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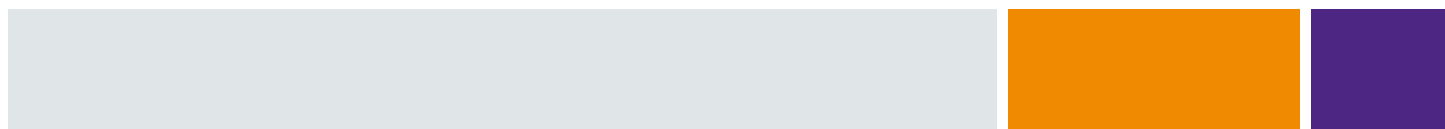
Deal Insight:

**Protherics and AstraZeneca
(Licensing and Co-Development Agreement
for CytoFab[™], December 2005)**

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1. Introduction

1.1. Purpose of analysis

The purpose of this report is to provide Biotech Pharmaceuticals with an insight into the key features and strategic rationale of the deal between Protherics and AstraZeneca, for the development and commercialisation of the severe sepsis treatment CytoFab™, signed in December 2005 (Deal no. 22850).

1.2. Methodology

This Deal Insight has been prepared by PharmaDeals® Research using a combination of proprietary, purchased and public information sources including, PharmaDeals® Agreements, Evaluate Pharma, Adis Insight and corporate websites.

1.3. Presentation of Results

In order to provide the written commentary in the context of the supporting data, the results are presented as a combination of figures, tables and text. Data sources are referenced where appropriate. Deal numbers refer to the corresponding entries in the PharmaDeals® Agreements database.

2. Executive Summary

Severe sepsis currently represents a significantly unmet clinical need and a commercial opportunity in a market that is worth over US\$1 B annually worldwide. Protherics is a UK-based biopharmaceutical company that has developed an ovine polyclonal anti-TNF α Fab fragment, that neutralises TNF α and has been shown in Phase IIb trials to have clinical efficacy in the treatment of severe sepsis. In 2004, having explored its options, the company decided to seek a partner to complete the drugs development and commercialise it for sale. In December 2005, Protherics signed a deal with AstraZeneca, potentially worth US\$ 339.3 M dollars for the development and commercialisation of CytoFab™ for the treatment of severe sepsis, securing an upfront payment and equity investment worth a total of over US\$41 M and a 20% royalty on all sales. Since the deal was signed, AstraZeneca has expanded its development plan and Protherics has met the requirements for the first development milestone, receiving a US\$10 M payment in April 2007. The deal represents the successful implementation of Protherics' original strategy and should provide them with substantial short-, mid- and long-terms revenues. It also forms part of AstraZeneca's ongoing strategy to supplement a relatively weak late-stage pipeline through externally-source products. The relatively high value is the combination of a strong product candidate, an open market opportunity and the sustained pressure that AstraZeneca is under to fill a relatively weak late-stage pipeline.

3. Company Profiles

3.1. Company profile: Protherics

Protherics is a publicly-traded, integrated biopharmaceutical company, with a focus on the development and marketing of products for critical care and oncology. Headquartered in London, UK, the company also has operations in the US and Australia. The company was formed in 1999 through the merger of Therapeutic Antibodies with Proteus International, already a publicly listed company (Deal no. 04381). Protherics’ original strategy was to develop its niche products in-house, in order to generate revenue streams to fuel the development of its other, higher market-value products, to a point at which they could be out-licensed to larger, global pharmaceutical companies for full commercialisation.

By December 2005, Protherics had largely realised this strategy, building a portfolio of both marketed niche products, as well as progressing its other major market products to various stages of clinical development (Table 1).

Product	Status	Indication	Partners (Deal no.)
CroFab™ (Crotalidae polyvalent immune Fab (Ovine))	Launched	Croatalid envenomation	None
DigiFab™ (Digoxin immune Fab (ovine))	Launched	Digoxin toxicity or overdose	None
ViperaTAb™ (Viperidae polyvalent immune Fab (ovine))	Launched	Vipera berus envenomation	None
Voraxaze™ (Glucarpidase)	Registration	Treatment of methotrexate toxicity	None
CytoFab™ (Anti-TNF alph polyvalent Fab (ovine))	Phase II	Severe sepsis	None
Prolarix™ (Caricotamide/tretazicar prodrug combination therapy)	Phase I	Liver cancer, solid tumours	None
Angiotensin therapeutic vaccine	Phase I	Hypertension	CoVaccine (24387)

Table 1. Protherics’ product portfolio at the start of December 2005 (Source: Protherics)

The successful implementation of its business plan has provided Protherics a reliable revenue stream, with net sales growing from US\$6 M in 2000 to US\$36 M in 2003 (Figure 1).

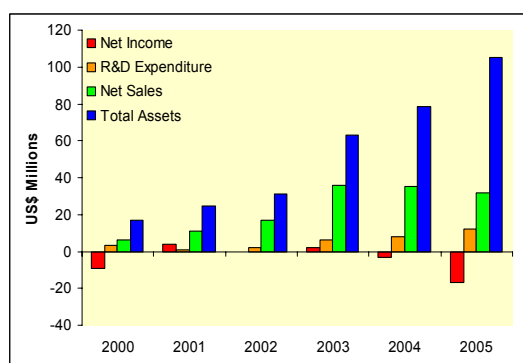


Figure 1. Selected Protherics financials.

However, these revenues decreased in 2004 and again in 2005. Overall, the company has performed relatively well, achieving positive net incomes in a number of years, increasing its investment in R&D and growing its assets to over US\$100, including an acquisition of Enact Pharma for US\$11.5 M in 2003 (Deal no. 13041)

Following a review of the product and having invested heavily in its development, in 2004, Protherics decided that it was ready to seek a partner to complete the development of CytoFab™. Therefore, one of the key strategic goals for 2005 was to secure an appropriately-valued deal in order to generate a return on its past investment.

3.2. Company profile: AstraZeneca

AstraZeneca is a global pharmaceutical company that has ranked amongst the top ten since it was created through the merger of Astra AB and the Zeneca Group in 1998. With a diverse portfolio of marketed products in a number of key therapeutic areas, the company had seen sustained growth in the five-year period up to 2005, with net sales increasing from US\$15.6 B in 2000 to just under US\$24 B in 2005 (Figure 2). Overall, in 2005, the company delivered a 43% increase in operating profit compared to the previous year.

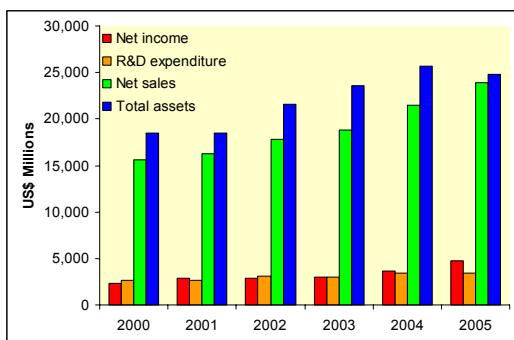


Figure 2. Selected AstraZeneca financials.

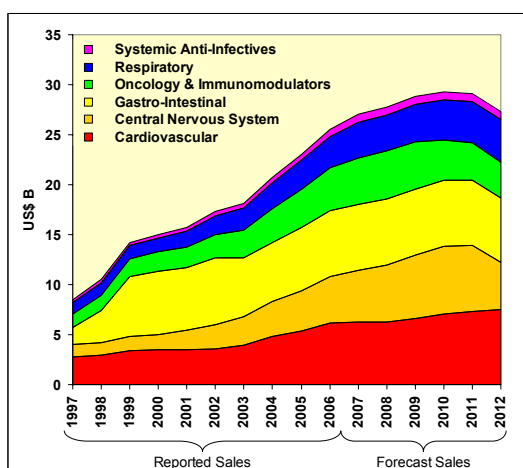


Figure 3. AstraZeneca's reported and forecast sales figures by therapy area (Source: Evaluate Pharma).

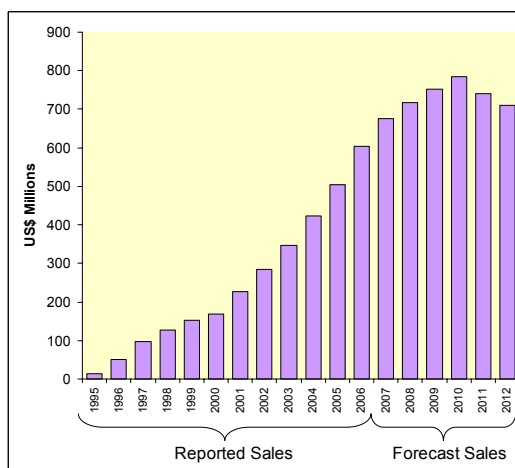


Figure 4. Reported and forecast sales for Merrem® (meropenem) (Source: Evaluate Pharma).

This performance was driven by increased sales across all therapy areas, in which AstraZeneca had marketed products (Figure 3). The two key areas from which AstraZeneca derives its income are cardiovascular and gastrointestinal; systemic anti-infective products comprise only a very small percentage of its overall revenues, which are primarily derived from a single product, Merrem® (meropenem), an ultra-broad spectrum beta-lactam antibiotic for the treatment of bacterial infections, including meningitis and pneumonia. Annual sales reached US\$500 M for Merrem® in 2005, and are forecast to reach around US\$800 M at their peak in 2010 (Figure 4).

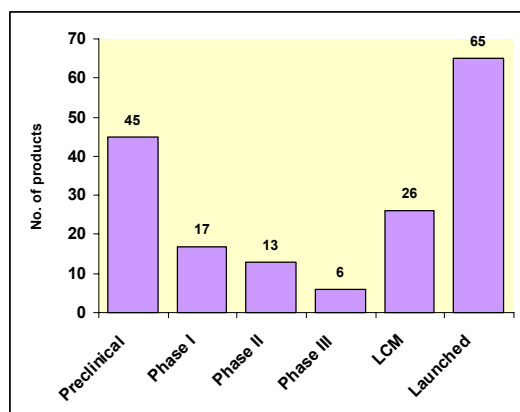


Figure 5. AstraZeneca's portfolio and pipeline by phase in December 2005 (Source: AstraZeneca).

At the time the with Protherics was signed, AstraZeneca had been performing well in general, but there were concerns regarding the long-term prospects of its late-stage R&D pipeline: With only 6 products in Phase III trials, AstraZeneca were heavily reliant on line-extensions and life-cycle managements to create new revenue streams (Figure 5). Despite the fact that the early-stage pipeline was relatively well-stocked, the pressure was on to take steps to strengthen the pipeline, particularly in view of the impending loss of future revenues, as its blockbuster products Seloken[®], Pulmicort[®] and

Casodex[®] faced patent expiry in 2007/2008.

Therefore, one of the key aspects of AstraZeneca's ongoing strategy was to seek to acquire additional products through licensing deals and collaborations.

4. Key products

4.1. Market overview

It is estimated that there are about 750,000 cases of severe sepsis in the US each year, with nearly half of these patients requiring admission to intensive care units (ICU) and between 200,000 and 300,000 going on to develop septic shock. Estimations place the incidence of severe sepsis in Europe at similar levels. What is more, as sepsis occurs most often in the very old and the very young, these incidence rates are likely to increase over the next few years as a result of the expanding elderly population. As the mortality rate for severe sepsis varies between 20% and 60%, this condition represents a major cause of death in a number of countries. The significance of the health burden is further emphasised when the cost of care is taken into account. In the UK, severe sepsis represents around 27% of ICU admissions and 46% of all ICU bed days, and the cost of treating an ICU patient is estimated to be six times more expensive than treatment on a standard care ward. In the US, the treatment of patients with severe sepsis costs approximately US\$17 B annually. Additionally, many of the patients who survive an episode of severe sepsis or septic shock will also require long-term health care because of permanent organ or tissue damage.

Overall, severe sepsis and septic shock represent a major health and financial burden, and a significant unmet clinical need. The treatment of severe sepsis can be broken down into three different components. The first is the identification and treatment of the underlying infection; where possible, the therapy should be tailored to the infectious organism. However, this process is time critical and empirical treatment with wide-spectrum antibiotics is routinely employed until blood cultures can be completed. The second treatment component is haemodynamic and respiratory resuscitation: relieving respiratory distress by providing oxygen, and the intravenous administration of fluids and vasoactive drugs to restore blood volume and treat low blood pressure. Both of these components use a range of both branded and generic drugs which are designed to treat these medical conditions both in and out of the context of severe sepsis. However, there has been much effort on developing novel products for the third treatment component: modulation of the host inflammatory response.

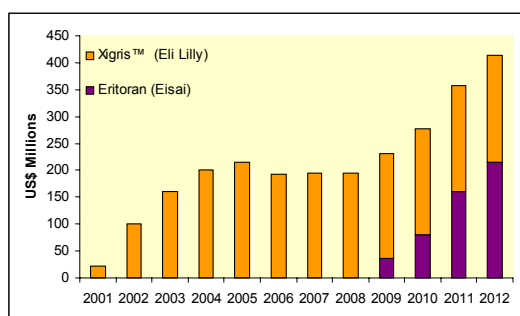


Figure 6. Reported and forecast sales for severe sepsis therapies (Source: Evaluate Pharma).

Currently, there is only a single approved product that has been shown to improve patient survival during severe sepsis: Eli Lilly's Xigris™ (drotrecogin alpha), which is a recombinant form of human activated protein C that modulates microvascular function by decreasing inflammation and coagulation, and increasing fibrinolysis. Xigris™ sales (*Figure 6*), have failed to deliver the blockbuster returns that were hoped for, and have been hindered by the fact that the major side-effect of Xigris is a risk of serious bleeding events, so its use is contraindicated in patients with active internal bleeding, haemorrhaging stroke and trauma with life-

threatening bleeding. As this patient group represents a significant proportion of the at-risk population and dysfunction of the coagulation process is common in severe sepsis, as few as 25% of patients may be eligible for Xigris treatment. Additional issues with the relatively high cost of treatment (about US\$1700 per day) have also hindered sales progress. Therefore, with the current potential market estimated to worth at least US\$1 B worldwide, there is a considerable market opportunity for effective new therapies in this area.

4.2. Product summary

CytoFab™ is an ovine, polyclonal anti-Tumour necrosis factor (TNF)-alpha Fab fragment that was developed by Protherics', using the same technology that it used to develop its currently marketed Fab fragment products (*Table 1*). It exerts its effects by binding to and neutralising TNF- α , a key part of the inflammatory response and largely responsible for amplification of the inflammation cascade. TNF- α has been implicated in the aetiology of a number of diseases and conditions, with TNF- α antagonist therapies generating over ten billion dollars of sales in 2006 alone.

During its development, Protherics has conducted clinical trials to assess the potential of CytoFab™ in transplant rejection (Phase I), graft-versus host disease (Phase I), malaria (Phase II), Crohn's disease (Phase II) and Jarisch-Herxheimer reaction (Phase II), all of which were discontinued due to poor clinical efficacy.

Successful results for CytoFab™ in the treatment of severe sepsis were obtained in 1998, from an 81 patient, randomised, placebo-controlled, Phase IIb study conducted in the US. Although the results showed significant clinical benefits in terms of a reduction in the number of days spent on ventilation and in intensive care, Protherics decided not to pursue further development at the time, preferring instead to investigate other indications that might require fewer patients to demonstrate efficacy. As mentioned, in 2004, the company undertook a review of the product and came to the conclusion that its best option was to seek a licensing partner to commercialise the product for use in severe sepsis.

CytoFab™ is presented as having two key advantages over other anti-TNF- α antibody products:

- 1) It is a polyclonal product and hence multiple epitopes are targeted by different individual molecules, achieving potentially higher neutralisation levels than possible with monoclonal antibodies.
- 2) Antibody fragments (Fabs) are smaller in size than whole immunoglobulin molecules and so have greater and more rapid distribution into tissues, and a faster clearance rate. They also have better safety profiles as they do not bind to antibody (Fc) receptors causing inappropriate immune activation.

4.3. Competitor products

At the time of the deal, there were a number of other products in Phase II/III development that could be direct competitors to CytoFab™, which use various modes of action to inhibit the inflammatory response that occurs during severe sepsis (including a TNF α antagonist in Phase III), a number of which have now progressed from Phase II to Phase III (*Table 2*).

The most similar product to CytoFab™ is Abbott's afelimomab, which is a humanized monoclonal anti-TNF α Fab₂ fragment, which showed a modest increase in the 28-day mortality rates in a 998 patient Phase III trial in 1998. However, its current development status is not clear, and an internal product review has yet to determine this products' future.

It is important to note there have been a number of products that have reached late-stage development for the treatment of severe sepsis that have been discontinued due to poor clinical efficacy (*Table 3*).

Status		Drug	Mechanism Of Action	Originator
Dec-05	Jun-07			
Phase III	Phase III	Segard™ (Afelimomab)	TNF antagonists	Abbott GmbH & Co. KG
Phase III	Phase III	Pyridoxalated haemoglobin polyoxyethylene	Nitric oxide synthase inhibitors	Ajinomoto
Phase III	Phase III	TAK 242	Signal transduction pathway inhibitors	Takeda
Phase II	Phase III	Alkaline phosphatase	Endotoxin antagonists	AM-Pharma Holding
Phase II	Phase III	Eritoran	Lipid A antagonists, Toll-like receptor antagonists	Eisai
Phase II	Phase II	NOX 100 (Norathiol)	Nitric oxide antagonists, NMDA antagonists	Medinox
Phase II	Phase II	PMX 622 (Polymixin B-dextran 70)	Endotoxin antagonists	Novartis

Table 2. Competitor products in clinical development for the treatment of severe sepsis or septic shock in December 2005 (Source: Adis Insight)

Year Discontinued	Highest Phase	Drug	Product Type	Originator
1997	Phase-III	Humicade (CDP 571)	Anti-TNF mAb	Celltech Group
1998	Phase-III	Tilarginine	Small molecule	Cornell Research Foundation, M. D. Anderson Cancer Center
1999	Phase-III	Lenercept	TNFr:IgG1 fusion protein	Roche
2002	Phase II	IC 14	Anti-CD14 mAb	ICOS Corporation
2003	Phase-III	Tifacogin	Natural protein anticoagulant	Novartis
2006	Phase II	E 5531	Endotoxin-binding lipid emulsion	Eisai
2006	Phase II	270773	Synthetic endotoxin-anatagonist	Sepsicure

Table 3. Discontinued products for the treatment of severe sepsis or septic shock (Source: Adis Insight).

5. Deal terms

5.1. Details of terms

Under the terms of the agreement signed between Protherics and AstraZeneca on 8 December 2005, AstraZeneca took responsibility for developing CytoFab™ as a treatment for TNF-alpha mediated diseases in man, with an initial target indication of severe sepsis. AstraZeneca agreed to undertake all clinical development work for CytoFab(TM) and Protherics was to be primarily responsible for bulk drug manufacturing, including the supply of clinical trial material. The agreement became effective upon the expiration of the Hart-Scott-Rodino waiting period in the US in January 2006.

In the first instance, AstraZeneca indicated that it would begin a Phase III trial for severe sepsis in the US and Europe, sometime in 2007, upon completion, by Protherics, of improvements to the current manufacturing process.

The financial terms of the agreement place a total potential value of US\$339.3 M, comprising an upfront payment to Protherics of US\$28.36 M, a US\$13 M equity investment into Protherics by AstraZeneca (to be paid at 68.24 pence, 30% premium over previous three months average closing share price prior to signing the deal), and milestone payments totalling US\$297.5 M.

The milestone payments were to be made in accordance with the following events:

- a) Upon the decision by the process manufacturing and supply committee to progress the process science program to the manufacture of the first batch of the product
- b) Upon the commencement of the first Phase III trial
- c) Upon the decision to continue the first Phase III trial after the first interim analysis of the clinical outcome of the trial
- d) Upon filing of the application for the first health registration approval with respect to CytoFab™ in severe sepsis, wherever in the territory
- e) Upon the first commercial sale of the product in the United States
- f) Upon the first commercial sale of the product in any major European country
- g) Upon the first commercial sale of the product in Japan
- h) Upon the grant of the first health registration approval of the product for use in the first secondary indication in any major market

Protherics also stand to receive a royalty of 20% of all net sales and receive additional payments in return for the commercial supply of the product to AstraZeneca.

5.2. Commentary

The key feature of these deal terms is that Protherics secured a significant, non-stepped royalty rate of 20%. This means that it is not dependent on an increase in sales to achieve this relatively high royalty rate. Although the large upfront payment and equity investment provided a sizeable cash injection, Protherics will have needed to invest a proportion of this into improving its manufacturing capabilities in order to qualify for the later milestone payments. However, these improvements should be beneficial to Protherics overall and useable for its other antibody-based products.

Deal Rational

5.3. Key features, strategy and value

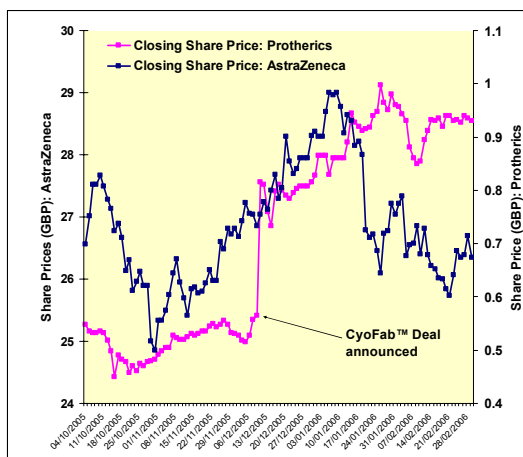


Figure 7. Protherics' and AstraZeneca's share prices (Source: LSE).

The announcement of the deal on 8 December 2005 resulted in an immediate 44% increase in Protherics' share price on the LSE, but made little difference to AstraZeneca share price. As it represented a significant landmark in Protherics drug development strategy, it was unsurprising that investors saw the deal as a very positive move for the company.

From the perspective of Protherics, the rational behind the deal was simple: having explored a variety of applications for CytoFab™, it had decided to pursue severe sepsis as its primary indication and needed to find a partner to complete its development and full commercialisation. This was always part of its strategy and the deal that was signed with AstraZeneca is a successful implementation of this. The key value areas for Protherics were the

direct cash payments and capital investment into the company that would allow it to improve its manufacturing facilities and help fund its other developmental programmes. If the drug is successful, the 20% royalty should provide it with a revenue stream that could more than double its annual income from its other marketed products and further enable the company to progress its other products, perhaps internally, without the need to seek development partners, thus increasing the potential for it to maximise its returns.

From AstraZeneca's perspective, the deal with Protherics forms part of an ongoing strategy to strengthen its developmental pipeline through licensing and collaboration deals. In addition to the deal with Protherics, AstraZeneca signed another four major licensing deals in 2005, committing a total of nearly US\$2.0 B to fund them (Table 4) This is in addition to its US\$210 M acquisition of KuDOS Pharmaceuticals, also in December 2005.

Date deal announced (Deal number)	Company	Product	Indication uses	Status	Total deal value
11/07/2005 (21012)	AVANIR Pharmaceuticals	AVP-26453 (AZD2479)	Cardiovascular disease	Phase 1	340
27/07/2005 (21184)	Astex Therapeutics	protein kinase B (PKB) inhibitors	Cancer	Discovery	275
22/12/2005 (22987)	AtheroGenics	AGI-1068	Atherosclerosis	Phase 3	1000
28/12/2005 (23000)	Targacept	TC-1734 (AZD3481)	Alzheimer's disease, schizophrenia, other cognitive disorders	Phase 1/2	300

Table 4. Additional major licensing and collaborative R&D agreements entered into by AstraZeneca in 2005.

The disparity of comparable deals within this therapy space makes it difficult to benchmark the headline value of this deal. However, US\$339 M is certainly in-line with the other deals that AstraZeneca entered into in 2005, indicating that the company was committed to expanding its pipeline through external sources and willing to spend what was necessary to secure the products. CytoFab™ represented an opportunity to gain access to a late-stage product in a market with a high unmet clinical need; with the only marketed product to treat sepsis, Xigris™,



critically failing to meet the market demand, leaving it wide open to competitor products. Although other companies are developing therapies to meet this clinical need, the majority use unproven mechanisms, and CytoFab™'s safety profile and the wealth of information available for other marketed anti-TNF α therapies, marginally decrease the risk that AstraZeneca would be taking. Given the nature of the condition and unavailability of alternative therapies, it is unlikely that pivotal Phase III trials will be overtly complex and lengthy, increasing the attractiveness of the product as a development candidate. Overall, it appears to be a simple case of supply meeting demand: AstraZeneca was looking to expand its pipeline and Protherics had a good product for sale. As a result, Protherics was able to negotiate favourable deals terms whilst AstraZeneca was able to add a promising novel therapy to its portfolio.

6. Progress and success

6.1. Current status of deal

Since the signing of the deal, CytoFab™'s development has progressed well. On 3 November 2006, AstraZeneca announced its intentions to expand its development plan following discussions with regulators in the US and the EU. It now intends to conduct an additional Phase II trial in order to support and aid in the design of its planned Phase II trial. On 12 March 2007, it was announced that Protherics had achieved its first milestone as a result of successfully scaling-up the CytoFab™ manufacturing process to a 600-litre batch size, receiving a US\$19 M payment in April 2007.

More positive news came at the beginning of 2007, when AstraZeneca announced a strategic review, re-focusing the companies R&D focus on key therapeutic areas, including infection. The company also reaffirmed its commitment to product acquisitions through externalisation, by signed another four deals worth over US\$2 B. It also reaffirmed its commitment to building its biologics business following its US\$1.1 B acquisition of Cambridge Antibody Technology in May 2006, with a US\$15.6 B acquisition of MedImmune in April 2007 (Deal nos. 24261, 27024).

However, AstraZeneca has suffered in recent years with a number of late-stage drug failures. In February 2006, AstraZeneca decided to withdraw its anticoagulant Exanta® (melagatran/ximelagatran), from the market owing to potential risk of liver side-effects. In May of the same year, the company discontinued the development of Galida™ (tesaglitazar), following safety concerns identified in Phase III trials. Further disappointment followed in October 2006, when the results of a Phase III trial for the ischaemic stroke drug Cerovive® (NXY-059) failed to demonstrate efficacy, ending both the development of the drug and the partnership with **Renovis** (Deal no. 12931). Most recently, AstraZeneca's and **AtheroGenics** anti-inflammatory cardiovascular product, AGI-1067, failed to deliver in Phase III trials; here, again, the partnership dissolved along with the considerable hopes of blockbuster returns that AstraZeneca had for the drug (Deal no. 22987). Termination of the partnership was announced on the 23 April 2007, the same day as the acquisition of MedImmune. These terminations must serve as warnings to Protherics, highlighting that there is no room for failure in a late-stage alliance with AstraZeneca, as the company does not have the financial flexibility to change track and invest capital in exploring opportunities for failed drugs in other indications.