in lung shows an impressive efficacy and safety profile supporting further development in solid tumours; (2). With c.125,000 patients with metastatic breast cancer in the US and Europe, and the high prices achieved for novel treatment modalities (up to US\$100,000), there exists significant commercial opportunity. (We forecast peak sales of c.US\$600m pa); (3) To date, ASA404 has shown greatest synergy with the taxane drugs docetaxel and paclitaxel (see Appendix 1). Consequently, indications where taxane usage is high (eg, breast cancer) are favoured for further development; and (4). Metastatic breast cancer is in its late stages (IIIb/IV), and prognosis is poor with only 20% of sufferers surviving for more than five years after diagnosis. This means that clinical trial endpoints (typically progression free survival and overall survival) are more rapidly reached, suggesting shorter timelines to approval.

Our model in breast cancer is shown in Figure 5. In the absence of further detail on the ASA404 clinical trial programme we are only able to make loose assumptions when modelling the breast cancer indication. Antisoma's guidance on milestones allows us reasonably to assume that ASA404 will be initiated in metastatic breast cancer in a phase II study, rather than a phase III. Assuming the phase II, which could be an adaptive study, is initiated in 2010F, we see possible launch in 2014F. Guided by CMR transition phase data for novel anticancer therapies, we attach a conservative probability of 12% of achieving the sales tabled in our NPV. We assume an average price per patient of US\$25,000 in the US and US\$21,250 in Europe. We have estimated the number of eligible patients, by assuming that the number of deaths from breast cancer is equivalent to late stage metastatic breast cancer and that HER2-negative breast cancer accounts for some 70% of all cancers. Taken together, our peak sales expectation for this indication is over US\$600m pa.

**Fig 5 ASA404 - HER-2 negative metastatic breast cancer (US\$m)**

	2014F	2015F	2016F	2017F	2018F	2019F
All breast cancer deaths ('000)	124	124	123	123	122	122
Eligible patients ('000)	87	87	86	86	86	85
Patients treated ('000)	2.4	9.4	16.4	21.0	23.3	29.9
Blended price per patient (US\$)	22,819	22,819	22,819	22,819	22,819	22,466
Penetration (%)	3	11	19	24	27	35
<b>ING forecast peak sales (US\$m)</b>	<b>54</b>	<b>214</b>	<b>374</b>	<b>479</b>	<b>531</b>	<b>672</b>

Source: ING estimates

## AS1413, a second phase III product

AS1413 (amonafide, formerly Xanafide) was the key attraction of Xanthus. It is a chemotherapy which acts by blocking topoisomerase II, and is undergoing a phase III trial in the US for secondary AML (see panel below) under a Special Protocol Assessment (SPA); an FDA agreement that a phase III trial's design, clinical endpoints, and statistical analyses can form an acceptable basis for regulatory approval). Antisoma intends to retain US marketing rights to this drug and to out-license it elsewhere.

### Secondary AML (sAML)

AML can be induced by prior haematological disease (typically myelodysplastic syndrome) or by treatment with chemotherapy and/or radiation therapy, in which case it is termed 'secondary' AML (as opposed to *de novo* AML; see AS1411). The annual incidence in the US, according to Antisoma, is approximately 3,000-5,000 patients, although we believe the number is rising as more patients survive cancer treatment. There are no drugs approved to treat sAML, and we believe patients have a poorer prognosis than those with *de novo* AML as a result of multi-drug resistance: clinical studies (eg, SWOG 9031, SWOG 93333), using a combination of daunorubicin and cytarabine, have shown response rates in sAML of 24-26%, well below the 50%-plus rates seen in the treatment of *de novo* AML (eg, clofarabine plus cytarabine has achieved a 67% response rate, according to *Blood* 2008;112:1638-1645).

An 88-patient phase II trial of AS1413 was conducted in sAML, in which the drug was administered with cytarabine. This showed a complete response rate (CR) of 38.6% (34 patients), with an additional 3.4% (three patients) showing CRi (complete response without recovery of blood cell count), yielding an overall response rate of 42.0%. This result was substantially higher than the CR seen in studies with the unapproved standard treatment of daunorubicin plus cytarabine. Furthermore, complete response rates were broadly consistent across various sub-groups of patients, including those with higher risk factors (eg, aged >60 years or with unfavourable cytogenetics). Importantly, many of the responses seen with AS1413 were durable: 18 months after treatment, 40% of responders remained in remission and 43% of responders were still alive (versus 21% of patients overall in the study). In terms of safety, the profile of the AS1413 combination was as expected for a chemotherapeutic regimen, with grade 3+ events including infections, hypotension, diarrhoea and fatigue.

Antisoma believes that AS1413 evades cellular multi-drug resistance mechanisms, notably the 'P-glycoprotein pump' that extrudes chemotherapies from cancer cells, and that this may explain the durable responses and superior response rate in the phase II study. In support of this contention, leukaemia cells from 15 patients in the phase II

study were tested to see whether they accumulated or extruded AS1413 and daunorubicin. AS1413 was retained to a significantly greater extent than daunorubicin.

AS1413 is now in a phase III registration trial, known as ACCEDE. This will compare the combination of AS1413 plus cytarabine with daunorubicin plus cytarabine in 450 sAML patients. Patient dosing began in October 2007. The primary endpoint is response rate, defined as CR + Cri. The starting assumption (which underlies the statistical powering of the study), we believe, is that the two study arms will replicate the response rates seen in prior studies (specifically, the study has >90% power to detect relative response rates of 40% versus 25% at p=0.05). Results are expected in late-2010 or early-2011, ie, in a similar time-frame to the pivotal NSCLC studies of ASA404. US launch could therefore take place in early 2012.

Antisoma intends to market AS1413 in the US via its own salesforce. Ideally, should ASA404 gain approval (and the timelines are similar), the two products could be detailed alongside one another, albeit to slightly different groups of oncologists – solid tumour specialists versus haematological malignancy specialists. In the event of ASA404 disappointment, Antisoma would still market AS1413 via a proprietary salesforce, the only difference being that the reps would not benefit from Novartis' field experience and sales training. Accounting for manufacturing and SG&A overhead costs of 30%, we assume the product will generate a 50% operating profit.

Antisoma believes the peak sales potential of ASA1413 to be in the 'US\$m hundreds' range, citing US\$200-300m on one investor conference call. This number assumes a high penetration rate for sAML (given that AS1413 would be the only candidate with such specific labelling), and reasonable penetration in de novo AML given its multi-drug resistance evasion properties versus the standard of treatment, daunorubicin and cytarabine. (It is worth noting the American Cancer Society estimates AML incidence of 13,000 in 2008). It is unclear whether the company forecast includes use in additional haematological cancers or non-US regions. Our model is more conservative and assumes only US revenues until such time as the pathway to commercialisation outside the US is clear, ie, a partnership deal is signed with clear regulatory time-lines. Based on a high penetration rate (c.50%) in the US, reflecting the lack of competition, and a US\$30,000 price per patient, we incorporate a tentative peak sales forecast of US\$80m pa in our model. We attach a 33% probability to this in our NPV, in-line with the average odds of success for an oncology drug in phase III (based on CMR's 'Industry success rates, 2004' report). Clearly, were we to assume broad level coverage outside the US, peak sales forecasts would exceed US\$100m pa.

**Fig 6 AS1413 sales and profitability model**

AS1413 – sAML	2012F	2013F	2014F	2015F	2016F
Patients ('000)	4.6	4.8	4.9	5.1	5.2
<b>Price per patient (US\$)</b>	<b>30,000</b>	<b>30,000</b>	<b>30,000</b>	<b>30,000</b>	<b>30,000</b>
Price per patient (£)	22,222	22,222	22,222	22,222	22,222
Penetration (%)	10	23	38	45	50
Sales (US\$m)	13.9	32.2	55.3	68.4	78.3
Sales (£m)	10.3	23.9	41.0	50.7	58.0
Overhead (%)	30	30	30	30	30
<b>Net operating profit</b>	<b>7.2</b>	<b>16.7</b>	<b>28.7</b>	<b>35.5</b>	<b>40.6</b>
Tax (%)	30	30	30	30	30
After tax profit	5.0	11.7	20.1	24.8	28.4
<b>Risk adjusted profit</b>	<b>1.7</b>	<b>3.9</b>	<b>6.6</b>	<b>8.2</b>	<b>9.4</b>

Source: ING estimates

With reference to the competitive landscape, there are currently no drugs approved to treat sAML and an extensive search of late stage development haematological cancer therapies reveals no candidates seeking this as a specific indication. Indeed the closest competitor we find is Genzyme's clofarabine (in pre-registration in the US and phase III/filed in EU). Genzyme has filed an MAA with the EMEA to expand the label for clofarabine to include sAML, though to our knowledge the specific labelling has not been filed with the FDA for the US market. We see the AS1413 phase III study design supporting a unique sAML labelling and marketing campaign for high penetration in the US, suggesting at least 50% penetration. While the FDA's acceptance of the phase III study design implies that the regulator accepts the sAML as a bona fide indication, we see a risk to AS1413 market penetration being that sAML still remains a sub-set of AML, and as such any treatment indicated for AML could equally be prescribed for sAML. In terms of currently marketed therapies, we do not see an issue as the standard of care is daunorubicin and cytarabine, which has shown modest efficacy. However, we cannot rule out competition from development stage candidates indicated for AML at large (see Figure 7).

**Fig 7 AML late-stage competitor landscape**

Compound	Company	Phase	Indicated for sAML	Mechanism of action	Comments
AS1413 (amonafide)	Abbott; Antisoma; ChemGenex	III	Y	DNA topoisomerase inhibitor II; DNA intercalator	Undergoing pIII trial in the US for sAML
Clolar (clofarabine)	Genzyme	Pre-registration (US); pIII/filed (EU)	N	Purine nucleoside analogue	Included sAML patients among those recruited
Trisenox (arsenic trioxide)	Cephalon	Marketed	N	Apoptosis inducer	AML
Lestaurinib	Cephalon; Takeda	III	N	Tyrosine kinase inhibitor	
Cloretazine (laromustine)	Vion (Yale)	III	N	Alkylating agent	Seeking partner
midostaurin	Novartis	III	N	Protein kinase inhibitor	Phase III initiated in August 2008 in the US
flavopiridol (alvocidib)	Sanofi-Aventis	III	N	Cyclin dependent kinase inhibitor	Relapsed/refractory AML
Genasense (oblimersen)	Genta (IDIS)	III	N	Apoptosis inducer	Received a complete response from FDA in CLL (Dec 2008)
Proleukin (IL-2)	Novartis	III	N	Immunostimulant (cytokine)	In phase III in USA for AML
Dacogen (decitabine)	SuperGen; J&J	II	N	Antimetabolite	Acute AML; 24% complete response

Source: IMS data & ING Equity Research

## AS1411 gains support from data at ASH

AS1411 is in phase II for AML and renal cancer. It is a novel 'aptamer' (DNA or RNA molecules that can bind specifically to nucleic acids and proteins) which causes cell death when it binds to the protein nucleolin. The latter is normally found inside cells but presents on the cell surface in a variety of cancer cells (including renal, colon, breast, lung, prostate, and blood cancers). AS1411 itself is a short oligonucleotide which is rapidly excreted and so must be given by prolonged (up to seven-day) infusion. Antisoma plans to retain US marketing rights to this drug – which is complementary to AS1413, given its development in AML – and to out-licence it for non-US territories.

The most striking observation from a phase I study of AS1411 – which included 29 patients with a range of cancers – was that, of the 12 patients with advanced renal cell carcinoma (kidney cancer), 11 showed at least stabilisation of their disease. Of these, two had objective responses, including one complete response. For example, one patient experienced major tumour shrinkage (c.70% after six months) despite having relapsed after three prior therapies. Based on these findings, Antisoma entered the drug into phase II studies in AML (in August 2007) and in renal cancer (in September 2008, following additional pre-clinical toxicology work).

The AML study includes 70 advanced patients who have been randomised to either the standard current therapy, cytarabine, or to cytarabine plus AS1411 at one of two doses (ten or 40 mg/kg/day, with the low dose being used in the first c.20 patients as a safety check). Encouraging results from the first 11 patients on the low AS1411 dose were reported in July 2008. These showed that one patient had a complete response (CR) and two had incomplete responses (for an ORR of 27%). By comparison, none of the five patients in the cytarabine control arm had any form of response and one of two patients who were then 'crossed over' to receive AS1411 showed a 90% reduction in blasts (leukaemic cells). Full data from the low-dose arm were then reported at ASH in December 2008. These showed the response rate in the AS1411 group was 16% (3/19; comprised two CRs and one CRp) compared with zero in the control group (Figure 8). Encouragingly, there were no severe side-effects attributed to AS1411 and there was no evidence that it potentiated the toxicity of cytarabine. If the two sets of data are put side-by-side, it could be concluded that the last eight patients on AS1411 (and the third cross-over patient) experienced no benefit. We would caution that this is potentially misleading (as we do not have data on other efficacy measures, such as disease stabilisation, plus the AS1411 patient group was fairly diverse, including 29% with sAML) and that the data from the high dose group is needed to give a fuller picture. Final data from this study is expected in mid-2009 (we assume at the ASCO meeting taking place from 29 May to 2 June 2009). Should this also be supportive we would expect Antisoma to move this product into a phase III programme by late-2009 or 1H10.

**Fig 8 Efficacy data in AML with low-dose AS1411**

	Patients	Response rate	Response in cross-over patients
<b>First data (July 2008)</b>			
AS1411 + cytarabine	11	27% (3/11)	1 of 2 had 90% reduction in blasts
Cytarabine alone (%)	5	0	
<b>Interim data (Dec 2008)</b>			
AS1411 + cytarabine	19	16% (3/19)	1 of 3 had 90% reduction in blasts
Cytarabine alone	9	0s	

Source: Company data

The phase II study in renal cancer is a single-arm trial that will include around 30 patients who are intolerant to, or have relapsed after, a treatment regimen that includes a tyrosine kinase inhibitor, ie, Bayer's Nexavar (sorafenib) or Pfizer's Sutent (sunitinib). Patients will receive AS1411 at a dose of 40 mg/kg/day for four days every 28 days for up to two cycles. Efficacy measures in the trial will include ORR, TTP and PFS. With the study recruiting well, according to the company, first results are expected in 2009 with final results in 2010. As with the AML indication, we would expect positive results to result in the product being moved into phase III.

# Earlier-stage clinical candidates

## AS1402 enters phase II in breast cancer

AS1402 (formerly known as R1550 and Therex) began phase II testing in advanced breast cancer in September 2008. It is a humanised monoclonal antibody that targets MUC1, a glycoprotein that is over-expressed on the surface of many types of cancer cell and is found in c.90% of breast cancers. We are sceptical about the chances for this compound given its protracted development history. Originally licensed by Antisoma from Imperial Cancer Research Technologies in 2000, it was later out-licensed to Roche and spent three years in a phase I dose-escalation study in metastatic breast cancer before the rights were finally returned to Antisoma in 2006. While the phase I study showed that the drug was well tolerated, there was no compelling evidence of efficacy as the time to progression (TTP) for patients was around 40 days at all doses tested (1, 3, 9 and 16 mg/kg). We understand that Roche felt the data did not show clear evidence of activity and that, having gained insufficient comfort from mouse models, it chose to return all rights to AS1402 to Antisoma.

Antisoma, however, has cited studies that suggest that MUC1 is involved in the oestrogen-signalling pathway and believes that this provides a scientific rationale for combining the drug with hormonal therapy. To this end it has begun a 110-patient study in first-line breast cancer treatment, with patients being randomised to receive the aromatase inhibitor, letrozole (Novartis' Femara), plus AS1402 or letrozole alone. Final results are expected in 2010. We apply a low probability of success in our NPV model.

## Phase I compounds not valued

We do not place any value in our model on Antisoma's two early-stage compounds as each is extremely risky, in our view:

- **AS1409** is an antibody-cytokine fusion protein in phase I clinical studies in renal cell carcinoma and melanoma. It combines the anti-tumour cytokine, IL-12, with the tumour-targeting antibody BC1. Through delivery of IL-12 directly to tumour blood vessels, Antisoma hopes to minimise the systemic side effects of IL-12 (which arise as a result of increased endogenous interferon gamma production).
- **P2045** is a synthetic peptide-based targeted radiopharmaceutical in phase I studies. Radioactivity-associated distribution and safety issues have dogged the commercial prospects of the few marketed therapeutic radiopharmaceuticals.

# Valuation

We have made numerous adjustments to our valuation, the net effect of which has been to increase our price target by some 15%, to 62p/share (from 54p/share). Despite removing one project from our rNPV valuation, the overriding factor has been the positive currency effect of the falling pound against the dollar. Both pre- and post adjustments, our target price still lies far north of the current stock price reflecting the strong commercial potential we believe lies in the company's IP, combined with a poor market environment for small caps (particularly loss-making biotechs).

## Fundamental rNPV valuation

We use ING's standard risk-adjusted NPV method to value Antisoma. This is our preferred methodology for development-stage cash-burning companies, and discount revenue streams at 13%, ING's standard for the biotech sector. We set our 12-month target price at 62p based on this valuation (Figure 9). This implies 158% upside from the current share price and justifies our **BUY** rating.

**Fig 9 rNPV SOTP valuation summary**

Drug	Indication	Stage	Launch	Peak sales (US\$m)	Probability (%)	Net royalty (%)	rNPV (£m)	rNPV per share (p)	% total
<b>ASA404</b>	NSCLC	Phase III	2012	809	33	21	197.5	32.2	52
	Breast	Phase II	2014	672	12	21	28.4	4.6	7
<b>AS1413</b> (Xanafide)	Secondary AML	Phase III	2011	78	33	50	54.5	8.9	14
<b>AS1411</b>	Renal	Phase II	2011	256	8	50	24.6	4.0	6
	AML	Phase II	2011	80	8	50	7.7	1.3	2
<b>AS1402</b>	Breast cancer	Phase II	2012	248	8	14	8.1	1.3	2
<b>AS1409</b>	Renal, melanoma	Phase I	2013	102	8	15	4.4	0.7	1
<b>Telomerase</b>	Cancer	Pre-clinical							
<b>Cash (end-2009)</b>							55.8	9.1	15
<b>NPV inc cash</b>							<b>381.0</b>	<b>62.0</b>	100

Source: ING estimates

### Key adjustments

- **Exchange rate:** we have shifted the US\$:GBP rate in-line with current levels of US\$1.42 (from US\$2.00). Given the degree of sales expected to be derived from the US, Antisoma, quoted in the UK and reporting in sterling, will always have a valuation sensitivity to the US\$/GBP rate.

**Fig 10 Sensitivity to US\$/GBP rate**

FX rate	Technology value (£m)	Cash (£m)	NPV (£m)	NPV/sh (p)	Impact on valuation (%)
0.80	580	56	636	103.6	67
1.00	463	56	519	84.5	36
1.20	385	56	441	71.8	16
<b>1.42</b>	<b>325</b>	<b>56</b>	<b>381</b>	<b>62.0</b>	<b>0</b>
1.60	289	56	344	56.1	-10
1.80	256	56	312	50.8	-18
2.00	231	56	287	46.7	-25

Source: ING estimates

- **NPV shifted forward:** we have rolled our NPV discount forward by one year following the publication of company's half-year results, such that 2009 is the first year of discounted income in our cash flow streams.
- **Removed the ASA404 project for prostate cancer:** Pending further details on the clinical trial programme for ASA404 (expected later in the year), we have removed the prostate cancer indication from our valuation, including associated milestones. Had we chosen to keep the project in our valuation in this indication, we would have certainly rolled the milestones forward one year to account for the delay to the start of the phase III (a milestone triggering event) implicit in Novartis' prioritisation of the breast cancer indication over the prostate indication.
- **Introduced ASA404 into our rNPV valuation in the breast cancer setting:** ASA404 in HER2-negative metastatic breast cancer now accounts for 4.6p/share, making a 7% contribution to our overall rNPV SOTP valuation. We award a conservative probability of success of 12% guided by CMR data for anticancer therapies, and forecast launch in 2014F with peak sales of c.US\$650m pa (see ASA404 section above for further valuation details).
- **Relocated oral fludarabine:** In the light of Antisoma's confidence to secure a buyer for its oral fludarabine chemotherapy by June 2009, and its preference for a straight divestment, we have relocated this project from the rNPV, directly into the cash flow statement as a cash in-flow in the 'divestment' line. Clearly, at 100% probability of success (the project was approved by the FDA in December 2008), whether the project is picked up in the rNPV as a project or as straight cash, makes no material difference to our overall valuation.

**At current levels, the market is applying a +30% discount rate**

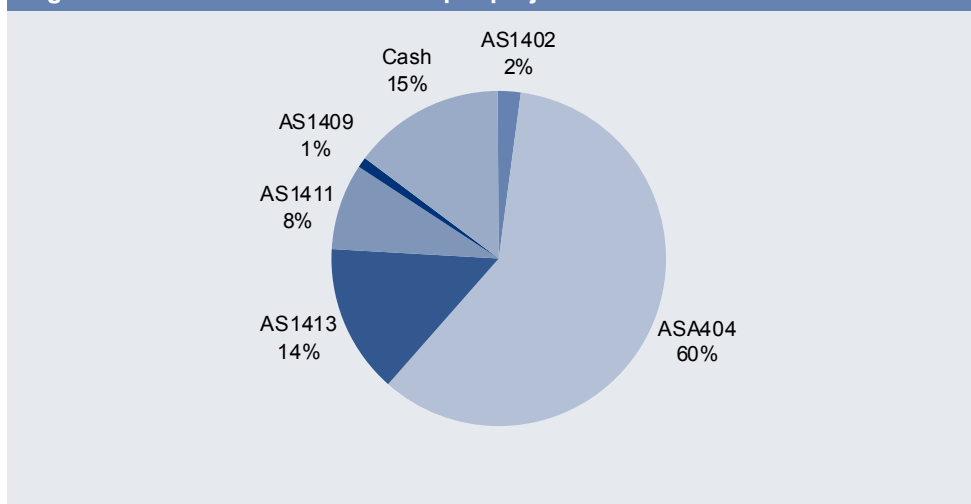
We use ING's standardised discount rate of 13%. To highlight the severity of the market's valuation of Antisoma, we have run a sensitivity analysis to discount rate. At current levels the market applies a punitive +30% discount rate, which we believe is unjustified, particularly given the company's current position of strength from both a cash and clinical data viewpoint.

**Fig 11 Sensitivity to discount rate**

Discount rate	Technology value (£m)	Cash (£m)	NPV (£m)	NPV/sh (p)
10%	397	56	453	73.7
<b>13%</b>	<b>325</b>	<b>56</b>	<b>381</b>	<b>62.0</b>
20%	209	56	265	43.2
30%	118	56	174	28.3
40%	70	56	126	20.5

Source: ING estimates

**Fig 12 rNPV SOTP contributions per project**



Source: ING estimates

### Speculative takeover valuation

Novartis, in our view, is the logical acquirer of Antisoma, although Novartis itself has made no comment. Should ASA404 reach its potential, and by that we mean book peak sales of at least US\$1.4bn pa, we see Novartis’ pay-away to Antisoma (discounted at pharma’s 8% cost of debt) being nearly 10x in excess of Antisoma’s current technology value. In this eventuality – and of course it will depend on the market value of the stock at the time – we see a takeover as highly likely on two counts: firstly it will be a financially sound manoeuvre, and secondly Novartis is likely to pay up in order to gain full managerial control over the project. Assuming Novartis does have intentions in this direction, we see the phase III interim data in 2H09/1Q10 on ASA404 in lung cancer as the earliest possible trigger, though we acknowledge that this initial ‘futility check’ will only uncover extremes, and be of limited use in determining the approvability of the candidate. Clearly, the longer Novartis waits, which could be beyond final phase III data in lung (in late 2010/early 2011), the longer it runs the risk of the current downward pressure on biotech valuations easing.

### Next catalysts

Below we highlight the key catalysts in the coming 18-24 months.

**Fig 13 Next catalysts**

Estimated date	Candidate	Indication	Event	Comments
1H09	Oral fludarabine	CLL	Divestment	Antisoma should generate at least £20m cash for the divestment of US rights
Mid 2009	AS1409		Phase I data	
2H09	AS1411	Renal cancer	Initial phase II data	
2H09/1Q10	ASA404	Lung cancer (NSCLC)	Interim phase III data	
2009	ASA404	All	Trial programme update	Details of clinical trial programme including breast cancer trial design and prostate status update
2009 onwards	-	-	IP acquisition	In-license/acquire further Oncology drug candidates (not gene therapy or cancer vaccines)
Late 2010 - early 2011	AS1413	sAML	Phase III data	
Late 2010 - early 2011	ASA404	NSCLC	Regulatory filing (US)	

Source: Company data, ING estimates

# Forecasts

## Adjustments to forecasts

Following the half-year results (July-December 2008) we have made some minor alterations to our forecasts. The two changes were: (1) raising the R&D costs and reducing the SG&A costs to reflect the company's reclassification of its operating costs to bring the proportions more in-line with industry peers; and (2) Raising the net interest line to reflect the foreign exchange gain of £6.7m that the company achieved in the half-year.

**Fig 14 Income statement forecasts (£m)**

Year end June	2005	2006	2007	2008	2009F	2010F	2011F	2012F
Product sales	0.0	0.0	0.0	0.0	0.0	0.0	36.1	90.1
Reimbursed R&D costs	0.4	0.0	0.7	0.5	0.0	0.0	0.0	1.0
Upfront payments	5.9	1.63	7.3	32.0	0.0	0.0	0.0	0.0
Milestones	0.0	0.0	0.0	7.0	5.5	22.9	10.0	58.1
Royalties	0.0	0.0	0.0	0.0	0.0	0.0	17.2	17.2
<b>Revenue</b>	<b>6.3</b>	<b>1.6</b>	<b>8.0</b>	<b>39.5</b>	<b>5.5</b>	<b>22.9</b>	<b>63.2</b>	<b>166.4</b>
CoGS	0.0	0.0	0.0	0.0	0.0	0.0	(5.4)	(13.5)
S,G&A	(4.7)	(4.9)	(7.3)	(10.3)	(6.4)	(11.7)	(17.5)	(26.3)
R&D	(12.3)	(16.6)	(14.5)	(18.4)	(33.6)	(44.1)	(52.9)	(63.5)
<b>Operating profit</b>	<b>(10.7)</b>	<b>(19.8)</b>	<b>(13.9)</b>	<b>10.8</b>	<b>(34.5)</b>	<b>(32.9)</b>	<b>(12.7)</b>	<b>63.0</b>
Net interest	1.5	0.9	1.2	2.6	9.0	1.2	1.7	7.0
<b>Profit before tax</b>	<b>(9.2)</b>	<b>(18.9)</b>	<b>(12.7)</b>	<b>13.4</b>	<b>(25.4)</b>	<b>(31.7)</b>	<b>(11.0)</b>	<b>70.0</b>
Tax	2.5	2.0	3.0	(1.0)	(1.0)	(1.0)	(1.0)	(24.5)
<b>Profit after tax</b>	<b>(6.7)</b>	<b>(16.9)</b>	<b>(9.7)</b>	<b>12.3</b>	<b>(26.5)</b>	<b>(32.8)</b>	<b>(12.0)</b>	<b>45.5</b>
Average shares (m)	294.2	370.5	413.0	457.0	613.5	623.1	623.1	624.7
<b>EPS (p)</b>	<b>(2.29)</b>	<b>(4.55)</b>	<b>(2.36)</b>	<b>2.70</b>	<b>(4.32)</b>	<b>(5.26)</b>	<b>(1.93)</b>	<b>7.29</b>

Source: Company data, ING estimates

**Fig 15 Cash flow forecasts (£m)**

Year end June	2005	2006	2007	2008	2009F	2010F	2011F	2012F
Operating result	(10.7)	(19.8)	(13.9)	10.8	(34.5)	(32.9)	(12.7)	63.0
Timing adjustments	0.0	0.0	17.5	0.0	0.0	0.0	0.0	0.0
Depreciation	0.4	0.4	0.3	0.2	0.3	0.3	0.3	0.3
Amortisation	0.5	0.7	1.0	1.1	1.1	1.1	1.1	1.1
Working capital	(5.1)	(1.0)	15.3	(27.5)	(4.0)	(3.0)	(5.0)	(7.0)
<b>Cash flow from operations</b>	<b>(14.9)</b>	<b>(19.7)</b>	<b>20.2</b>	<b>(15.5)</b>	<b>(37.1)</b>	<b>(34.6)</b>	<b>(16.3)</b>	<b>57.4</b>
Interest	1.6	0.9	1.1	2.8	9.0	1.2	1.7	7.0
Tax	0.9	1.6	2.1	2.0	(1.0)	(1.0)	(1.0)	(24.5)
Capex	(0.1)	(0.1)	(0.2)	(2.0)	(2.0)	(2.0)	(2.0)	(1.5)
Divestments (acquisitions)	(1.1)	0.0	(1.8)	(1.8)	20.0	0.0	0.0	1.0
Financing	(0.0)	7.2	25.0	20.0	0.0	0.0	0.0	1.0
<b>Cash inflow/outflow</b>	<b>(13.8)</b>	<b>(10.1)</b>	<b>46.4</b>	<b>5.5</b>	<b>(11.1)</b>	<b>(36.4)</b>	<b>(17.7)</b>	<b>40.4</b>
Net cash (at end period)	25.0	14.9	61.4	66.9	55.8	19.4	1.7	42.1

Source: Company data, ING estimates

**Fig 16 Balance sheet forecasts (£m)**

Year end June	2005	2006	2007	2008	2009F	2010F	2011F	2012F
Goodwill	6.2	6.1	5.5	5.6	5.6	5.6	5.6	5.6
Intangible assets	19.1	19.0	19.1	47.1	47.1	47.1	47.1	46.1
Tangible assets	1.0	0.6	1.2	2.4	2.3	2.2	2.1	2.0
<b>Fixed assets</b>	<b>26.3</b>	<b>25.8</b>	<b>25.8</b>	<b>55.1</b>	<b>55.0</b>	<b>54.9</b>	<b>54.8</b>	<b>53.6</b>
Trade and other receivables	2.7	2.8	4.5	2.1	2.1	2.1	2.1	2.1
Short-term deposits	7.5	5.5	10.0	33.0	33.0	33.0	33.0	33.0
Cash and cash equivalents	17.5	9.4	51.4	33.9	22.8	(13.6)	(31.3)	9.1
<b>Current assets</b>	<b>27.7</b>	<b>17.7</b>	<b>65.9</b>	<b>69.0</b>	<b>57.9</b>	<b>21.5</b>	<b>3.8</b>	<b>44.2</b>
Current liabilities	(5.8)	(5.0)	(39.7)	(16.2)	(16.2)	(16.2)	(16.2)	(16.2)
Deferred tax	(6.2)	(6.1)	(5.5)	(5.6)	(5.6)	(5.6)	(5.6)	(5.6)
Trade and other payables	(0.9)	(0.6)	0.0	0.0	0.0	0.0	0.0	0.0
Provisions	(0.0)	(0.0)	(0.2)	(0.1)	(0.1)	(0.1)	(0.1)	(0.1)
Total liabilities	(12.9)	(11.7)	(45.4)	(21.8)	(21.8)	(21.8)	(21.8)	(21.8)
<b>Net assets</b>	<b>41.1</b>	<b>31.8</b>	<b>46.3</b>	<b>102.2</b>	<b>91.0</b>	<b>54.5</b>	<b>36.8</b>	<b>76.0</b>
Share capital	7.7	8.0	8.8	10.5	10.5	10.5	10.5	10.5
Share premium	84.9	76.2	100.5	121.9	121.9	121.9	121.9	121.9
Other reserves	5.0	20.2	18.6	38.0	38.0	38.0	38.0	38.0
Retained loss	(56.5)	(72.7)	(81.5)	(68.2)	(79.4)	(115.9)	(133.6)	(94.4)
<b>Shareholder's equity</b>	<b>41.1</b>	<b>31.8</b>	<b>46.3</b>	<b>102.2</b>	<b>91.0</b>	<b>54.5</b>	<b>36.8</b>	<b>76.0</b>

Source: Company data, ING estimates

# Appendix 1: more on ASA404

## Background

ASA404 (previously known as AS1404 or DMXAA) is Antisoma's most advanced product. It is a small-molecule 'vascular disrupting agent' (VDA) and acts by selectively disrupting established tumour blood vessels. This distinguishes it from the angiogenesis inhibitors (see Figure 17), pioneered by Genentech/Roche's Avastin, which prevent the growth of *new* tumour blood vessels (neovasculature). As discussed in the body of this report, Antisoma's partner Novartis has entered ASA404 into phase III in NSCLC in combination with taxane-based chemotherapy, and is examining potential clinical programmes in other indications.

**Fig 17 Vascular disrupting agents versus angiogenesis inhibitors**

	Vascular disrupting agents	Anti-angiogenic agents
Examples	ASA404, CA4P, Exherin, AVE8062	Avastin, Sutent, Nexavar
Tumour type	Larger solid tumours – established blood vessels	Smaller solid tumours – new blood vessels
Target	Central part of tumour	Tumour periphery
Effect	Cause vessel occlusion and necrosis	Inhibit endothelial proliferation and migration

Source: Antisoma and Cancer Research Technology joint seminar, September 2006

ASA404 has a unique dual mechanism of action, producing direct apoptotic (cell-killing) effects on endothelial cells in the vessel lining and indirect secondary effects on the blood vessel via the release of vasoactive substances, notably serotonin (5HT) and the pro-inflammatory cytokine TNF. The combined effect of these actions results in increased vascular permeability, increased hypoxia (reduction in tissue oxygen levels) and a shutdown in tumour blood flow. Animal studies have shown that this results in massive necrosis of the central area of solid tumours, although the outer rim of the tumour tends to remain viable (presumably because it can still attract oxygen and nutrients from surrounding tissue). The latter observation led to the hypothesis that ASA404 would act synergistically with chemotherapy (as the latter would kill the cells in the so-called 'viable rim') and was followed by a series of studies that showed greatest synergy with the taxane drugs docetaxel and paclitaxel. Importantly, there were no overlapping dose-limiting toxicities seen between ASA404 and chemotherapy.

The promising pre-clinical data led to the drug entering into two phase I trials in the late 1990s, under the auspices of the Cancer Research Campaign (CRC), with funding provided by Parke-Davis (now part of Pfizer). Antisoma acquired the rights to the drug in 2001 after Parke-Davis returned the rights to the CRC (we understand on the grounds that it did not fit with the rest of its R&D portfolio). The consideration included an upfront payment of £700,000 inclusive of an equity component, plus (unspecified) future milestones and royalties (the latter are understood to be in low single digits). Antisoma then began a phase I study of its own which was completed successfully in March 2004. QTc prolongation was seen at high doses of the drug and the dose-limiting toxicities were confusion and visual disturbances. This benign side effect profile encouraged Antisoma to initiate a phase II study in non-small cell lung cancer in September 2004, followed by further phase II studies in ovarian and prostate cancer.

## Phase II data

### Lung cancer

The first phase II study ASA404 to report was in the treatment of locally advanced and metastatic non-small cell lung cancer (NSCLC). In this randomised study 84 patients were given ASA404 plus standard chemotherapy (paclitaxel plus carboplatin) or chemotherapy alone. Patients received up to six cycles of treatment (three weeks per cycle) and ASA404 was administered as a 20-minute infusion at a dose of 1,200mg/m<sup>2</sup>. Evaluable data was obtained from 70 patients. This showed that:

- Addition of ASA404 to chemotherapy appeared to extend median survival by a striking 5.2 months (14.0 versus 8.8 months). This exceeded the c.two-month benefit seen in Avastin's phase III trial in NSCLC (12.5 months versus 10.2 months) and is higher than seen with any agent other than Avastin. Note that, while the study was not powered for statistical significance, the control arm result was consistent with the 8-10 month survival seen in other studies of taxane-based chemotherapy.
- Other efficacy measures were supportive of an incremental benefit from ASA404, including independently-assessed response rate (31% versus 22%) and median time to progression (which showed a 20% uplift, to 5.4 months).
- In terms of safety, there was no major difference in the incidence of serious adverse events, with 16 patients affected on ASA404 plus chemotherapy versus 17 on chemotherapy alone. There was no impact on the QTc interval, although several cardiac events were seen in ASA404 group (four versus one). These were thought to be due to pre-existing cardiovascular risk factors. In addition, no safety differences were observed between squamous and non-squamous histologies (unlike Avastin).

The impressive median survival was closely replicated in an uncontrolled extension of this study, which examined the benefit of a 50% higher dose of ASA404 (ie, 1,800mg/m<sup>2</sup>) in 24 patients with advanced NSCLC. This showed a median survival of 14.9 months. Other efficacy measures were consistent with the lower-dose study. When the results of the two studies were pooled, there was very little difference observed in response between patients with squamous and non-squamous NSCLC.

**Fig 18 Summarised phase II results in NSCLC**

	Median survival in months (change vs control*)	Median TTP in months	Response rate (%)
Chemotherapy	8.8 (N/A)	4.5	22
ASA404 1,200 mg/m <sup>2</sup> + chemotherapy	14.0 (+5.2)	5.4	31
ASA404 1,800 mg/m <sup>2</sup> + chemotherapy	14.9 (+6.1)	5.5	38
Squamous patients (all ASA404 doses)	10.2 (+4.7)	5.6	40
Non-squamous (all ASA404 doses)	14.9 (+3.9)	5.5	32

Note: \* higher dose did not have a control arm (comparison is against control arm of low-dose phase)

Source: Company data

### Ovarian cancer

The phase II study of ASA404 in ovarian cancer was the second to report, but yielded disappointing results. Patients were again treated either with ASA404 plus standard chemotherapy (paclitaxel plus carboplatin) or chemotherapy alone. Results in July 2007 showed that, despite a higher response rate in the ASA404 arm (61% versus 55%), there was no benefit in time to progression and one-year survival was *lower*

(74% versus 92%). Given that no new safety signal emerged, we deem the latter to be due to the relatively small numbers of patients involved (75 in total) rather than a detrimental impact of ASA404. There are no development plans in this indication.

## Prostate cancer

The third phase II study of ASA404 was conducted in hormone-refractory prostate cancer (HRPC). In this study 74 men were randomised to receive ASA404 plus docetaxel or docetaxel alone. Docetaxel is the standard-of-care in HRPC following the results of the TAX 327 study in 2004, which showed that the drug improved survival by 24% (18.9 versus 16.5 months) compared with mitoxantrone. Given that the treatment time in HRPC was longer than in the other phase II studies (up to ten cycles, meaning up to 30 weeks of treatment versus 18 weeks in the lung and ovarian studies), final data did not emerge until August 2008. In the event it was not clear-cut. On the downside, the addition of ASA404 did not provide a benefit to median survival (17.0 versus 17.2 months). On the other hand, the totality of the survival dataset was positive given that the survival hazard ratio was 0.8 – meaning that the addition of ASA404 reduced the risk of death by 20% – and that the drug lifted two-year survival from 23% to 33%. The latter correlated with the benefit seen in surrogate endpoints: Antisoma had previously reported that addition of ASA404 in this study produced a higher tumour response rate (23% versus 9%) and a higher PSA response rate (59% versus 37%). PSA is a protein produced by the prostate gland that is frequently elevated in the presence of prostate cancer. Several studies with other drugs have shown that PSA reductions of over 50% correlate with increased survival in prostate cancer, although the regulators do not accept PSA response as an endpoint. As with the lung and ovarian studies, the addition of ASA404 was well-tolerated, without exacerbation of chemotherapy side-effects.

## Patent position

The US composition of matter patent (5,281,620) for ASA404 runs only to January 2011 in the US, while its European equivalent (EP0278176) has already expired (in 2007). We are untroubled by this (as, clearly, was Novartis when striking the partnership deal) and expect the drug to enjoy up to ten years of market exclusivity:

- Antisoma has received method of use patents (eg, US patent 6,667,337) for the combination of ASA404 with taxane chemotherapy, which run to 2021. As ASA404 is not being developed as a monotherapy, it is likely that this will provide relatively strong protection (and extensions may anyway be granted to the basic patent).
- As an approved drug, ASA404 would of course gain market exclusivity in the US (under Hatch/Waxman) of five years and ten years in Europe.

## Competition

According to IMS Health, there are up to nine compounds in the clinic that may ultimately compete with ASA404 in the vascular disrupting market, albeit most are in early-stage clinical trials. The two most advanced compounds are Oxigene's CA4P (which is in phase II/III in thyroid cancer and phase II in NSCLC) and sanofi-aventis' AVE 8062 (in phase II in NSCLC). Each is a derivative of combretastatin, a naturally-occurring inhibitor of tubulin (which is used in cell division) and each has had a protracted development history, spending a large amount of time in phase I: CA4P completed phase I trials in 2001 and finally entered a randomised phase II trial in 2006, while AVE 8062 moved into phase II in 2008, some four years after entering phase I. Even if the issue(s) that resulted in these development delays have been fully resolved, we note that neither is as advanced in development as ASA404 and neither

has controlled clinical trial data with which to compare efficacy or safety. At this stage, therefore, ASA404 is the clear class leader among vascular disrupting agents.

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