

25 June 2007

Price: 146.5p

## York Pharma (YRK)

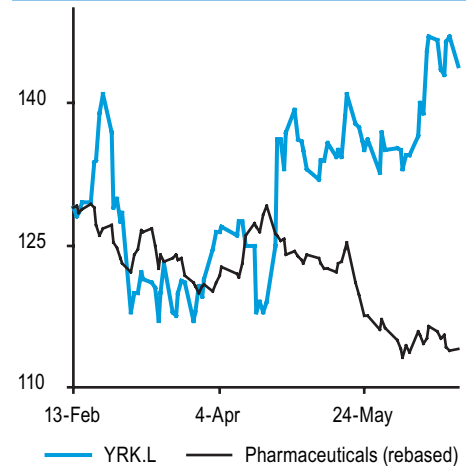
Pharmaceuticals and biotechnology

*With the stock up 53% since our initiation report, further progress this year should add to investor confidence.*

### KEY POINTS

- **Nine eventful months bring the company closer to its goals** – two financings and one acquisition later, the achievements since our November 2006 initiation have inched York towards its corporate goals.
- **Abasol should come good near-term** – it is dicey to predict the timing of regulatory approval, but York's best guestimate is a mid-year approval after delays of 3-6 months. We have no reason to doubt this.
- **Formulations of Abasol Nail, Sabarep and Vampex are essentially completed** – York will be able to initiate clinical testing in these programmes shortly.
- **The pipeline presages good news-flow** – with Sabarep and Vampex on target to enter the PoC clinical trial concept stage, we expect much news in 2007.
- **Application extensions for abafungin are already on the way** – apart from nail, where a final formulation should reach Phase II by year-end, York has developed an opportunity in the vaginal candidosis market surely driven by the prospect of a potential partnership.
- **The acquisition of Rosanto is an intriguing addition to the portfolio** – York's 'value' acquisition of Rosanto and its cyclopentenone prostaglandin-derived portfolio of compounds has multiple dimensions on the anti-inflammatory, anti-viral and anti-cancer fronts. Psoriasis is the topical derm target.
- **Non-derm applications are a goldmine after the PoC stage** – the antiviral and anticancer applications of this class of compound are early candidates for licensing. This makes them a potential source of early cash flow for York to fund the derm application.
- **Story still driven by the approval of Abasol and partnership deals** – the near-term is still focused on the UK approval of the antifungal Abasol. Our sales estimates remain conservative but as Lamisil has now gone generic and the derms are looking for something new with an improved profile, could Abasol be what Doctor Derm ordered?
- **This should be the year when York Pharma wins investor confidence** – we expect the 'approvable' letter from the MHRA to lead to a 2007 approval and a series of Abasol deals and partnerships.
- **We have tweaked our valuation model to reflect advances in development and our thinking** – the new formulations in Sabarep, Vampex and abafungin for nails have pushed the probabilities of success up a tad and our core valuation up from £3.74 to £3.93.
- **If York hits its milestones in 2007, the price should benefit** – we expect a flurry of milestone achievements which should move the price northwards. With the stock up over 50% since our initiation report, we would not be surprised to see this as a trend.

### Price chart (p)



### Company details

Quote

Shares

- London AIM YRK

Hi-Lo last 12-mos. (p) 146.5 - 76.5

Market Cap'n (£m) 46.2

Stockbroker: JM Finn  
www.jmfinn.com

Collins Stewart  
www.collins-stewart.com

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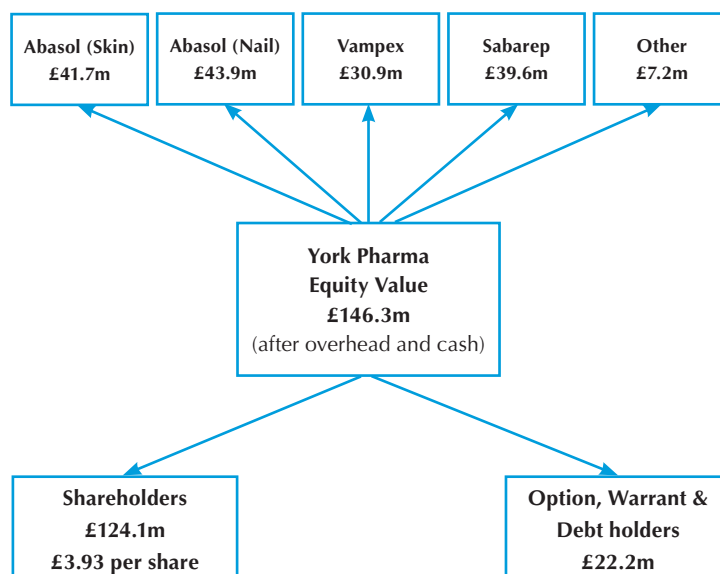
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## Valuation summary (£m)

Scenario	Core	Pessimistic
Development drugs		
Abasol		
- Skin	41.7	19.1
- Nail	43.9	26.7
Vampex	30.9	21.2
Sabarep	39.6	32.0
YP004 - Melanoma	7.2	6.9
Less overhead	(27.0)	(27.0)
<b>Expected value of pipeline</b>	<b>136.3</b>	<b>78.9</b>
Add: starting cash + new funds	10.0	10.0
Total current value for firm	146.3	88.9
Less: total liabilities	(1.8)	(1.8)
Total value to equity claims	144.5	87.1
Less: warrants and options	(20.4)	(20.4)
Ordinary equity holders	124.1	66.7
Value per share (£)	3.93	2.12

## Components of York Pharma's entity value



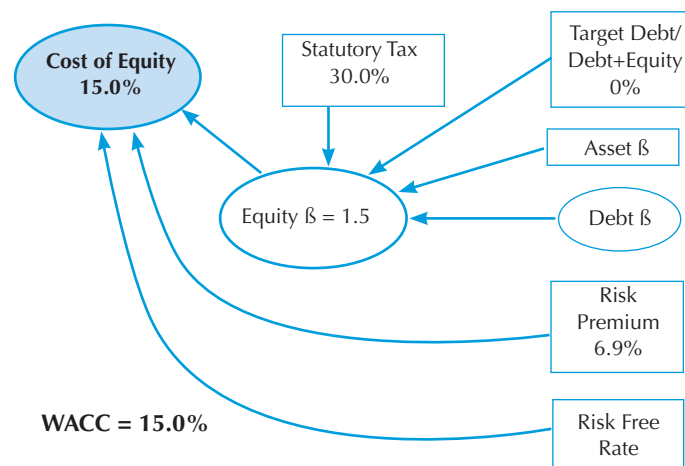
## Comparable speciality pharma companies

	Symbol	Market cap (m)	Shares out. (m)	Price	Revenues latest (m)	Cash/Equiv latest (m)	Cash/share	Price to cash	Market Cap to Sales	Comment/Partners/Deals
<b>Dollar Zone</b>										
Medicis	MRX (NYSE)	\$1,715.9	55.8	\$30.75	\$376.0	\$447.0	\$8.01	3.8	4.6	Dermatology specialty pharma
Connetics	CNCT (Nasdaq)	\$722.2	41.3	\$17.47	\$184.3	\$30.0	\$0.73	24.1	3.9	Taken out by Stiefel at 17.50 per share
Barrier Therapeutics	BTRX (Nasdaq)	\$186.4	29.4	\$6.34	\$2.5	\$16.9	\$0.57	11.0	73.4	Derm development
Collagenex	CGPI (Nasdaq)	\$263.5	21.3	\$12.37	\$26.4	\$26.2	\$1.23	10.0	10.0	Derm spec. pharma & develop.
DUSA	DUSA (Nasdaq)	\$55.0	17.0	\$3.23	\$11.3	\$4.2	\$0.25	13.1	4.9	Photodynamic therapy
Average								12.4	19.3	
<b>Sterling Zone</b>										
York Pharma	YRK (AIM)	£44.3	31.0	£1.43	£0.00	£5.00	£0.16	8.9	NM	
AGI Therapeutics	AGI (AIM)	£82.2	67.4	£1.22	£0.00	£30.00	£0.45	2.7	NM	Self develop/Specialty pharma
Antisoma	ASM (LSE)	£204.2	446.3	£0.46	£1.60	£25.00	£0.06	8.2	127.6	Abbott/Roche cancer Drug Dev.
Ark Therapeutics	AKT (LSE)	£228.5	166.2	£1.38	£0.30	£6.29	£0.04	36.3	761.8	CNS vascular drug development/outlicensing
Sinclair Pharma	SPH (AIM)	£116.3	93.4	£1.25	£9.10	£10.87	£0.12	10.7	12.8	Specialty pharma In licensing
Vernalis	VER (LSE)	£190.3	313.3	£0.61	£14.30	£40.20	£0.13	4.7	13.3	Novartis, Endo, Biogen Idec CNS drugs
CeNeS	CEN (AIM)	£24.2	483.9	£0.05	£0.05	£8.46	£0.02	2.9	483.9	CNS late stage drug development/outlicense
Average								10.9	228.9	
<b>Other</b>										
Basilea Pharmaceutica	BSLN (SWX)	SFr. 1,554.96	7.4	SFr. 209.00	SFr. 34.90	SFr. 28.00	SFr. 3.76	55.5	44.6	Jnj/Phase III

## Comparables

	Price to cash		
	Median	Simple mean	Weighted mean
US panel	11.0	12.4	5.6
UK panel	6.5	10.9	7.0
Swiss example	55.5	55.5	55.5
Simple mean	24.3	26.3	22.7
York	8.9	8.9	8.9

## Weighted cost of capital



### Seven months and York is closer to its near term goals

Since our initiation report in November much has happened, although investors await the MHRA's decision on **Abasol™**. Unfortunately, the company has no control over the timetable of such an approval; a mid-year nod remains on the cards. This represents a delay of over three months from the company's expectations at the end of last year and has set back the launch of Abasol by some nine months to date. Elsewhere, progress has been made with **Sabarep™**, **Vampex™** and abafungin for nails making their way towards Phase II clinical trials. According to York, the rest of the portfolio is 'on schedule'. Other than for Abasol, there are no changes to report in our original timelines.

### York has busied itself to raise additional capital

Last October, York raised £3 million. It then took the opportunity of the Rosanto acquisition to raise the money for the deal plus a few million extra for the kitty. York has also made noises to the effect that partner discussions are proceeding apace and that we might expect transactions shortly. We take this to mean York should sign one or more deals with up-front payments in the relatively near future.

### Abasol™'s approval in the UK is just the beginning

The UK's MHRA decision is far from the end of the abafungin story. The potential for a nail formulation was addressed in our initiation report. Subsequently, York announced a 'pessary' formulation for gynaecological applications, which we hinted at in our initiation review. This has now become a reality: as detailed in our May update and we believe that York is squaring up for a battle royal in the 'Women's Health' arena. Bayer is the current front-runner, but could always be outbid. Either way, York is playing the 'line extension' game to the fullest and should reap the ultimate benefits.

### The bounties of Phase II clinicals lie ahead

The avalanche of data from Phase II studies should consolidate York's position as a speciality Derm play and help to boost valuations. As we detail below, abafungin for nail, Sabarep and Vampex are approaching their Phase II initiations over the next few months and we expect a flurry of announcements. In addition, Sabarep's status as a GRAS<sup>1</sup> formulation for Atopic Dermatitis should lead to advanced US PoC clinical trials (Phase II/III most likely) in the not too distant future.

### The rest is chugging along apace and 'on plan'

According to York, the remainder of the portfolio is advancing as expected and we have no reason to doubt this. We expect further news over the next six to nine months.

### The company has added to products addressing markets of close to £1.2 billion

The addition of Rosanto and a 'pessary' version of abafungin for vaginal candidosis adds some portfolio candidates and markets, as well as eventual up-fronts and milestones. Our current valuations exclude these as too early stage, together with the skin diagnostics and acne products. This said, we see some up-front and milestone payments on the horizon for the pessary formulation of abafungin.

<sup>1</sup> Generally Recognised as Safe

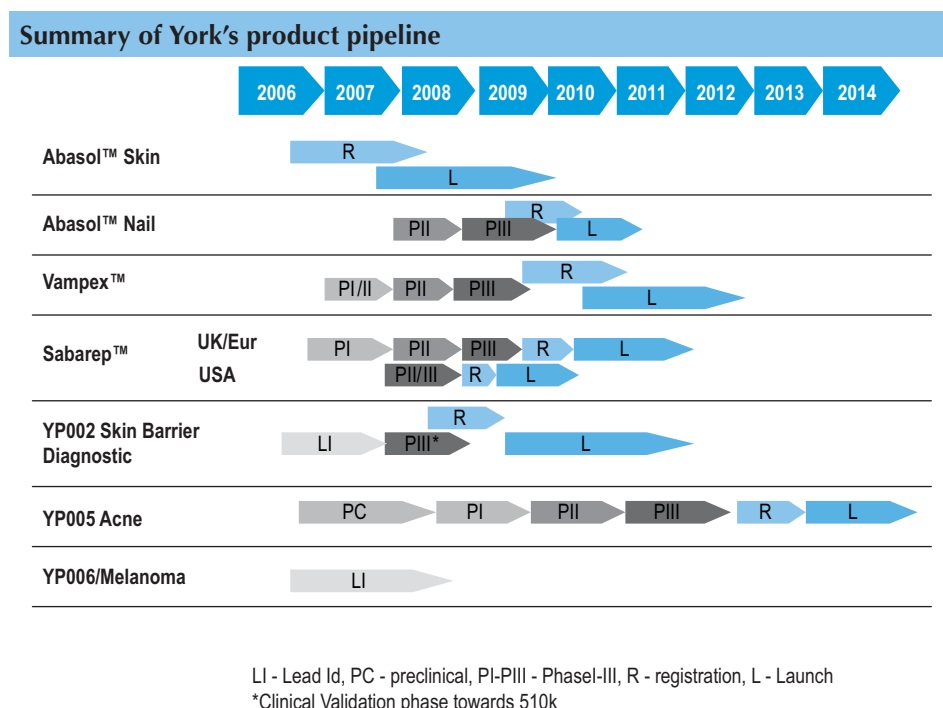
Our preliminary market estimates for the identifiable potential of York's products is around £1.2 billion. With the addition of the entire pipeline this expands by another £1.95 billion to £3.1 billion. We have included the melanoma project (YP004) with a low probability, because we believe that the latter will qualify for early up-front payments as York farms it out to a partner post lead identification. This is akin to the anti-cancer and anti-viral application of cyPG derivatives, also in early development, but where the identification of leads has not begun. These projects are too early in their development for their value to be quantified.

### The acquisition of Rosanto Pharmaceuticals adds another dimension

It is too early to tell whether Rosanto's **RPL228** will be the basis of an additional entry into the mild to moderate topical psoriasis market. The science behind Rosanto's portfolio is world class and the pharmacological targets of this class of drug (HSF-1 induction and NF-κB inhibition) are as hot as can be. Nonetheless, there are many barriers to overcome and the path to market fraught with risk. Net-net the gamble seems worth it. As with YP004, York intends to establish a preclinical PoC for the anti-viral and anti-cancer indications and then seek a development partner to take the project on. York has a pool of 600 compounds to choose from and Rosanto brings screening capabilities. The job is daunting but feasible and exciting.

### News flow should abound over the next 12 months

We expect 2007 to be eventful with the approval of Abasol for skin conditions pending, the entry of Sabarep and Vampex into Phase II trials imminent, clinical testing of a nail formulation for abafungin in view, and significant partnerships in prospect. Any pharma business may give rise to disappointment, but we are not aware of any untoward risks. In this instance, the stock offers attractive firepower through abundant news-flow, which we see propelling the stock towards the valuation levels we have set.



Source: Objective Capital

We have taken a fresh look at the valuation in our initiation report and the updates since. The following summarises the changes that we have brought to the model:

- the delay in the approval of Abaso<sup>l</sup><sup>TM</sup> has deferred revenues and pushed some costs into 2008;
- for the balance of the year and thereafter, we recognise the effects of the acquisition of Rosanto by way of incremental G&A and development costs;
- we have accounted for the most recent financing and the share issue;
- we have revisited our development costs for the lead portfolio candidates and adjusted where appropriate;
- we have updated the balance sheet and cash-flow statements in light of guidance at the time of the half-year results;
- our view of the potential for abafungin in nails (Onychomycoses) has improved on the basis that a fast drying 'lotion' formulation would be convenient and if effective, could take a big slice of the market;
- finally, we have improved the probabilities of selected programmes (Sabarep, Vampex and abafungin nail) on the news that appropriate formulations have been developed and are ready to enter advanced Phase II testing.

We have not accounted for:

- the potential of up-front and milestone payments on Rosanto nor the value of the lead development and preclinical work to be carried out over the next 15-18 months.
- the 'pessary' formulation of abafungin for vaginal candidosis for the time being, although we accept that this will generate corporate interest and offers the potential of up-front payments.

As a result, the improved probabilities in some of the lead programmes has been sufficient to offset the increase in the number of shares and the delay suffered in the approval of Abafungin. This pushes the valuation published in our note of 28 March 28 from £3.74 to £3.93.

The stock has risen over 50 percent since our initiation report of 28 November 2006. We believe that this reflects increasing confidence that the company's pipeline contains interesting candidates. Nevertheless, the price remains a far cry from our own. As with most AIM listed companies, the market continues to have a healthy dose of scepticism about development stage companies: as in the recent cases of Ark Therapeutics, Antisoma and Oxford Biomedica, only a validating corporate partnership will change perceptions. York have indicated that their partnership discussions are at an 'advanced stage' but experience tells us that deals can take longer than expected to close—shades of 'Waiting for Godot'! But such events certainly trigger revaluations.

York lacks revenues or profits, so the only applicable metric is price to cash. We present median, simple and weighted means of panels of US and UK stocks and a single Swiss exemplar, Basilea. Of course this approach is less than perfect, in that it captures only the value the market attaches to that fraction of the research programme for which finance is to hand. This recognised, we observe that York is at a discount to the US panel and Swiss exemplar, as well as the mean of UK, US and Swiss stocks, however computed.

## The acquisition of Rosanto Pharma

It is worth exploring the rationale for York's acquisition of Rosanto, as on the surface, this purchase might look like a diversion from York's main thrust. We do not suggest that the acquisition outweighs Abasol™, Sabarep™ and Vampex™ in the near term. To the contrary, it is unlikely that Rosanto's lead compound RPL228 will see the light of clinical day for some time.

Even so, we see the acquisition as an astute, value-orientated purchase of a technology complementary to York's position in topical psoriasis with Vampex, but with significant fringe benefits. To understand this, we need to delve into the science behind the cyclopentenone-derived products developed by Rosanto. Only then can we grasp the potential treasure trove. Nonetheless, a note of caution must be sounded at this point - the biological pathways involved are complex and not always fully understood.

As with Cox-2 inhibitors (with Merck's Vioxx the most egregious example), a good idea does not always translate into a safe drug. The central role of prostaglandin biosynthesis, the actions that these have in fundamental cellular processes and the complexity of the pathways that they affect leave room for devastating effects when unwanted pathways are blocked or turned on. Nevertheless, cyclopentenones are a legitimate therapeutic vehicle with specific effects on crucial pathways involved in inflammation, as well as the battles against viruses and cancer. The preliminary *in vitro* and *in vivo* data in all of these areas is encouraging. How much can be turned into useful drugs remains to be seen.

### **Cyclopentenone prostaglandins: exciting new therapeutic agents**

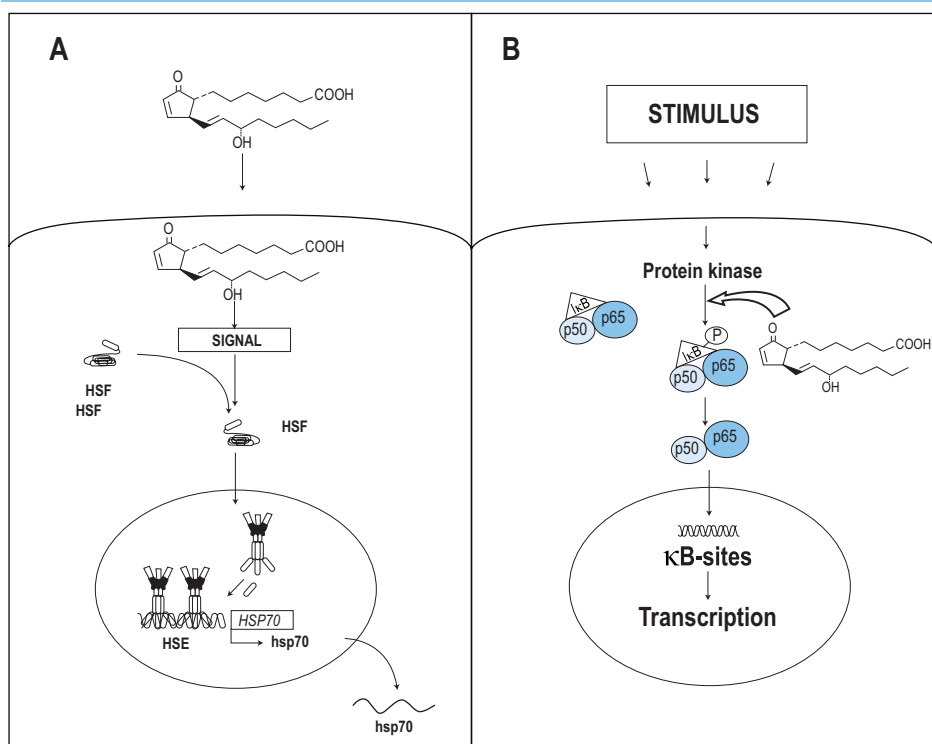
Over the past 25 years, much has been done to elucidate the role of prostaglandins (PG's). PGs are naturally occurring fatty acid derivatives which exert potent biological actions. They are synthesised from a pool of cell membrane components (called phospholipids) in response to external stimuli and act as a signal to regulate various physiological functions which when disrupted, can result in serious pathologies. They act as mediators in these pathologies regulating a wide variety of processes including inflammation, immune responses, cytoprotection and cellular proliferation and differentiation.

A subclass of PG's are called the cyclopentenone PG's, the most potent of which is 15-deoxy  $\Delta^{12,14}$  PGJ2 (or cyPG). cyPG was discovered to have potent antiviral activity by Professor Gabriella Santoro, one of the founders of Rosanto. She and others established its anti-inflammatory action and subsequently it has become clear that the activity of this class of molecules on the cell cycle make them ideal potentiators of cytotoxic chemotherapeutically induced cell death in cancer therapy.

There are two actions of cyPG's that have been extensively elucidated. cyPG's act specifically to induce a heat shock protein called HSP-70 via the activation of a factor called HSF-1 (heat shock factor-1). Evolution has caused cells of all species to develop a robust mechanism for defending their structural integrity. They do so via the activation of a complex defence mechanism in response to external environmental and chemically injurious stimuli, such as heat, nitrous oxide, cytokines<sup>2</sup> and others. This defence mechanism is complex and beyond the scope of this review. Suffice it to say that it is able to suppress cell death via a process called Cytoprotection. The latter acts to protect the integrity of folded three-dimensional cellular components (proteins), insuring that they are correctly refolded after damage from external stimuli. Similarly, the heat shock system has the ability to ensure that cells die when appropriate. These cellular functions are squarely aimed at the survival of the organism as a whole, but can also serve as a useful pharmacological target for certain pathological conditions where these protective or destructive actions can be galvanised into action.

The second mechanism cyPG's affect is a central DNA transcription factor that is an early mediator of immune and inflammatory responses in many pathological conditions. This central role has made it an important pharmacological target and cyPG's have been shown by Professor Santoro's group to inhibit the activation of this factor in human cells<sup>3</sup>. They further showed that this inhibition seems to be temporally correlated with the activation of HSF-1 in the heat shock system. Both of these are outlined in the accompanying diagrams.

### cyPG pathways



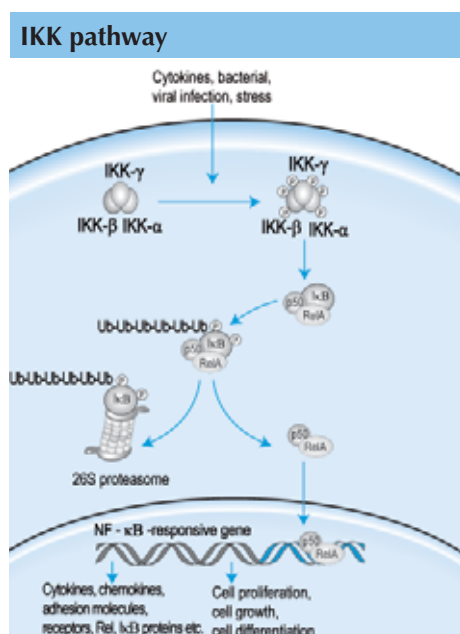
Source: Santoro M.G., *Biochem Pharmacology* **59**; 1;55-63 (2000)

<sup>2</sup> Cytokines signal peptides and proteins released by many types of cells and are particularly important in the immune response, inflammation and wound healing.

<sup>3</sup> Rossi A. et al, *PNAS*, **94**, p746-750

## cyPG and psoriasis

cyPG's function centres around its dual action in promoting the cytoprotective effects of the heat shock system on the one hand, and in inhibiting the NF- $\kappa$ B system. We now turn to the implications for inflammation and the role of this family of drugs in the resolution of inflammation in general and psoriasis in particular. Of the two, our knowledge of the NF- $\kappa$ B system is most comprehensive. TNF- $\alpha$  is intimately involved in the promotion of inflammatory responses. As seen on the accompanying diagram, NF- $\kappa$ B sits centrally in the pathway that ultimately releases it, translocates it to the cellular nucleus and promotes the transcription of genes responsible for the synthesis of a variety of factors (including TNF- $\alpha$ ). These promote further inflammation, tissue damage, cell proliferation, growth and differentiation; all part of the aetiology of psoriasis but also other auto-immune diseases such as rheumatoid arthritis, Crohn's Disease and the like. As we shall see, the NF- $\kappa$ B system also sits squarely in pathways involved in virus replication and the inability of cells to respond to cytotoxic drugs in cancer chemotherapy.



Source: Karin M. et al., *Nature Reviews*, 3, (2004), p17

As we describe later in this report, psoriasis is a hyperproliferative disease of the skin combined with the infiltration of immune cells which are secreting inflammatory factors triggering the visible skin pathologies seen in the disease (psoriatic plaque, inflammation, scaling, etc.). cyPG's are known to block the activation of NF- $\kappa$ B and reduce the levels of cytokines such as TNF- $\alpha$ . As reviewed recently<sup>4</sup>, NF- $\kappa$ B is activated in psoriasis, among other factors such as STAT1 and 3. Its activators include TNF- $\alpha$  or IL-1, through its cell surface receptor but also other more recently discovered cytokines such as IL-20 and IL-22. We will not run our readers through the scientific wringer, as there are 1300 genes that are known to be activated in psoriasis. Suffice it to say that blocking the activation of NF- $\kappa$ B by cyPG's obstructs a key step in the onset of inflammatory processes and possibly triggers other mechanisms aimed at the resolution of inflammation.

cyPG's are able simultaneously to block NF- $\kappa$ B and activate the synthesis of HSP70, a known cytoprotective and anti-apoptotic protein through the activation of a heat shock factor HSF-1. The links between these two mechanisms are unknown at present, but the rationale for using cyPG's to block inflammation and repair the damage inflicted by this psoriatic process can be derived readily from these two concomitant mechanisms.

## Rosanto's cyPG derivative library: the data

Rosanto Pharmaceuticals began life as Charterhouse Therapeutics. Prior to its recent acquisition by York Pharma, the company was a VC-backed venture seeking to build a family of cyPG derivatives using structure/activity and screening combined with chemistry to generate a library of around 600 compounds. A quick peak at the patent databases reveals a series of patents that describe a multitude

<sup>4</sup> Lowes M.A et al, *Nature*, 445, 22 February 2007, p866-873

of cyPG derivatives with different properties. The lead compound RPL228 is a potent cyPG mimetic that has been shown in an *in vivo* and various *in vitro* models to have potent activity in the inhibition of NF- $\kappa$ B, by comparison with the potent natural cyPG as well as the orally active anti-psoriatic drug dimethylfumarate (BG-12, Biogen Idec). In an *in vitro* study, RPL228 was found to be consistently more potent than all of these in keratinocytes and endothelial cells and as a blocker of TNF- $\alpha$  induced adhesion of Jurkat cells (immortalized T-Cells) and endothelial cells.

In an *in vivo* model (carrageenin-induced edema in rat paw), local application of low-dose RPL228 to a rat paw edema was shown to be effective in reducing the edema of acute inflammation.

In another *in vitro* study, RPL228 was shown to be effective at blocking the proliferation of both human keratinocytes and human endothelial cells. In keratinocytes it was more potent than the oral anti-psoriatic BG-12 and less potent than the anti-proliferator methotrexate, but more potent than both in endothelial cells.

In all these experiments, the dose required was low and non-toxic to the cells or animals involved.

### **Status and development path**

It appears that RPL228 is ready to enter into its pre-clinical phase testing, once an appropriate formulation has been developed. It is not anticipated that this drug will enter the clinic for twelve to eighteen months. The anti-viral and anti-cancer applications are at the lead identification stage, calling for extensive screening of Rosanto's library of six hundred compounds.

### **Other applications**

The central role played by NF- $\kappa$ B in cell proliferation and inflammation is only one of its attributes. It is also key to processes that viruses use to hijack the cellular machinery of their hosts to replicate. One of the key functions of this transcription factor is its anti-apoptotic function. As such, its ability to prevent cellular death is thought to be the reason that some cancers become resistant to both chemo and radiotherapy; elevated NF- $\kappa$ B levels have been seen in a number of cancers. This has led to the notion that the inhibition of NF- $\kappa$ B could be used to improve the efficacy of cytotoxic drugs in cancers that display multiple-drug resistance.

Both these functions lead to programmes, similar to YP004 in melanoma, where a degree of preclinical proof of concept can generate value by way of up-front and milestone payments, as well as royalties (albeit at a low rate) after launch. York has taken this on board and will attempt to mine the treasure trove of compounds in Rosanto's library to identify such candidates.

### Abasol™

In October 2006, York Pharma received the equivalent of an 'approvable' letter from the MHRA for the treatment of dermatophytic skin infections. This letter outlines the additional information that the company will need to provide in order to gain approval. Much of this information had already been anticipated by York and had been in preparation prior to receiving the letter and most has now been submitted. Delays now approach nine months and have set the company back against its development timelines. Nonetheless, delay does not necessarily translate into a non-approval. We see no reason, *a priori*, for the MHRA to reject Abasol; the data seems clear to us but we will have to await the final decision before opining further.

We accept management's view that a mid-2007 approval of Abasol remains on the cards. Were the drug approved by third quarter, we would anticipate launch in the UK in September/October; effectively pushing its launch into fiscal 2008. Pre-launch activity has been in full swing with opinion leader driven seminar programmes, significant work with the NHS at all levels (national, regional and local) and the targeting of Dermatologists, GP's and specialist nurses to make the launch as smooth and rapid as can be. Our take on this process is that by the time York is ready to launch, the uptake should be rapid. The market is hungry for a new drug that has an improved therapeutic profile. Lamisil's loss of proprietary status diminishes its value to the market. It is probable that our estimates for Abasol are conservative. We remember that Lamisil's achieved market penetration was beyond anyone's expectations: every time Sandoz (now Novartis) reported Lamisil results, estimates of its market potential had to be increased. We are not suggesting that this will necessarily be the case here but we do believe that the scope to underestimate the market potential for abafungin-based products is significant.

Following UK approval, the mutual recognition process for the EU would be initiated with a focus on Germany where York Pharma intends to engage in direct marketing and a roll-out would take place for the rest of Europe through mid 2008.

In parallel, we anticipate the signature of one, or a series, of partnership deals. The company has already indicated that discussions have reached the stage of term sheets, so closings should be in the air. We will await the identity of partners before opining on the significance for investors of these partnerships beyond cash for up-fronts and milestones (if any) and rates of royalty. In our view, York's management is fully aware of the financial community's appetite for credible, technology-validating partnerships and are unlikely to sign with minor players. Terry Sadler and his team know the drill.

## ***Other abafungin indications***

### **Onychomycosis indication**

York has announced that it has chosen a novel formulation for the delivery of abafungin (the API<sup>5</sup> of AbasoI™) for delivery through the nail to treat onychomycoses or skin fungal infections. The formulation is a fast-drying gel (called Abagel™) developed by what York claims is one of the world's foremost dermatological formulation teams. This means it will be squarely aimed at Sanofi Aventis's Penlac (a lacquer formulation of cicloprox), the leader in this market segment.

Abagel has been tested in a standard horse hoof membrane model as well as in human nail and infected human nails. This gel is hydrophilic (likes water!) and facilitates penetration of the drug through the nail. Initial data provided by the company demonstrates that Abagel, versus a standard lacquer formulation, enables roughly four times more drug to get into the hoof membrane in a 24 hour test; it also allows over ten times more drug to get through the hoof membrane in the same timeframe.

In our initiation report, we presented the failings of this treatment modality (significant relapse rates and 12-month treatment regimen) as an opening for a new, more convenient and effective treatment for this condition. Developing a formulation that improves drug penetration is the key to shortening treatment time.

According to York, the new formulation achieves this target. In addition it offers a broader spectrum of action (yeast and gram-positive bacteria in addition to Dermatophyte fungi), activity against both resting and active organisms and a dual mechanism of action (fungistatic and cell wall membrane disruption). Forthcoming clinical trials should demonstrate relative efficacy but any ability to show improved relapse rates will have to await longer-term trials and market usage.

York are planning to take Abagel into a Phase II dose ranging and safety study in H207 to be completed in late 2007. It estimates a further two years of testing before registration which is consistent with the 2009/10 timeframe we had previously estimated.

### **Lifecycle management redux: Vaginal candidosis**

In our initiation report, we hinted at the possibility that abafungin's highly active candidosis-related profile might trigger an additional programme for abafungin but that this would best be developed along with a third party. Infections of *Candida albicans* are a common cause of vaginal yeast infections.

York Pharma has developed an intra-vaginal ('pessary') formulation for which it has begun pre-clinical testing. We believe that the perceived demand for such a formulation is likely to trigger a partnership in the not too distant future.

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<sup>5</sup> Active Pharmaceutical Ingredient

The main market protagonist here is Bayer whose Canesten controls about 75% of the market with annual (2005) sales of an OTC formulation of around £114 million. Canesten's patent expiry and the switch to OTC is a beacon for the industry. One would think that Bayer (the original licensee of abafungin) might be the lead candidate for any such partnership if only to protect its franchise. However, other 'Woman's Health' players may wish to challenge Bayer, putting York in the middle of a possible bidding contest.

We have not assigned any value to this formulation as the product is still at a pre-clinical stage with no visible data.

## **Sabarep™**

### ***Summary and background***

Our initiation report of November 2006 covered the rationale for Sabarap™ in great length. In summary, the skin barrier formed through the dynamic process of keratinocyte migration, terminal differentiation and cell death results in a structure consisting of proteins and lipids tightly bound and providing tensile strength. This barrier is the skin's primary defence against environmental injury which, when broken down, can lead to serious inflammatory conditions.

The regenerative process underlying the integrity of this barrier is regulated by a system of factors and enzymes that ensure the continuous supply of the building blocks for this dermal barrier. Any disruption of this homeostatic<sup>6</sup> system can result in breakdown of the barrier, allowing the entry of damaging environmental substances, the genesis of inflammation and a cascade of defensive mechanisms. If left untreated such injury can lead to more serious conditions including Atopic Dermatitis (AD; atopic eczema). AD is particularly prevalent in infants and can have serious developmental and psychological effects. It has been shown to act as a platform for the longer-term development of allergies and asthma<sup>7</sup>.

### ***Formulation and clinical update***

In our initiation report we described the development of a novel formulation based on the work of Professor Michael Cork and Dr Simon Ward both at the University of Sheffield. This work is the result of 15 years of research and observation at the UK's largest pediatric atopic eczema clinic. The fundamental research was carried out in close collaboration with the University of Sheffield and York Pharma has taken the resulting clinical approach forward.

Inhibiting proteases in the skin (or anywhere else), completely, is not an appropriate therapeutic approach because this interferes with normal differentiation of the skin and impairs skin barrier function; what is required is reduction of the protease levels back to normal. Only this approach will result in a restoration of the normal skin barrier in patients with atopic eczema.

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<sup>6</sup> **Homeostasis** is the set of systems and conditions in cells and organisms that are essential for the proper maintenance of the latter's internal environment and the ability to sustain life

<sup>7</sup> The so-called 'Atopic March' as described by Spergel et al *J. Allergy Clinical Immunol.* (2003), 112;5;p118

Sabarep contains components that are classified as GRAS substances in the US which do not require clinical testing for FDA approval. However, a formulation of these substances that makes therapeutic claims will require full clinical trial validation to be credible with treating physicians and achieve the status of an ethical pharmaceutical product.

The other difficulty here, and this is where the key technological barriers lie, is to enable the penetration of key components through the skin. This seemingly intractable problem has taken several years to resolve, but has now been overcome, and will form the basis of a fundamental new patent to be filed shortly by York Pharma.

Initial clinical testing with a standard formulation has been conducted in volunteers with a variety of clinical histories including atopic eczema, irritant contact dermatitis sensitive skin and dry skin. These studies take the form of Functional Mechanistic Studies (FMS) in which known skin irritants (eg, topical steroids, tape stripping and soap) are used to damage the skin. Damage is measured by Trans-Epidermal Water Loss (TEWL) and the activation of skin proteases implicated in the homeostatic maintenance of the skin barrier.

The preliminary results showed that use of each of the main components of this formulation results in a significant reduction of TEWL at 24 hours and that the combination of the two has a synergistic effect as seen in the accompanying graphic. When tested against Diprobace™ (Schering Plough), Sabarep displays a greater than 50% reduction in IGA (Investigator Global Assessment) scores. The model used was dry skin induced by soap washes with the main advantage that soap, and the pH changes that it triggers, interacts directly with protease genes by increasing their activity and accelerating the breakdown of the skin barrier.

Dr Adrian Davis of Limeway Pharmaceutical Consultants, a renowned developer of dermatological formulations, has now developed a lead formulation for Sabarep™ which York is planning to take into Phase IIb clinical trials. A recent meeting with the MHRA has yielded a clinical pathway and proposed trial protocol.

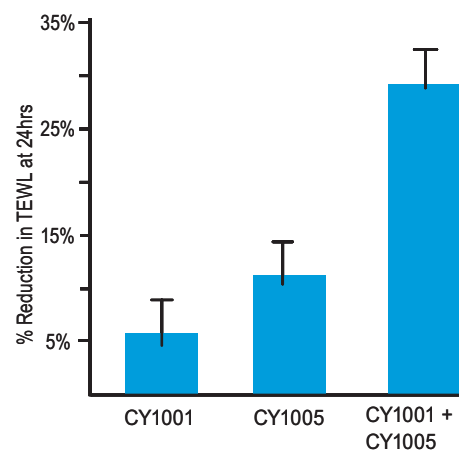
Two trials will be conducted: one in adults and the other in children. The adult trial will collect dose-escalation data to assess safety, tolerability and lack of irritation. The treatment sites for each patient will be located in areas that are historically predisposed to eczema. To ensure homogeneity; patients will be aged between 18 and 30 years of age. There will be 4 dosing regimens using a 2.5gr dose from once to 4 times a day for 8-12 weeks versus a placebo arm of the base/vehicle alone. York intend to recruit about 25 patients per arm of the study.

The endpoint measurements will include the number of flares, various standard objective/subjective measures of disease and the level of steroid rescue within the context of the patient's history one year prior to the trial.

The trial in children, between 2 and 8 years of age, will be similar to the adult trial except that the comparator arm will use Diprobace as a reference treatment. The latter will be applied twice daily and will continue for 6 months beyond the 8-12 week trial to provide additional safety and efficacy data. Patient enrolment will be comparable at 25 per arm although York will recruit up to 50 patients for both of the Sabarep and Diprobace twice-daily treatment study arms.

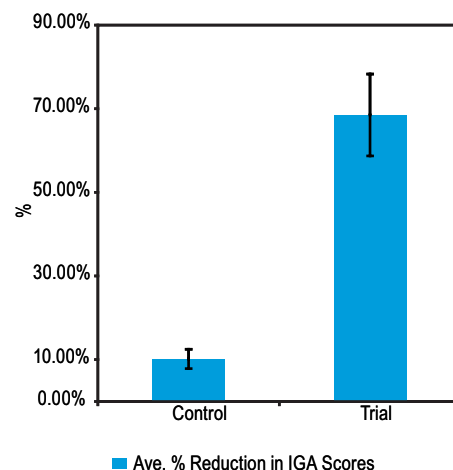
### Skin protease inhibitors

in reduction of TEWL



### Clinical assessment

Sabarep™ vs Diprobace™



Source: York Pharma

The company have said that they will enter into this Phase IIb trial in H2 2007 which, from the protocol above, looks like it would run into early 2008 with the initiation of a Phase III trial in the UK slated for mid 2009. In the US, given the GRAS nature of the product, York are planning to file a 'paper NDA' based on the conduct of, what will most likely be a Phase II/III type clinical trial with some safety testing.

### ***Market potential and competitive environment***

There are two major drivers in the topical treatment of atopic eczema: the prevention of flares and their treatment once they have developed. There are many therapeutic options for treating flares, including a range of potent topical corticosteroids and calcineurin inhibitors. These treatments are effective and, for the most part, regarded as safe if used appropriately. However, when topical corticosteroids are used excessively, their effects are lessened and they can damage the skin barrier.

The major unmet medical need in the treatment of atopic eczema is in the prevention of flares which can be achieved by effective restoration of the skin barrier. While emollients are useful products in producing a partial repair of the skin barrier, it is only by modulating protease activity that normal function of the skin barrier can be restored. The resulting reduction in the number of flares can also lead to a reduction in their severity when they do develop. This also means that the quantities of topical corticosteroid and calcineurin inhibitors required to control the eczema, can be reduced; the positive health economic implications of this are self-evident.

### **Vampex™**

#### ***Background and summary***

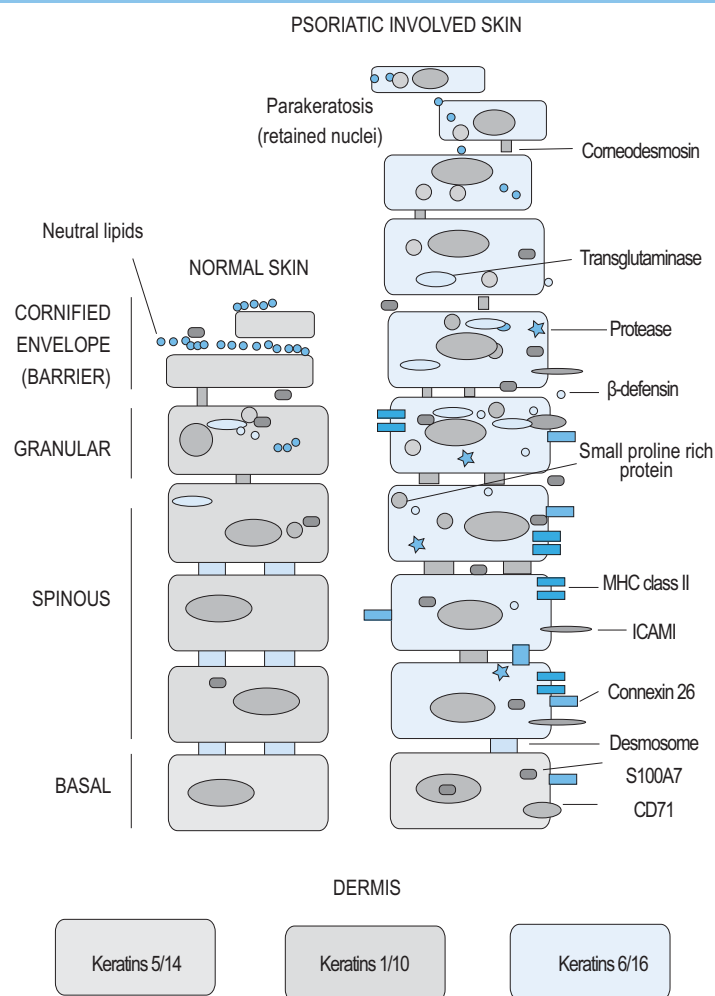
How lucky can a company get? To discover a completely new pharmacological/therapeutic class on the basis of a 35 year old drug for a completely different disease is serendipity that appears infrequently in this industry. The discovery that carbenoxolone, a drug previously used as a cytoprotective agent in ulcers for over 30 years, is also an effective inhibitor of retinol dehydrogenase is the basis for the use of Vampex in the treatment of psoriatic plaque.

As detailed in our initiation report, the body's Vitamin A (retinol) and D (D3 in this case) pathways are intimately linked to cellular proliferation and differentiation of the skin. The ultimate phenotype (ie morphological symptom) of psoriasis is based on the malfunction of this proliferation/differentiation pathway so delicately maintained in the regeneration of skin.

It is believed that psoriasis is an immune-mediated disease resulting in the hyperproliferation of keratinocytes in the skin and a general reduction in terminal differentiation of the latter. The resultant thickening of the epidermis (shown in the accompanying diagram) contains a granular layer of incompletely differentiated keratinocytes that aberrantly contain a cell nucleus (a process called parakeratosis).

The characteristic scaling seen in psoriatic lesions results in a breakdown of the skin barrier caused by a failure of the psoriatic cells to stack normally, secrete extracellular lipids and to adhere to each other<sup>8</sup>. As explained previously, the finding in embryos that the triggering of a local Vitamin A deficiency promotes premature cellular differentiation and maturation<sup>9</sup> led to the concept of blocking Vitamin A biosynthesis through the inhibition of the enzyme retinol dehydrogenase. This underlies the view that pushing undifferentiated or incompletely differentiated keratinocytes into terminal differentiation would tip the balance of skin regeneration towards its normal state and thus restore the integrity of the skin barrier.

### Cellular molecular anatomy of psoriasis



Source: Adapted from Liu Y. et al *Genes and Immunity* (2007) **8**, 1-12

<sup>8</sup> Lowes M. et al., *Nature*, **445**, p866 (2007)

<sup>9</sup> Kastner P. et al, *Development*, **124**, p4749

### ***Formulation and clinical update***

After completing a successful Phase IIa study in 2006 (a Proof of Concept trial with 12 patients) York have met with the MHRA and mapped out a development path for the drug. They are currently optimising the formulation and are leaning towards a cream that enables high penetration of the active ingredient while resulting in limited systemic uptake. The process of narrowing all of this down is likely to take a few more months.

It is likely that once basic animal work has been completed, York will jump to a Phase IIb study rather rapidly. The design of the Phase IIb trial will most likely include 4 arms comprising 3 dosage arms against a control. This trial should be initiated sometime in the second half of 2007 and will last for around 6 months thus enabling a mid 2008 initiation of a full Phase III study. Given the size of the trials that need to be conducted in this therapeutic category, we do not exclude the possibility that York may opt for an early partnership while retaining certain geographical rights.

With the acquisition of Rosanto, York have bought into a different path to the resolution of psoriatic conditions. RPL228 focuses primarily on the resolution of inflammation. RPL228 is the lead compound to be taken forward for the treatment of inflammatory conditions associated with psoriasis. While cyclopentenones are also believed to induce keratinocyte differentiation, their primary therapeutic targets are anti-inflammatory in nature. Hence, while there is some crossover between Vampex and RPL228, there is also the potential to segment patients to one or the other.

### ***Market and competitive analysis***

We have previously estimated that the topical anti-psoriasis market will grow to around £900 million by 2014 (from around £400 million in 2007). The market is dominated by Vitamin D3 analogues (Dovonex) and corticosteroids (bethamethasone). All of these products are less than ideal. The need for a safe, well-tolerated, efficacious product for mild to moderate psoriasis is great. Our previous estimate for peak sales for York Pharma of £150 million by 2015 was based on a 14% penetration of the market. These numbers could prove to be conservative as ever in a market where the therapeutic void is so great.

## Rest of portfolio

Not to minimise the importance of 'the rest' of the portfolio, there is little new to report. The programmes are all advancing according to plan.

### **YP002 diagnostic**

Aimed at developing a test to diagnose and profile an impaired skin barrier, its main function is as a companion diagnostic to Sabarep. However, it has much wider application as a 'Point of Care' (10-15 minute 'skin strip' test) diagnostic to classify/profile skin condition patients that are at age's below 25 years.

The approach uses proteomics<sup>10</sup> which looks at the integrity of a particular protein marker to evaluate the degree to which a patient is afflicted with skin barrier dysfunction (eg, normal, mild sensitive, moderate sensitive, dermatitis). If an appropriate marker can be identified (and York is on a path to do just that), the degree to which it has been digested can be measured using this technique. York have indicated that it expects to have the biomarker id/optimization phase completed by Q4 of 2007.

### **YP004-Melanoma**

Based on the concept of VAMP inhibition, YP004 is aimed at blocking a protein called RPE65 which is required for the uptake of the native, transported form of retinol (all-trans retinol). This blockage is meant to create a Vitamin A deficiency which should reduce cellular proliferation by shifting cells into differentiation. The application of this concept to melanoma forms the basis of a novel intellectual property platform with possible applications to other cancers. The company has been conducting proof of concept testing using novel technology such as Fab fragments, RNA interference and small molecule blockers with an *in silico* modelling system (computer modeling). York expects to have a licensing package ready by the end of fiscal 2007.

### **YP005-Acne**

YP005 is based on a patented application of a naturally occurring skin lipid called sphingosine-1-phosphate which is involved in the turnover of skin cells. It is currently in pre-clinical testing with the University of Berlin, funded by a significant grant from the German government. It is being positioned as a naturally-based treatment for acne, blocking the progression of the disease through a dual mechanism of action. It acts to inhibit the proliferation of keratinocytes around the hair follicle and appears to have both anti-inflammatory and anti-bacterial properties. York is exploring a liposome-based nanoparticle formulation of the drug to facilitate its delivery and improve its half-life and duration of action.

Our expectations for market potential remain unchanged.

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<sup>10</sup>Proteomics is an analysis that looks at the proteins synthesised as markers for the underlying genes that are activated. If one knows what one is looking for, differences detected can be markers of an underlying pathology.

# Financials

<b>Income statement</b>						
Year ending September (£m)	2004	2005	2006	2007E	2008E	2009E
Total sales	—	—	—	—	5.00	13.50
Cost of sales	—	—	—	—	1.00	2.70
Gross profits	—	—	—	—	4.00	10.80
Licencing	—	—	—	—	—	1.90
Milestones & upfronts	—	—	—	9.00	16.00	51.00
<b>Total revenue</b>	<b>—</b>	<b>—</b>	<b>—</b>	<b>9.00</b>	<b>20.00</b>	<b>63.70</b>
SG&A						
Depreciation	—	—	—	—	—	—
Amortisation		0.30	0.30	0.38	0.34	0.31
SM	—	—	0.44	2.41	5.40	6.35
G&A		0.55	1.86	2.15	2.55	3.75
Development costs		2.35	3.84	4.70	14.10	16.70
Total SG&A	0.42	2.80	6.44	9.64	22.39	27.11
Other operating income			0.36			
Earnings before financing costs (EBIT)	(0.42)	(2.80)	(6.08)	(0.64)	(2.39)	36.59
Interest receivable	0.01	0.11	0.20			
Other finance costs						
<b>Pretax profit (loss)</b>	<b>(0.41)</b>	<b>(2.69)</b>	<b>(5.88)</b>	<b>(0.64)</b>	<b>(2.39)</b>	<b>36.59</b>
Taxes(credit)	—	—	—	—	—	6.67
Net income (loss)	(0.41)	(2.69)	(5.88)	(0.64)	(2.39)	29.92
- Dividends	—	—	—	—	—	—
<b>Net retained income</b>	<b>(0.41)</b>	<b>(2.69)</b>	<b>(5.88)</b>	<b>(0.64)</b>	<b>(2.39)</b>	<b>29.92</b>
Average shares outst.	5.81	14.94	22.63	27.00	31.55	31.55
<b>Earnings per share (pence)</b>	<b>(7.00)</b>	<b>(18.01)</b>	<b>(26.00)</b>	<b>(2.37)</b>	<b>(7.59)</b>	<b>94.83</b>

<b>Cash-flow statement</b>						
Year ending September (£m)	2004	2005	2006	2007E	2008E	2009E
From operating activity						
Net income (loss) from continuing operations	(0.42)	(2.80)	(5.88)	(0.64)	(2.39)	29.92
Depreciation	0.00	0.01	—	—	—	—
Accounts receivable	(0.06)	(0.20)	(0.06)	(0.17)	(0.70)	(0.26)
Accounts payable	0.05	(0.24)	0.20	0.41	0.84	1.71
Inventory		—	—	—	(1.25)	(3.38)
Intangible assets amortisation	0.05	0.30	0.30	0.38	0.34	0.31
Cash from operations	(0.37)	(2.94)	(5.45)	(0.02)	(3.16)	28.31
Tax Paid	—	—	—	—	—	—
<b>Cash flow from operating activities</b>	<b>(0.37)</b>	<b>(2.94)</b>	<b>(5.45)</b>	<b>(0.02)</b>	<b>(3.16)</b>	<b>28.31</b>
From investing activities						
Capex	(0.00)	(0.04)	(0.04)	—	—	—
Purchase of intangible assets	(0.27)	(0.03)	(0.20)	—	—	—
Acquisition transaction costs	0.02	(0.17)	—	—	—	—
Cash acquired on acquisition	—	2.02	—	—	—	—
Payment of deferred consideration	—	—	0.20	—	—	—
Net interest received	0.01	0.11	0.19	—	—	—
<b>Net inflow (outflow) from investments</b>	<b>(0.24)</b>	<b>1.90</b>	<b>0.15</b>	<b>—</b>	<b>—</b>	<b>—</b>
From financing activities						
Issue of ordinary shares	1.10	7.52	0.11	8.25	—	—
Net Cash Provided for(used in)						
Financing Activities	1.10	7.52	0.11	8.25	—	—
<b>Net Change in Cash</b>	<b>0.49</b>	<b>6.48</b>	<b>(5.19)</b>	<b>8.23</b>	<b>(3.16)</b>	<b>28.31</b>
Cash position and cash per share						
Net funds						
Beginning of year	—	0.27	7.00	1.81	10.04	6.88
End of year	0.49	7.00	1.81	10.04	6.88	35.19

## Balance sheets

Year ending September (£m)	2004	2005	2006	2007E	2008E	2009E
Fixed Assets						
Intangible						
Patents & licences	0.65	0.63	—	—	—	—
Goodwill	0.45	3.53	—	—	—	—
Total	1.10	4.16	3.74	3.35	3.01	2.70
Tangible assets	0.00	0.05	0.06	0.06	0.06	0.06
Total fixed assets	1.10	4.21	3.80	3.41	3.06	2.75
Current assets						
Inventories	—	—	—	—	1.25	4.63
Other debtors and prepayments	0.06	0.28	0.35	0.53	1.22	1.48
Cash and equivalents	0.52	7.00	2.94	10.04	6.88	35.19
Total current assets	0.58	7.28	3.29	10.57	9.35	41.30
Current liabilities						
Deferred consideration	0.40	0.20	—	—	—	—
Accounts payable	0.05	0.19	0.39	0.80	1.64	3.35
Trade creditors	0.02	0.06	0.34	—	—	—
Other creditors	0.01	0.03	0.05	—	—	—
Accruals/other	0.03	0.10	1.38	(0.08)	(0.08)	(0.08)
Total current liabilities	0.45	0.39	1.77	0.72	1.56	3.27
Net current assets	0.12	6.89	1.52	9.68	7.63	37.86
Total assets- current liabilities	1.22	11.10	5.32	13.09	10.70	40.62
Long term financial liabilities	—	—	—	—	—	—
Total long term liabilities	—	—	—	—	—	—
<b>Net assets</b>	<b>1.22</b>	<b>11.10</b>	<b>5.32</b>	<b>13.09</b>	<b>10.70</b>	<b>40.62</b>
Shareholders equity						
Common stock	0.45	1.12	1.13	1.50	1.50	1.50
Share premium account	0.78	7.89	7.98	15.86	15.86	15.86
Share option reserve	—	—	—	0.16	0.16	0.16
Merger reserve	0.40	5.19	5.19	5.19	5.19	5.19
Retained earnings (Loss)	(0.41)	(3.10)	(8.98)	(9.62)	(12.01)	17.90
<b>Total</b>	<b>1.22</b>	<b>11.10</b>	<b>5.32</b>	<b>13.09</b>	<b>10.70</b>	<b>40.62</b>

Source: Objective Capital

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