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In perspective: the new Crucell

The months since the last Crucell Quarterly Review have been among the most eventful in our company's history. Today, I can proudly talk about a new Crucell.



We have always been a company driven by ambition, applying our innovative technologies to unmet medical needs and untapped markets to build shareholder value. Now, with the acquisition of Berna Biotech, we have added 100 years of experience in vaccine development and manufacturing processes, and we have become stronger and better poised to grow than ever before. We have grown into a company with a global presence, employing more than 950 people, backed by substantial facilities and ready to make great strides in product development.

Already, we are busy pulling together new and established technologies. We are working to increase marketing and distribution areas. We are focused on combining our marketed products with an outstanding pipeline specializing in new vaccines. And, importantly, we are also going to leverage our leadership in vaccines towards new markets and higher therapeutic growth areas such as antibodies and proteins.

The combination of Crucell and Berna Biotech will enable us to effectively compete and achieve critical mass in operations as the leading independent vaccine player, and will give us the financial strength to exploit our potential for innovation. It is an exciting time to be part of Crucell. We will be striving to match our ambition with the results that will reward you, as our investors, for your support.

Ronald Brus
Chief Executive Officer

2005 Annual Results: Leon Kruimer

While delivered hot on the heels of the January 23 announcement that Crucell's exchange offer for Berna Biotech had been successful, the Company's Annual Results for 2005 were still impressive enough to attract attention. Chief Financial Officer Leon Kruimer looks back at the achievements of 2005, and ahead to how the numbers might unfold for the new Crucell.

CQR: What would you point to as the most important aspect of Crucell's performance during 2005?

Licensing Agreement with Merial

- [Crucell and DSM Announce Second PER.C6® License Agreement with Ferring Pharmaceuticals](#)

- [Crucell and DSM Announce PER.C6® Licensing Agreement with ZynGene Therapeutics](#)

- [Crucell Announces STAR\(tm\) Licensing Agreement with Genzyme](#)

- [Crucell Announces PER.C6® Licensing Agreement with Vakzine Projekt Management](#)

Upcoming Events

We keep a current listing of important shareholder news and events at www.crucell.com, in the [Investors section](#). Here are just a few of note in coming months:

- Analyst briefing, April 27, 2006. This event will be webcast at www.crucell.com.

- Crucell will be attending the [IEX](#) Biotech day at the Holiday Inn in Leiden, the Netherlands, on May 20, 2006.

- Crucell's Q1 Financial Results for 2006 will be announced on Tuesday, May 23, 2006 at 8.00 am CET (2.00 am EST). A conference call will take place at 2 pm CET, and a live webcast will be available via the homepage of the [Crucell website](#).

- Crucell's Annual General Meeting of Shareholders will take place on June 2, 2006, in Leiden.

- Crucell will be attending the 5th Annual Needham & Company, LLC Biotechnology & Medical Technology [Conference](#) at the New York Palace Hotel on June 15, 2006.

- Due to the enormous interest in Crucell's company visits, all visits for this year are fully booked. Therefore, it is no longer possible to register for one of the [scheduled company visits](#). New dates for 2007 will be announced at the end of 2006, and it will then once again be possible to register.

Financial snapshot

Key Figures Q4 2005 (€ million, except net loss per share)

	Q4 2005	% change	Q4 2004
Revenue	12.1	+85.4%	6.5
Net loss	(3.2)	(53.3%)	(6.8)
Net loss per share (basic and diluted)	(0.08)	(55.6%)	(0.18)

Cash and cash equivalents on:

December 31, 2005	111.7
December 31, 2004	76.7

LK: The past year has again demonstrated that Crucell's business model is successful in driving revenue growth, while cash burn is carefully controlled. The net cash used in operating, investing and financing activities was at the lower end of the guidance provided by the company during the year. Following on from the successes of 2004, a 66% increase in revenue was a good indicator of how strongly our development and licensing activity has been driving continued improvement in performance, and we now envisage that the combination with Berna Biotech will provide a powerful platform for further accelerated growth.



CQR: Can you give any cash-burn guidance for the new company in 2006?

LK: At this point, with the integration of Crucell and Berna unfolding, we cannot provide guidance for 2006. We need to get together with Berna, evaluate our combined plans and make choices in how we are going to spend money in research and development and where to invest. At this early stage, we've made big strides in the implementation of our integration processes, but in terms of consolidating financial results it's obviously still early days. We'll get back to the market when we've consolidated our plans and provide an indication of what can be expected. It would not be prudent to speculate at this time.

CQR: Have you settled upon a timetable for the announcement of financial results this year?

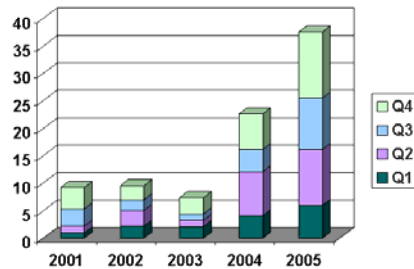
LK: We have. Our first quarter results will be announced on May 23, 2006. This is a month later than usual, but we are now reporting for a much larger concern. With the acquisition of Berna, Crucell has more than tripled in size, and as already indicated, we have some consolidation and integration to undertake over the next few months. Subsequently, the Q2 results will be published on August 29, Q3 on November 14 and the 2006 Annual Results will be announced on February 13 next year.

Introducing Berna Biotech

Berna 

Berna Biotech brings to Crucell more than 100 years of vaccine history and a Crucell Company experience. Founded in 1898 as the Swiss Serum and Vaccine Institute Berne, Berna grew from the merging of two companies involved in the development of ground-breaking products in the late 19th century. The most significant of these would prove to be the Lancy-Vaxina smallpox vaccine, which would become the most important vaccine for the worldwide eradication of smallpox. Even a century later, the vaccine returned to prominence in the wake of bioterror fears following the attacks on the World Trade Center on September 11, 2001.

Revenues per quarter
(€ million)



While this contribution alone makes Berna an important player in the history of the fight against infectious diseases, the company continued to make significant strides in vaccine development throughout the 20th and into the 21st century. The company produces state-of-the-art vaccines in the respiratory, paediatric and travel fields.

As with Crucell, influenza vaccines have been an important part of Berna's research and development. Following the successful production of Inflexal®, a whole virus influenza vaccine, Berna developed Inflexal V® using an innovative patented procedure: Inflexal V® is a virosomal vaccine. Virosomes are tiny spherical vesicles containing viral proteins embedded in their membranes. These proteins enable the virosome membranes to fuse with cells of the immune system and thus deliver their contents - the vaccine-specific antigens - directly to their targets. Once they have delivered the antigens, the virosomes are completely degraded within the cells. Berna is also producing a virosomal vaccine against hepatitis A, known as Epaxal®. This is the only aluminium-free vaccine with superior tolerability and excellent efficacy. Vivotif®, the first oral, attenuated live vaccine against typhoid fever, is another unique Berna vaccine in the traveller franchise.

Despite its rich history, Berna's vision is clearly not restricted to the past. The company has been involved in wide-ranging research with new technologies, prompting UNICEF to rate Berna among the most innovative vaccine manufacturers worldwide. In combination with Crucell, already at the forefront of innovative technologies taking the fight to infectious diseases, Berna's greatest successes are undoubtedly ahead.

Introducing Kuno Sommer

Kuno Sommer, formerly the CEO of Berna Biotech, has now been appointed as Crucell's Chief Business Officer:



"The fact that we have now managed to complete and close the deal on the merger of Berna Biotech with Crucell is a great achievement and very good news from my perspective. This event, which is significant in our long history and tradition of success, will put us in pole position for the future development of our operations.

"Berna Biotech, with its great know-how about developing, producing, marketing and selling vaccines in many countries around the world, fits extremely well with Crucell's knowledge and experience of developing new technologies.

"The aim is now for us all to concentrate on establishing a new organization that takes the very best of both companies and creates an even stronger enterprise. If we get it right and succeed in fitting Berna Biotech and Crucell together, which I am sure we can do, we will have a very powerful combination with a high potential for growth and the confidence to compete successfully on the world market in the future."

On trial: What happens in the clinic?

December 2005 saw Crucell's West Nile virus vaccine program enter clinical trials - the first of the Company's candidate vaccines to do so. In 2006, the Company's Ebola, malaria and influenza vaccine programs are all set to follow. This is what Crucell's research and development teams have been working towards over the past few years, but what do clinical trials actually involve?

Clinical trials for a new vaccine are intended to determine whether it is safe and effective for use in humans. Before reaching this point, a vaccine is likely to have already been in development for a number of years and undergone rigorous preclinical testing. Crucell has regularly reported on the results of such preclinical studies in recent times.

Classically, clinical trials unfold in three phases in order to gather data and information about a medicine and its performance. This will form the basis of a dossier submitted to regulatory authorities by way of an application for licensure. In drug trials, Phase I usually investigates the safety profile of a new medicine in a small group (10-50) of healthy adult volunteers. Efficacy is explored in phase II when the target population (numbering 50-100) is first involved. Different dosage levels will also be explored at this stage to determine the optimum dose. Finally, Phase III takes the trial to a large-scale safety and efficacy study in a relevant patient population, usually in excess of 3,000. Contrary to popular belief, each phase of a clinical trial does not constitute a single study. More often than not, each phase will involve numerous separate trials, all aimed at generating the data necessary for further progression.

For vaccines, however, the progression of clinical trials differs somewhat from conventional drugs. This is because vaccines are primarily given to healthy individuals as a preventative measure while drugs are for use in patients already suffering from a condition. As such, different measures of efficacy are required. Most regularly, researchers will look for 'surrogate markers' in the bloodstream of subjects to indicate that the vaccine is working. This will involve assessing the levels of T-cells or antibodies generated by the vaccine that are capable of neutralizing the target virus or bacteria. As such, safety and effectiveness are less likely to be assessed in distinctly separate stages. Clearly, data concerning the generation of antibodies will be available right from the outset of the early-stage safety trials and it would be foolish to ignore it. The population size undergoing testing can therefore be the most significant difference as the phases progress.

If an approved vaccine already exists, comparative studies will most likely be required during phase III. When it is known that a particular level of antibodies can protect against the disease, this "efficacy marker" will become the hurdle the vaccine will need to clear before being deemed successful. However, such a marker cannot be proven in many cases, necessitating extensive field trials to assess protection afforded by the vaccine against the natural occurrence of the disease. When a large 'at-risk' target population can be identified, a vaccinated group can be compared with a control

group to see if a significantly different rate of infection can be observed.

Should a human challenge model for the disease exist, vaccine development can sometimes be accelerated in a phase IIb study which allows a preliminary assessment of vaccine efficacy by comparing disease attack rates in vaccinees and unvaccinated control volunteers. These studies can be ethically justified if they are conducted by qualified investigators with rigorous adherence to a scientifically valid protocol with clear safeguards for volunteers.

However, for a virulent and deadly disease such as Ebola, for example, challenge trials are an ethical impossibility. The speed of the disease's onset in remote areas also makes it almost impossible to trial a vaccine during an outbreak. It is for these reasons that the Bioshield Act in the US has incorporated an "animal efficacy rule", requiring proof of efficacy in two animal models, with phase III focusing on safety and dosage. This could speed up the vaccine development process for bioterror threats such as Ebola.

It is a long and intensive process, and with good reason - no drug or vaccine should find its way onto the market without a thorough examination of its benefits and potential side effects.

Questions from investors

Q: Can you tell me when the Crucell 2005 PFIC statement will be released and put on the website? As you probably know, this is crucial tax information for US investors.

A: In 2003 and 2004, Crucell shares were subject to "Passive Foreign Investment Company" (PFIC) tax rules for US investors. In 2005, Crucell no longer qualified as a PFIC. Crucell would encourage US investors to consult their tax advisor before taking any action concerning PFIC rules.

Q: Crucell has previously given great information concerning projected timelines for the entry of programs into clinical trials. However, it is very difficult to make predictions in this regard and the Company has not always managed to reach the goals it has set itself. As such, why does the company provide such specific timelines?

A: Crucell always endeavours to provide the best information it can at the moment forecasts are provided. However, it is true that in partnered programs it is often very difficult to provide accurate timelines as we are dependent on others to assist in the realization of those goals. As such, it was no coincidence that our West Nile vaccine, the only one of Crucell's core programs that is run entirely in-house, was the first of our programs to enter the clinic, doing so within the timeframe we had communicated long beforehand.

We will continue to keep investors and other stakeholders informed regarding clinical timelines and will do so to the best of our ability. We have already indicated that 2006 is set to be a big year with all of Crucell's core programs set to enter the clinic. And now, with Berna Biotech onboard, we

will also have products exiting the clinic. We will provide the market with the best information we have available, and while that information will always be as accurate as possible, it will also reflect the ambitious nature of the company. We believe that the timelines we communicate externally also provide great motivation internally, setting lofty goals for our employees who will continue to strive to deliver the best possible results.

Questions, Suggestions, Remarks? Please contact Crucell

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