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Therapeutic focus – Vertex success raises bar for thin CF pipeline

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Hopes that Vertex would follow its Kalydeco success with a second effective cystic fibrosis product might have been dented somewhat yesterday, but the fact remains that the company has made a big step forward in this incredibly challenging illness. Emerging signs that its agents might modify the course of the progressive lung disease, where in the past only symptom management could be offered, have rightfully raised hopes that real progress is finally being made.

However, with impressive improvements in lung function, Vertex's products have also significantly raised the bar for other agents being pursued in cystic fibrosis. A look at the development pipeline reveals slim pickings - anti-inflammatories look to be a dead end while gene therapy has well known and multiple challenges, leaving a couple of early-stage sodium channel blockers as the most hopeful avenues of research (see table).

On the market

Cystic fibrosis (CF) is a recessive genetic disorder characterised by an accumulation of thick, sticky mucus leading to chronic lung infections and progressive lung damage. Symptoms such as persistent cough, chronic chest and lung infections and poor weight gain occur in early childhood.

According to the World Health Organisation the prevalence of CF in the EU is 1 in 2,000-3,000 births, and 1 in 3,500 in the US. The median age of survival for a person with CF is 33.4 years with lung damage as the primary cause of morbidity and mortality.

The majority of CF drugs on the market are for symptom management. Antibiotics play a big part as patients are prone to bacterial lung infections, while digestive enzymes are also routinely taken, to help nutrition.

The biggest CF drug commercially is currently Pulmozyme from Roche, predicted to sell $550-$600m annually until 2018, according to consensus data from *EvaluatePharma*. A recombinant enzyme called deoxyribonuclease, the product has been on the market for 18 years and is used to manage respiratory complications.

It works by selectively cleaving extracellular DNA in the mucus, reducing its adhesiveness and viscoelasticity and helping in the removal of sputum.

Route cause

CF is caused by mutations in the gene encoding the cystic fibrosis transmembrane conductance regulator (CFTR) protein.

CFTR is an epithelial chloride channel involved in the transport of salt and fluid in multiple organs, including the lungs and digestive system. It facilitates the production of thin, freely flowing mucus, which is important for the lubrication and protection of the lining of the airways and other tissues and organs. Missing or defective protein leads to the symptoms of CF.

Numerous mutations have been identified in the CFTR gene, which cause a loss of function of the CFTR protein through different mechanisms. The most frequent mutation seen in around 70% of patients is a deletion of phenylalanine at position 508 on the gene – a mutation called F508del. This disrupts intracellular trafficking leading to a lack of functional protein at the cell membrane.

One of the next most common mutations is G551D, expressed by around 4% of patients. These sufferers have CFTR present at cell membrane but the protein has a gating defect, severely decreasing the opening of the channel.

Targeting CFTR

Modifying the underlying cause of the disease is ultimately the target for new therapies. CF patients typically lose 1-2% of their lung function each year, so a major goal has been to arrest this decline, possibly even

reverse it.

Until Vertex's Kalydeco, no drug treatment had managed to prove this might be possible. A CFTR potentiator that helps to improve the function of the CFTR protein once it reaches the cell surface, Kalydeco increases gating activity, allowing chloride ions to move in and out of the cell. Due to this mechanism of action Vertex tested the pill in patients who carry the G551D mutation.

Phase III data released in early 2011 created huge excitement and it took the FDA only three months to grant marketing approval. Impressive improvements in lung function compared to anything seen in CF before prompted the warm reception.

The drug significantly improved an important measure of lung function, FEV1, that measures the volume of air that can be expelled in one second. Over 24 weeks mean absolute change in FEV1 over placebo was 10.6 percentage points in one trial and 12.5 percentage points in a second, improvements that were sustained over 48 weeks and were much greater than expected (*Vertex's cystic fibrosis candidate exceeds hopes, February 24, 2011*).

"The effect size makes it highly probable that this will be disease modifying and will have an impact on prognosis," says Professor Stuart Elborn, Chair of the Scientific Advisory Committee at the Cystic Fibrosis Trust.

"Quantifying that at the moment is quite difficult because there is only really about three years of experience of using it, two of those have been in the clinical trial."

Data due in the next few years from longer term studies will shed more light on the durability of Kalydeco's affect, he says.

Approved at the end of January this year, within three months 600 people with CF had started treatment with Kalydeco, Vertex says. Sales reached $18m in the first quarter, analysts reckon that figure could grow to $1.47bn by 2018.

Considering the drug will not work for the majority of CF patients who carry the most common gene mutation, that is a substantial figure. Vertex hopes to expand the patient pool by studying it in patients with other, rarer mutations.

Expanding options

Earlier this month Vertex seemed to score again with encouraging interim phase II data from a second candidate, VX-809. The data blunder announced yesterday as well as further detail released punctured some of the excitement around the compound – in the eyes of investors at least – but overall the signs remain promising (*Vertex data blunder punctures high risk cystic fibrosis candidate, May 29, 2012*).

The compound, generically called lumacaftor, is a CFTR corrector, which works by increasing the movement of CFTR to the cell surface. It is targeted at patients with the most common mutation, F508del, whose symptoms are caused by a lack of functional protein at the cell membrane. The drug is being studied in combination with Kalydeco in an attempt to improve the gating of the protein's ion channel, once it is on the cell surface.

The trial from which data is gradually emerging was conducted in patients with both one and two copies, homozygous or heterozygous, for the F508del mutation; results from the latter group have yet to emerge and hopes are lower for success in this population.

Vertex reported yesterday that in the homozygous group, 35% of patients experienced an absolute improvement in lung function of at least 5 percentage points and 19% had at least a 10 percentage-point improvement. The figures were lower than results released previously (*Vertex's life after Incivek looking up after positive VX-809 data, May 8, 2012*).

In new information, the company said that patients on the drug combination experienced an 8.5 percentage point mean absolute improvement in lung function compared to patients treated with placebo, an impressive result tempered by the fact that the placebo arm experienced a surprisingly steep decline in lung function, more than 4%.

Raising fears

The corrected data raised fears that the drug might not help as many patients as first thought, and that the strong effect seen might be due to outlier patients. Meanwhile the placebo reading prompted some to speculate that replicating these results in larger, rigorous studies will be harder.

Despite undoubtedly looking riskier many financial analysts continue view the product as a likely success and approvable, and of much greater commercial potential than Kalydeco, given the broader patient pool.

"We believe the program is still game-changing for many patients with delF508 mutation," analysts at UBS wrote yesterday, pointing to the "highly robust" change in lung function.

“We believe there remains a notable efficacy signal even after the correction, although the signal does become meaningfully weaker, in our view, and the totality of full data, expected mid '12, becomes more crucial,” Leerink Swann analysts commented today.

UBS believes sales of the product could reach $791m by 2016, Leerink reckons they could tip $1bn by then.

However important questions remain to be answered before that potential can be realised. Confirmation of a dose response, ruling out an outlier effect and sweat chloride measures - elevated levels are a hallmark of CF due to dysfunctional CFTR – will all be closely scrutinised as more data emerges.

Vertex still plans to start a pivotal trial of the combination towards the end of this year, while a second corrector, VX-661, should yield phase II results later this year.

A place for sodium channel blockers?

Vertex’s recent successes with its small molecules might be dominating the field for now but other mechanisms of action are being explored, with sodium channel blockers identified as another area that might yield a breakthrough.

As well as functioning as epithelial chloride channel, research has shown that CTFR also regulates sodium transport. Sodium transport activities, airway surface liquid volume and clearance of mucus are all associated.

“Inhibitors should increase airway surface liquid and potentially have a physiological effect in CF,” says Professor Elborn. “The slight difficulty with these agents has been their off target effects particularly on the kidney with hyperkaelemia, but it is a very promising route forward.”

A known inhibitor of epithelial cell sodium channels, amiloride has been extensively studied without much clinical success; hopes are higher for analogues in development, with longer durations of action.

Most advanced is P-552-02, an epithelial cell sodium blocker from Parion Sciences. Earlier clinical studies have shown potential therapeutic benefit and although the company states on its website that further phase IIb studies will be conducted, when this might happen is unclear.

Ocean Therapeutics has a sodium channel blocker called Brevenal in preclinical development although very little information is available on the product.

Considering progress with modulating CFTR directly it remains to be seen whether there is place for sodium channel blockers as a therapeutic option; applicability across all mutation types might be enough to encourage further work.

Selected marketed cystic fibrosis drugs and pipeline					
	Product	**Generic Name**	**Company**	**Pharmacological Class**	**Trial ID**
Marketed	Kalydeco	ivacaftor	Vertex Pharmaceuticals	CFTR potentiator	NCT00909727
	Pulmozyme	dornase alfa	Roche	Deoxyribonuclease I	-
Phase III	Ataluren	ataluren	PTC Therapeutics	Transcription modulator	NCT00803205 NCT01140451
Phase II	VX-809	lumacaftor	Vertex Pharmaceuticals	CFTR corrector	NCT00865904 NCT01225211
	VX-661	-	Vertex Pharmaceuticals	CFTR corrector	NCT01531673
	SB-656933	elubrixin tosylate	GlaxoSmithKline	CXCR2 antagonist	NCT00903201
	P-552-02	-	Parion Sciences	Epithelial sodium channel blocker	NCT00274313
Phase I	PUR118	-	Pulmatrix	Cationic airway lining modulator	NCT01543191
	Cystic Fibrosis Research Project	-	Copernicus Therapeutics	Cystic fibrosis gene therapy	-
Pre-clinical	RGN-457	thymosin beta 4	RegeneRx Biopharmaceuticals	Cystic fibrosis agent	-
	CFX1	-	Morria Biopharmaceuticals	IL-8 antagonist	-
	Meveol	-	Alaxia Biotechnologies	Cystic fibrosis agent	-
	Cystic Fibrosis Gene Therapy Project	-	DNAVEC	Cystic fibrosis gene therapy	-
	Brevenal	-	Ocean Therapeutics	Sodium channel blocker	-
	RV-1088	-	Johnson & Johnson	Kinase inhibitor	-

Challenging inflammation

Inflammation, mainly caused by chronic bacteria infection, contributes substantially to disease progression in CF and as such has been a big area of research. Unfortunately it has proven largely fruitless and with the emergence of disease modifying agents work in this area could diminish further.

“I have spent the last 20 years trying to figure out inflammation and anti-inflammatories in CF, but it is clear that by correcting the basic defect you have much more of an effect than anti-inflammatory or antibiotics,” says Professor Elborn.

Ibuprofen has long been researched in CF and while it has been shown to slow the rate of pulmonary decline, the effect emerged over many years. With Kalydeco, improvement was seen as early as two weeks after starting the therapy.

“Apart from ibuprofen there really is no other anti-inflammatory that has a proven place in the treatment of CF,” Professor Elborn says. Other anti-inflammatories such as LTB4 antagonists and anti-proteases have been tried but without success beyond phase II, he says.

GlaxoSmithKline completed phase II trials with an oral anti-inflammatory agent, SB-656933, in 2010. A selective CXCR2 antagonist, the agent blocks the receptor for the chemokine IL-8, a key mediator in inflammatory response.

The company hopes to publish the results later this year but no further work is planned at this time, a spokesperson told *EP Vantage*.

CFX-1, an IL-8 antagonist from Morria Biopharmaceuticals, and the narrow spectrum kinase inhibitors RV-568 and RV-1088 owned by Johnson & Johnson, have anti-inflammatory properties and are listed as in preclinical development. Little news on progress is available.

Excitement costs of past failures

As history shows, CF has proven a very challenging disease.

Recent failures include Inspire Pharmaceuticals's denufosol; the P2Y2 receptor agonist fell over in phase III last year (*Denufosol failure leaves Inspire at strategic crossroads, January 5, 2011*).

Meanwhile hopes are fading for another late stage hopeful, ataluren from PTC Therapeutics, which failed in muscular dystrophy in 2010 (*Failure for PTC muscular dystrophy drug leaves few treatment options, March 04, 2010*). A protein restoration therapy, in CF the product aims to produce functioning CFTR protein by overriding the premature stop signal caused by a nonsense mutation. Phase III results are slated for presentation at the European CF conference in June but the chance of a positive read out seem slim.

As a genetic disorder and with the identification of the CFTR gene back in the 1989, CF is an obvious target for gene therapy. However as in many other disease areas this approach is fraught with challenges; according to *EvaluatePharma* data since 2000 four CF gene therapy projects have been abandoned in phase II.

Interest remains, however. In March the UK CF Gene Therapy Consortium received £3.1m funding from the Medical Research Council and National Institute for Health Research for a phase II study to be conducted by Imperial College London and the Universities of Oxford and Edinburgh. Using a plasmid construct of CFTR in a liposome carrier, participants in the trial will receive a dose of gene therapy using a nebuliser once a month for 12 months. Results should be available in 2014.

Meanwhile in the US, Copernicus Therapeutics is researching the use of non-viral DNA to introduce normal copies of the CFTR gene to affected lung cells.

As with any gene therapy approach, any progress made here is likely to emerge very slowly.

As such, the search for alternative ways to modify the course of this progressive disease remains in early stages. Sodium channel blockers seem promising, but much work is still needed to fully understand their potential.

Meanwhile the durability of Kalydeco's affect and the full potential of the agents following behind it still need to be confirmed. However it seems likely that the work going on in Vertex's labs will be the main source of notable progress in this disease for the foreseeable future.