

DRUG DEVELOPMENT INFORMATION

SHEET 1

Blocviroc – an innovative treatment for HIV/AIDS



Background

There are over 40 million people in the world infected with HIV. Life expectancy in some African countries has been reduced to 33 years as a result of the epidemic. The virus infects and destroys white blood cells known as T cells, which are vital for the function of our immune system.

FAST FACTS

T cells are a group of white blood cells that identify, attack and destroy infectious agents.

A receptor is a protein on the cell membrane that binds to a specific molecule. This leads to a response in the cell.

THE SCIENCE

The virus enters T cells by first binding onto a receptor on their surface. One receptor used is called CCR-5 and another is CXCR4. In the early stages of infection the virus predominantly uses CCR-5 but later, with the infection more severe, it adapts to use CXCR4. GlaxoSmithKline scientists found two compounds, one that would bind to and block each receptor. Their chemists then very cleverly combined the two molecules so that different parts bind to each receptor. By blocking the two receptors the virus cannot enter the cell and the immune system is protected.

Phase II results

These were very promising. Patients taking Blocviroc showed a significant reduction in their viral count after just two weeks. It was well tolerated by patients, with no significant safety concerns – in particular no evidence of liver toxicity.

Risks for phase III

Other drug companies that have begun to develop drugs of this type found that patients suffered liver damage. There are also concerns about the long-term effects of interfering with the body's immune system and also whether the virus will adapt to find new ways of entering the cell. If a competitor developed an effective vaccine for HIV it would make Blocviroc redundant.

Benefits to patients

While treatments for HIV have improved, many patients have to take a complex cocktail of drugs, some with quite unpleasant side-effects. Many of them fail to maintain the required dosage. Blocviroc is taken once daily so is much easier to adhere to.

Benefits to the company

An HIV/AIDS drug is not likely to be a blockbuster. The majority of people with AIDS are in developing countries that can't afford the high price of newly discovered medicines. However, there are many people with AIDS in Western countries so there should still be a good market for Blocviroc. Pharmaceutical companies are often criticised for caring for profits more than patients, and pressure will be put on the company to sell Blocviroc cheaply or give it away to developing countries. GlaxoSmithKline could claim that it is prioritising a life-saving drug to tackle an out-of-control worldwide pandemic. This could enhance the reputation of the company and bring commercial benefits.

Predicted development costs

Costs will be large – estimates are around the \$500 million mark. Large numbers of volunteers must be recruited from many countries to show that the drug works with people of differing ethnicity and also blocks the different strains of the virus that are found around the world.

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SHEET 2

Hitetrapib – eliminating heart disease



Background

The biggest cause of premature death in the Western world is heart disease. Many thousands of people have arteries partially clogged with fat and cholesterol. This leads to a hardening and narrowing of the arteries, and heart disease. There are two types of cholesterol. 'Good' cholesterol is HDL or high-density lipoprotein. This actually reduces overall cholesterol, taking it back to the liver. 'Bad' cholesterol is LDL (low-density lipoprotein), which contributes to the artery clogging. Drugs called statins are widely used to reduce LDL levels; however, patients on statins still suffer from heart attacks and strokes.

FAST FACTS

Statins are a class of drugs used to lower cholesterol levels.

Atherosclerosis is the name for the blocking of arteries.

CETP is cholesteryl ester transfer protein.

THE SCIENCE

It is the balance between the two types of cholesterol that is now thought to be important, with low levels of HDL and high levels of LDL increasing the risk of heart disease. It is a research priority to find a drug that will increase HDL. It is known that high levels of a protein called CETP are associated with low levels of HDL. Glaxo scientists have found a compound that inhibits CETP thereby increasing the concentration of HDL.

Phase II results

Results were good although the trial was relatively small. The patients all had low HDL and some were already being treated with statins. Some were given Hitetrapib while others received a placebo. Those on a statin maintained that treatment. All patients treated with Hitetrapib showed an increase in HDL while those additionally on a statin showed a decrease in LDL. However five patients experienced an increase in blood pressure and their participation in the trial was halted.

Risks for phase III

A competitor that tried this approach had to cancel a phase III trial, incurring an enormous loss. In a study of 15 000 patients, 82 who were taking the new drug died from heart failure compared with 51 on placebo. There had been warning signs in their phase II study that blood pressure might be raised. Another concern is that the combined therapies – Hitetrapib and the statin – might not work effectively in combination. There might be some drug–drug interference.

Benefits to patients

Successfully lowering LDL and raising HDL will virtually eliminate heart disease. If a combination of Hitetrapib and a statin achieves this, many thousands of patients will want this medicine. Although it will be expensive, health services will save by not having to treat heart disease in emergency situations.

Benefits to company

Potential benefits are enormous. There is no treatment for increasing HDL. This would be the first medicine of its type and would be a blockbuster. The company desperately needs a big-selling medicine following the failure of other phase III drugs and impending loss of patents on two best-selling medicines.

Predicted development costs

Very large: at least \$600 million. It will have to be a very large study with many thousands of patients monitored for three to four years. It will be difficult to recruit volunteers.

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SHEET 3

Trimonabant – tackling the modern epidemic



Background

Obesity is the most common nutritional disorder in the Western world and is getting worse. Between 1993 and 2005, obesity rates in UK men rose by 75 per cent and in women by over 50 per cent. Approximately a quarter of the UK adult population is obese. Obesity leads to diabetes and cardiovascular problems that have a huge impact on healthcare costs. In 2002 the cost of treating obesity was estimated at \$50 million.

FAST FACTS

BMI is a measure of weight relative to height. It is calculated by dividing mass in kilograms by height in metres squared. A person of height 1.7 m and weight 85 kg has a BMI of $85/(1.7)^2 = 29.4$

The World Health Organization (WHO) defines the following categories for BMI

Underweight: <18.5

Normal: 18.5–24.9

Overweight:
25.0–29.9

Obesity: 30.0–39.9

Extreme obesity: >40

THE SCIENCE

The idea behind this new drug comes from observations of cannabis smokers. A common side-effect is 'the munchies' – a craving for food. The main cause is the effect of cannabis on proteins called endocannabinoid receptors (EC) in the brain. Cannabis stimulates these receptors, making the smoker hungry. Inhibiting these receptors can suppress appetite.

Phase II results

Volunteers chosen were obese, or overweight with risk factors for heart disease such as high blood pressure or high cholesterol levels. The participants were placed on a strict diet and were randomised to receive Trimonabant or a placebo. The study was 'double blind', so neither the doctors nor the patients knew who was receiving which treatment.

The study showed that the patients taking a high dose of Trimonabant lost more weight after one year than those who had taken just a placebo. In general, weight was lost from the abdomen, where fat is more harmful.

Risks for phase III and beyond

Side-effects in phase II were minor – slight nausea only. However, this was only a short-term study and in phase III other effects of long-term interference with a receptor in the brain might surface. A competitor's drug, which targeted the same receptor, caused anxiety, insomnia and even depression. There are concerns about the long-term impact of such drugs on the nervous system. Another concern is that obesity treatments do not always work long-term and they might not work on all patients.

Benefits to patients

There are medical conditions causing obesity that do not respond to diet and exercise. Additionally many people find it too difficult to diet – Trimonabant could provide the help they desperately need.

Benefits to company

There is a huge potential market to tap into with obesity predicted to rise. Although there is another drug on the market with the same mode of action, if Trimonabant became 'best in class' it would certainly be a blockbuster. However, critics will argue that this is a lifestyle drug; that exercise and diet can solve the problem and pharmaceutical companies should be targeting serious illnesses without cures.

Predicted development costs

Costs will be moderate – \$400 million. The study would not be complex and finding volunteers should be straightforward. One concern is that if successful, patients will stop taking the drug, so it might be difficult to get the long-term data that the regulatory authorities will want.