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On February 16, 2004, certain senior executives of Sanofi-Synthélabo made presentations at an Informational Meeting in London, United Kingdom. A video recording of the proceedings at that meeting was first made available for replay on the website of Sanofi-Synthélabo ([www.sanofi-synthelabo.com](http://www.sanofi-synthelabo.com)) on February 19, 2004. A transcript of that recording follows.

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## Important Information

In connection with the proposed acquisition of Aventis, Sanofi-Synthélabo has filed with the United States Securities and Exchange Commission (SEC), a registration statement on Form F-4 (File no: 333-112314), which includes a preliminary prospectus and related exchange offer materials, to register the Sanofi-Synthélabo ordinary shares (including Sanofi-Synthélabo ordinary shares represented by Sanofi-Synthélabo ADSs) to be issued in exchange for Aventis ordinary shares held by holders located in the United States and for Aventis ADSs held by holders wherever located. At the appropriate time, Sanofi-Synthélabo will file a Statement on Schedule TO with the SEC. **Investors and holders of Aventis securities are strongly advised to read the registration statement and the preliminary prospectus, the related exchange offer materials and the final prospectus and the Statement on Schedule TO (when available), and any other relevant documents filed with the SEC, as well as any amendments and supplements to those documents, because they will contain important information.** Investors and holders of Aventis securities may obtain free copies of the registration statement, the preliminary prospectus and related exchange offer materials, and the final prospectus and Statement on Schedule TO (when available), as well as other relevant documents filed with the SEC, at the SEC's web site at [www.sec.gov](http://www.sec.gov) and will receive information at the appropriate time on how to obtain transaction-related documents for free from Sanofi-Synthélabo or its duly designated agent.

At the appropriate time, Sanofi-Synthélabo will issue an offer prospectus in accordance with German law, which will be the only document applicable in connection with the public offer made by Sanofi-Synthélabo to holders of Aventis ordinary shares located in Germany (the German Offer). Any decision to tender Aventis ordinary shares in exchange for Sanofi-Synthélabo ordinary shares under the German Offer must be taken exclusively with regard to the terms and conditions of the German Offer, when it is commenced, as well as with regard to the information included in the offer prospectus which will be issued in Germany.

This document does not constitute an offer to purchase or exchange or the solicitation of an offer to sell or exchange any securities of Aventis or an offer to sell or exchange or the solicitation of an offer to buy or exchange any securities of Sanofi-Synthélabo, nor shall there be any sale or exchange of securities in any jurisdiction (including the United States, Germany, Italy and Japan) in which such offer, solicitation or sale or exchange would be unlawful prior to the registration or qualification under the laws of such jurisdiction. The distribution of this communication may, in some countries, be restricted by law or regulation. Accordingly, persons who come into possession of this document should inform themselves of and observe these restrictions. The solicitation of offers to buy Sanofi-Synthélabo ordinary shares (including Sanofi-Synthélabo ordinary shares represented by Sanofi-Synthélabo ADSs) in the United States will only be made pursuant to a prospectus and related offer materials that Sanofi-Synthélabo expects to send to holders of Aventis securities. The Sanofi-Synthélabo ordinary shares (including Sanofi-Synthélabo ordinary shares represented by Sanofi-Synthélabo ADSs) may not be sold, nor may offers to buy be accepted, in the United States prior to the time the registration statement becomes effective. No offering of securities shall be made in the United States except by means of a prospectus meeting the requirements of Section 10 of the United States Securities Act of 1933, as amended. In France, holders of Aventis securities are requested, with respect to the offer, to refer to the prospectus (*note d'information*), which has been granted *visa* number 04-0090 by the *Autorité des marchés financiers* (AMF) and which is available on the website of the AMF ([www.amf-france.org](http://www.amf-france.org)) and without cost from: BNP Paribas Securities Services, GIS-Emetteurs, Service Logistique, Les Collines de l'Arche, 75450 Paris Cedex 9.

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**Forward-Looking Statements**

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This communication contains forward-looking information and statements about Sanofi-Synthélabo, Aventis and their combined businesses after completion of the proposed acquisition. Forward-looking statements are statements that are not historical facts. These statements include financial projections and estimates and their underlying assumptions, statements regarding plans, objectives and expectations with respect to future operations, products and services, and statements regarding future performance. Forward-looking statements are generally identified by the words expect, anticipates, believes, intends, estimates and similar expressions. Although Sanofi-Synthélabo's management believes that expectations reflected in such forward-looking statements are reasonable, investors and holders of Aventis securities are cautioned that forward-looking information and statements are subject to various risks and uncertainties, many of which are difficult to predict and generally beyond the control of Sanofi-Synthélabo, that could cause actual results and developments to differ materially from those expressed in, or implied or projected by, the forward-looking information and statements. These risks and uncertainties include those discussed or identified in the public filings with the SEC made by Sanofi-Synthélabo and Aventis, including those listed under Cautionary Statement Concerning Forward-Looking Statements and Risk Factors in the preliminary prospectus included in the registration statement on Form F-4 that Sanofi-Synthélabo has filed with the SEC (File no: 333-112314). Sanofi-Synthélabo does not undertake any obligation to update any forward-looking information or statements. You may obtain a free copy of the registration statement and preliminary and final prospectus (when available) and other public documents filed with the SEC in the manner described above.

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**Sanofi Synthélabo  
Information Meeting: London  
16 February 2004**

**Introduction**

**Jean-François DEHECQ  
Chairman and CEO**

**I. Preamble**

Good afternoon. I think that you read the papers this morning. Perhaps you saw the meeting in Paris. What we try to tell you is the story of '03; then, some news on research; and you can have questions to the people on the desk.

**II. The Story of '03**

**1. Sales Growth**

So, '03 was again, once again, a new, very good, very strong year. First of all, I think that what is strong is the growth of our sales. On a comparable basis you will see consolidated sales 15.6% developed 20.4%. I think that the most important, because after all the P&L is coming from this line, and, yes, we appreciate this line, because it is certainly one of the best in this industry, first. Secondly, because that is a good increase in front of last year's.

**2. Regional Growth**

If we look at this growth, it is not only in one region: it is in all the regions. Clearly, in Europe we are above the market more than 10%. That is not usual in this industry today. In the States 33%. That is the best performance in this sector, and Hanspeter will give you more information. The rest of the world is also something very important, because at the future, on the two first points you have less than 20% of the population; on the last line you have 80% of the population so, for the future, I think it is very important to grow a lot, and that 13% is also good news.

**3. Portfolio Strength**

It is not only a strong growth in all the regions; it is also on all the products, and that is something which is a characteristic of this company. Sure that on the 10 first products, a growth of 27% is not so bad, and these 10 products represent now around 67% of our turnover, so good concentration on this 10 first products, but perhaps what is the most important, not the most, but very important also, is the capability of this company to support the rest of the portfolio: show that, to have the rest of the

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portfolio stable, or a little more than stable, is something very important in terms of results, in terms of supporting the growth, but, more than that, in terms of P&L, sure.

#### 4. Research

A good year in the sales, sure, but also a very good one in terms of research. I don't go back to the story of '03. You remember the very positive results for our strategic products. You know Plavix, Aprovel, Eloxatin, the big success of '03, Arixtra, even if it's coming step by step, it's coming on line, on the timing, and Uroxatral for the States. If you look at our portfolio early stage portfolio we have also a favourable evolution of this portfolio coming from Phase IIa and IIb, and now from Phase III, and Gérard Le Fur will give you new information on Rimonabant, Zolpidem MR and Dronedarone on his five new positive Phase III from the beginning, from the last six months. So, I think also everybody believes that this research is really a very productive research. For our size, it's clear, but it's a very productive research, and that's why, after a strong growth, we have sustainable growth. I think it's very important.

#### 5. Earnings Per Share

If you look at the results, once again very strong growth of our earnings per share. What is important is to look, yes at 21.5. I read that it's normal, that's what we expected, and so forth. At the beginning of the last year, what I said, I said that 20% for \$1 for '01. Then, in September, I said that, yes, okay, it's not \$1 for '01, but it's 1.1, and we continue to say around 20%. At the end of the year, it's more than 1.1, and we continue to say more, and it's more than 20%. So, yes, okay, everybody could say that it's normal to have 21.5, but 21.5, with the ratio between the euro and the dollar, I think it's a very good thing. Look at during the last five years, it's a little more than 36% per year. I think that the performance is not so bad. It's certainly one of the best of this industry.

#### 6. R&D Expenses

Perhaps, also, something which is very important. I go back to that because I think it's very important. When I say that the most important thing is the first line: the first line, the growth of the sales is the beginning of the story for the pharmaceutical industry, and we succeed this 21% more than 21% of increase with a strong increase of our R&D expenses. We are from 15% on a comparable basis. We don't cut our research to make results.

#### 7. Product Disposals

Second point, which is also very important, it's the results without any capital gains of product disposals, and that's something also important. It's a pure result. It's a pure result, despite unfavourable currency effects, and if we were at the level of last year, on a comparable basis it would be something like 35% again, more than 35% of growth for '03, so exactly on line with the past.

### III. Conclusion

I repeat, because as a story of our new project, strong growth, sustainable growth, profitable growth. So, Hanspeter will comment on this sales growth; Gérard will speak about research and new results of the research; and Marie-Hélène will explain some more in some words why it's this profitable growth. Hanspeter, you start.

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## Operations

**Hanspeter SPEK**  
**Executive Vice President, Operations**

### I. Preamble

Ladies and gentlemen, good afternoon. 2003 has then been the fourth consecutive year with a two-digit growth, as you see from the chart. It has been always a growth above the markets, and with a very strong acceleration as from 2001, as you see equally from the chart.

### II. Regional Growth

It is further growth which goes across all markets. It is not at all a growth concentrated only on one region. It is a growth which is strong in the United States, in Europe, and in the rest of the world and, last, but not least, it has been the strongest growth of the first leading 20 companies in the United States market.

#### 1. Europe

In our home market in Europe, 2004 has been the strongest growth of the 10 leading companies. You see it on the right side of the chart – the green bar, which is the market – and you see that leaves us with quite some distance to the market, have outperformed the market, and you see where the others are. You see, further, that also, in Europe, we have a continuous growth over four years. We have increased our sales since the emergence of the year 2000, and since we have achieved one billion of additional sales alone in Europe, and you see them from the right bottom of the chart, that this is a growth which is driven – it is true – largely by the new products, by the research products, but by far not only, and I will get back to this in a minute.

#### 2. United States

We have read and heard comments on our performance in the US and, frankly, we find them not very justified. We have started our business in the US from, more or less, zero, and our commercial presence in 2003 has amounted to \$4 billion, and I think there is not any other example in the pharmaceutical industry which would have done comparable. We have done this in adjusting our structures to the opportunity. You see the successful increase of field force people; you see that we had very strong increases in 2001/02, and then, last year, I told you that in 2003 we would maintain our size, more or less, before then increasing once again in 2004, and said 2003 would be the year to improve quality and also, there, we have achieved this. You see on the bottom of the page that we have remarkable success in the perception of being able to change prescription behaviour of prescribers in the US, where we place ourselves very, very favourably, and we are very content with this.

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### 3. Japan

Japan: traditionally weak, no direct presence. We had announced that we would concentrate more on research to fill the classical gap in delay of going to the market with research products, therefore we have significantly strengthened our R&D structures. We have further concentrated on the two major joint ventures; one with Uchisawa, the other one with Daiichi, and the first has succeeded, as you see from the chart, to put Myslee and Ambien on the first strength of this market of the hypnotics, and this is only two years after its launch in Japan. We have further taken back Ancaron, which is amiodarone, from our partner, Taisho and, since 1 February, we have our own direct commercial presence, because, for the first time, we have our own field force, and we will use this field force in context with the new upcoming products, and the next one is supposed to be Plavix, which registration, or deposit for registration, is imminent, and we will then use our once again extended field force in the Japanese market, which means we will build up our direct presence step by step, as we have done in the United States this, of course, in a standalone situation. If we should go together with Aventis, this situation is totally different, as you know.

### 4. Portfolio

On our portfolio, since 2000, our portfolio of blockbusters has doubled in terms of sales. You see that those products have been growing by 36% in 2003, and you see further that we estimate that they will, again, double until 2006, then to be added, also, Xatral, which will become a much more important product through the recent launch in the United States, and then those products blockbuster portfolio will achieve approximately 12 billion of sales as by 2006. Is this already remarkable? We feel that it is even more remarkable as far as the density of our blockbuster portfolio is concerned, because you see that these four blockbusters in our current portfolio, there are only three other companies which have more blockbusters at all, and then, perhaps, even more important, is the remarkable growth of our blockbuster portfolio as compared with others, which are, today, in a much more difficult situation.

### 5. Adapting to Local Markets

This is only part of the story, because we feel it is not enough. We feel it is important that you adapt to the needs of the local market, and what we see here is that, in the US, of course, where we have started very, very late, the blockbusters are, by far, the most important part of our portfolio, standing for 96%. In Europe it's already different, with 48%, and then 45% in the rest of the world, so we feel it is necessary and needed to adapt to local needs, and consequently to do enough for the mature products, for the so-called tail business, that this part of the business which represents approximately half of sales, in our case approximately 33-35% of sales, at least stays stable, which is the case here. I gave you one example, which is Europe, where you see that the sales of our tail business are exactly stable for the last three years, and we are very proud for it, because we feel those products are important for the patients, and they are also important for us, in terms of their contribution to the P&L.

### III. Lifecycle Management

Nevertheless, lifecycle management is key. We have remarkable success with lifecycle management. I gave you here one example, which is Eloxatin. Eloxatin has overtaken irinotecan in the United States, and this in both indications, and this, of course, is largely due to our clinical trial programmes in context with lifecycle management, and you see that, overall, the five products we

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are actively supporting today with lifecycle management measures include more than 100,000 patients, which means we not only intend to maintain our lifecycle management measures, but we also intend to expand them, in order to optimally take advantage of those products also in the coming years.

#### **IV. Conclusion**

Going back the last four years, the track record of this company is truly unique. We have been always among those companies showing a two digit growth in sales. You see that the number of those companies varies over those four years. You see further that we have climbed up in the ranks over the last four years, in terms of performance, among some best performing companies of our profession. We have done so on the basis of a truly successful merger, of an extremely productive research, of a very well-motivated and orientated commercial operation. We are proud of this. We continue like this. We are very optimistic for the ongoing year, and we are ready for new opportunities. Thank you.

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**Finance**

**Marie-Hélène LAIMAY**  
**Senior Vice President, CFO**

**I. Preamble**

Good afternoon. Hanspeter showed you how we managed to achieve a strong growth in 2003, and I will show you that this growth is also profitable.

Within four years, the earnings per share before exceptional items and goodwill amortisation has been multiplied by 3.5, and this has been done with a regular and sustainable improvement of the net results on sales ratio over these four years, and this doesn't include any exceptional items. You can see the evolution of the different lines on this slide.

**II. Gross and Operating Profit**

In 2003, consolidated sales increased by 15.6% on a comparable basis. Due to the currency negative impact, this increase becomes 8.1% on a reported basis. In 2003, we were able to increase the gross profit ratio by another 0.8%, and, as we already did it last year in 2002. This has been already achieved, benefiting from the product mix and productivity improvement, the increase of Plavix and Avapro US royalty. Even though this increase in royalty has been limited by the exchange impact, I must remind you that the evolution of the US currency, basing the Euro, decreased by close to 20% during 2003. So at 2002 exchange rates, it's a growth of two percentage points of the gross profit ratio, aiming 83.5%.

In 2003, the operating profit increased by 17.6%. That means a new improvement of three percentage points in terms of operating profit ratio on sales, and during the same time R&D expenses increased by 8% and, at the 2002 exchange rate, this increase is 15%. This is mainly due to the fact that part of our R&D expenses are located in the United States. Selling and general expenses increased by 2%, and this is due also to the sustained promotional effort in Europe, but also to the acceleration of these efforts in the United States, to support Ambien and Eloxatin, and also to prepare the Uroxatral launch.

**III. Operating Income and Expenses**

Another line, which is other operating income and expenses, in this line we have the profit coming from the alliance between Bristol-Myers Squibb and us, and the Avapro and Plavix world-wide results. You can see that the share of the alliance profits paid to Bristol-Myers Squibb mainly on the European side that we managed comes from 142 million in 2002, to 173 million in 2003. On the other side, the share of the alliance profits paid by Bristol-Myers Squibb to us, mainly coming from the US, comes from 348 million in 2002, to 436 million in 2003. This, of course, increased this line, other operating income and expenses, by more than 30% in 2003, and this was mainly due to the success of both Plavix and Avapro over the world.

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This operating profit is well-balanced between US, 45%, and Europe, 42%, and this is also something which is very important. It is good equilibrium. The financial income increased by 70 million, and this was mainly due to the hedging policy, and the weakening of the US dollar during 2003 facing Euro. Of course, the interest coming from the invested cash is lower than last year, and this is mainly due to lower interest rates, but also to the lower level of the average invested cash, and this was part of the share buyback programme we put in place in 2003.

#### IV. Income Tax

The income tax rate is close to 34% on a result before tax, and this is completely in line with our guidance for 2003, and this will be also the level we anticipate for 2004. Of course, I'm sure you remember that the tax rate for 2002 was very atypical, and it was 29%, and this was mainly due to the lack of tax on Lorex share profit, and also some withdraw in terms of provision. We have no minority interest after the Lorex profit last year of 83% before we buy it from Pharmacia. So, the net profit increased by 18% in 2003, with a new improvement of 2.2 percentage points in net profit ratio on sales.

#### V. Earnings per Share

So, the earnings per share growth is 21.5%. In September, we announced that the EPS growth should have been 20% with 1 for \$1.10. As you know that the average exchange rate of the dollar is \$1.13 per Euro, that means the EPS following this guidance should have been 19% increased. That's why we say this growth is referred to our guidance in September. So, the EPS, after all exceptional items, we are quite nothing, and goodwill and amortization, is 2.95 per share, which show an increase by 21.9%.

Now, on the financial part of it, the free cash flow generated in 2003, before the share buyback programme, is 1.3 billion, and we have bought 20 million shares following this share buyback programme authorised by the general shareholders' meeting in 2002 and 2003, and this says for about 1 billion. At the end of December, the Treasury share had, under this share buyback programme, represented 36.6 million shares, which represents 5% of the share capital. Taking into account shares held in context of stock option plans, this percentage comes up to 6.82%, and now, at the end of December, we had some net cash on hand, which represents 2.4 billion, excluding in fact the shares held in context of stock option plans, which is a very good standpoint for the future. Thank you.

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**Research and Development**

**Gérard LE FUR**  
**Senior Executive Vice President, Scientific Affairs**

**I. Preamble**

Good afternoon, everybody. We have 56 compounds in development right now but, maybe more important, we have 19 compounds in the late phase: 10 in Phase IIb, and nine in Phase III. This is true in our four main areas. I will not comment you have the details of the different compounds in these slides. Since I present to you quite a lot of data, I will not comment this slide.

**II. Terminated Developments**

So, what happened the past six months? First of all, we decided to stop the development of two compounds which were in Phase I. Both compounds are CCK1 receptor agonists. So, in fact, cholecystokinin is a neuropeptide which is able to induce satiety. So, in other words, if you stimulate the receptor, you might decrease the full intake. So, that's why we wanted to develop this compound in the area of obesity. However, first of all we got not a very nice safety margin. The side effects we got are mainly abdominal pain, which are certainly related to the mechanism of action of this compound, but maybe even more important, we got tachyphylaxia. These both compounds were able to decrease full intake after a single administration. However, they were no more active after two weeks' treatment, so unfortunately we believe that CCK1 agonists are not good compounds for obesity.

We also stopped the development of two compounds in two indications. First of all, the SR compound in rheumatoid arthritis, because we got some alopecia in the toxicological studies and, for sure, this is not interesting for compounds which might be efficient in arthritis. However, we still go on in oncology for such an effect might represent anti-proliferative activity. We also decided to stop the development of Tirapazamine in non-small cell lung cancer. I just remind you that, in the past, we got two Phase III studies in this clinical indication. One was positive, the other was not. So the third is not positive enough, so we stopped the development of this compound in non-small cell lung cancer, but we still go on in head and neck cancer, and I just remind you that, knowing the mechanism of action of this compound, which is much more important in hypoxic conditions, head and neck cancer is certainly the best target than non-small cell lung cancer, because head and neck cancer are mostly treated by radiotherapy.

**III. New Compounds in Pre-Clinical Development**

Finally, three new compounds enter into pre-clinical development. One more synthetic Oligo saccharides for thromboembolic diseases; one compound for solid tumours; and one compound is CNS. This compound is a partial agonist of the alpha 7 nicotine receptor, and might help for memory impairment in both schizophrenic patients and Alzheimer's patients.

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## IV. Major Clinical Trial Results

### 1. Overview

I will present mainly to you, in fact seven major clinical trial results: five positive results in Phase III studies; we got two positive results in two efficacy studies with anti-arrhythmic agent Dronedarone; one positive study with Ambien CR, the zolpidem modified release; and two very important results in Phase III, with Rimonabant (Acomplia) – one in smoking cessation, which is STRATUS US, and one in obesity, with patients who suffer from comorbidity, which is hyperlipidemia. This is the so-called rio-lipids.

Moreover, I will also present to you two positive Phase IIb studies: one with an NK2 receptor antagonist, Saredutant, in depression; and one with a V2 receptor antagonist in water retention, a symptom of inappropriate suppression of anti-diuretic hormones.

I will not have enough time to present all the lifecycle management of the Phase III studies that we are currently doing in all our research areas, but just remind you that we will have second quarter of this year a very important result with Plavix, with the MATCH results in neurology, and we have just finished the recruitment of the patients of CHARISMA study by the end of 2003. Moreover, I can tell you that the Phase III study that we are currently performing with both Arixtra and idraparinux are on time with both compounds.

In the central nervous system, as I mentioned to you, I will present data of rimonabant in smoking cessation, and some also good results in Phase IIb, with depression, with the NK2 receptor antagonist. Concerning oncology, I just remind you that we find, by the end of the previous year or the beginning of this year, Eloxatin for colon cancer adjuvant and this is a very important result, knowing what we got with this compound, and knowing the size of this market. Finally, for sure, in internal medicine, I will present to you the data of rimonabant in the first Phase III study we have in obesity.

### 2. Dronedarone

So, let's start with Dronedarone, the anti-arrhythmic agent. One year ago, we got bad news in the tolerance study in ANDROMEDA. The DSMB told us to stop the development of this study, not because we got very large amounts of events, but because we got two times more events in the Dronedarone group versus placebo. Last September, we presented to you that we study all the cases, and finally we were unable to know the exact reason of these so-called side effects, and that, possibly, maybe the best hypothesis at that time, we believe, was a play of chance. Just also remind you that the same DSMB allowed us to finish the two Phase III studies we had in efficacy, which are so-called RELEASE European trials, and ADONIS, the American trial, and I will give you all the results, but keep in mind that, fortunately, both studies are very positive, and with a very safe profile of Dronedarone.

#### *a. Objective of the study*

The main objective in this study was to compare Dronedarone to placebo one year's treatment, for the maintenance of normal sinus rhythm after either electrical, pharmacological, or spontaneous conversion of atrial fibrillation and, again, one more time, it was a one-year treatment, with roughly 1,200 patients. One-year treatment. Here you have the results of the first study, EURIDIS. Here you have the so-called adjudicated atrial fibrillation recorded by ECG, and adjudicated by a group

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of cardiologists, and you can see that Dronedaron is very efficient. Starting from the very beginning after two weeks, the effect was already significant, and in this study we got a decrease of recurrence of atrial fibrillation of 21.6%.

#### *b. Results*

Very interestingly, we also got roughly the same effect with symptomatic atrial fibrillation. In other words, what are the feelings of the patients? Do they feel any atrial fibrillation or not, and we got really the same effect, so a very good and strong protective effect of Dronedaron in EURIDIS treatment.

We got exactly the same results with the other study: the ADONIS one, the one which was done mainly in the US. And in this case, the decrease of risk of recurrence of adjudicated atrial fibrillation is 27.3% in this study. As it was the case with the previous study, we got roughly the same results with the symptomatic approach.

#### *c. Safety profile*

What about the side effects? First of all, the dropout in the placebo group was 47%, and 38% in the Dronedaron group, so less dropout in the Dronedaron group. We got no difference of side effects versus placebo, especially no amiodarone side effects, no dysteroidia, and no evidence of proarrhythmia especially no Torsade de Pointes reported after 12-month follow-up.

You can see here, all side effects roughly no different versus placebo, a decrease from 24% to 20% of serious adverse events. In fact, these serious adverse events are cardiovascular side effects. Keep in mind that this population, most of the patients were more than 60 years old, 50% of them were hypertensive patients, 20% of them suffer from coronary disease, and 80% from congestive heart failure.

#### *d. Conclusions*

So, in other words, this compound is very potent. It is highly effective in two pivotal separate studies for atrial fibrillation and is very safe. Of course, we got a similar profile than placebo. Also very important, both efficacy and safety are consistent across these two separate studies. So, in other words, we are more or less very close to get an amiodarone-like compound without side effects. And maybe this is an understatement.

So in the next couple of weeks or months we will discuss with the health authorities in order to see what we will do next with these dossiers. Bottom line: we have a very efficient and very safe compound.

### **3. Vasopressin V2 Receptor Antagonist (SR 121463)**

#### *a. A pure aquaretic compound*

A few words about our aquaretic agents. An aquaretic agent is a diuretic agent which only stimulates water excretion, and does not stimulate the excretion of ions. This is the main difference. And it is because of the mechanism of action of this compound; this compound is V2 receptor antagonist. Vasopressin is also name of anti-diuretic hormone, and this hormone suppresses the water excretion into urine. So if you have an antagonist of this compound, you stimulate aquaresis.

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*b. Results of Phase IIb study in SIADH*

So we already presented to you that this compound stimulates aquaresis, but here we have in Syndrome of Inappropriate AntiDiuretic Hormone Secretion the so-called SIADH Syndrome the effects of the compound versus placebo, 25mg once a day oral route versus 50mg once a day oral route. And you can see that following the second day, if we consider serum sodium as a marker, because you know serum sodium is the main constituent of the serum, so if you increase water excretion, that is to say that you will increase the plasma level of the sodium. And we got definitely an effect at the very beginning, which was also efficient after 22 months follow-up.

So here you can see the response rate, which is roughly 15% in the placebo group and it goes to 80% even at 25mg once a day oral route. The only side effect that we got, and we can't understand why, is thirst.

*c. Phase IIa study in cirrhotic patients*

Another water retention system which is cirrhotic patient. Here we compare a dose starting from 30mg to possibly 75mg of the V2 receptor antagonist once a day oral route, versus a classical diuretics Spironolactone, and versus placebo. As you can see, the change in diuresis; we got a dramatic increase in diuresis in fact, this is aquaresis induced by the V2 receptor antagonist and, in the same manner, an increase in the plasma sodium level. We got roughly no effect with spironolactone, except if we add the last day the V2 receptor antagonist to the spironolactone group, we got dramatic increase in diuresis and dramatic increase in the sodium levels in the plasma.

*d. Development Plan*

So we have a compound which is very active versus water retention, and we'll start second quarter this year a Phase III study where we'll compare placebo to 25mg or 50mg in SIADH. Also, we will set up a Phase IIb programme where we'll compare the placebo 5mg to 12.5mg, to 25mg of this compound, in Hyponatremia ascites, in the recurrence of ascites and in normal Hyponatremia ascites.

**4. Ambien CR**

A few words right now about the first Phase III study we have with zolpidem modified release, with Ambien CR. This is a three-week placebo-controlled polysomnographic study; that is to say, a very large study. When you have 200 patients with a polysomnographic study, this is really a very large study that is really for the treatment of patients with primary insomnia, but especially with sleep maintenance deficiencies. We also add to these objectives measurement some subjective measurements, with patient questionnaires.

*a. ZOLADULT results*

Concerning the results: first of all, in both of these studies we got a dropout rate of about 10% in the placebo group and less than 9% in the Ambien CR group. And we measured and we used three main parameters for sleep maintenance: this is the WASO, which I will mention to you is very efficient after six hours and no more active after eight hours; for the sleep duration we measured Sleep Efficiency (SE); and for the sleep induction the very classical parameter Latency to Persistent Sleep (LPS). In all the protocol assessments we performed, everything was very statistically different for the placebo. And the only we got very few side effects; we got 52% side

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effects in the placebo group and 57% in the Ambien CR group. And the only side effects we got were mainly GI disorders and some very few dizziness.

We've got very objective effects. I will present to you these in the next slide. The results we got with the subjective measurement, all these results are very consistent with the polysomnographic measurement we got. So you can see here the effect on sleep maintenance, the effect on WASO only 10 minutes decrease in the placebo group, and more than 33 minutes decrease in the Ambien CR group. Concerning SE, we got 5.5% increase in SE in the placebo group and 13% in the Ambien CR group. And concerning the induction of sleep, a decrease of 13 minutes in the placebo group and of more than 23 minutes in the Ambien CR group.

The most important thing concerning Ambien: one year ago we mentioned to you that we just wanted to file second quarter this year. We'll be on time and we will file these dossiers as expected in the second quarter of this year.

## 5. Saredutant (SR 48968)

### a. NK2 receptor antagonist

A few words about psychiatry. We have here the results of a Phase IIb study in Major Depressive Disorders (MDD). In this study this is the effect of Saredutant, which is an NK2 receptor antagonist. The endogenous ligand of NK2 receptor is one more time a neuropeptide whose name is Neurokinin A, but I will present to you a double-blind, randomised, placebo, Fluoxetine-controlled trial of roughly 120 patients per arm. This is both in male and female, in patients who suffer from recurrent, moderate-to-severe MDD episodes. For the specialists, the Median Hamilton Depression baseline total at the very beginning was 26. And this is very classical: one-week placebo run-in, following by six-week treatment.

### b. Phase IIb in MDD Results

So you can see here that we compare three doses of saredutant 30mg, 100mg and 300mg to 20mg of fluoxetine. And as you can see here at the primary end point, which is the Hamilton Depression Rating Scale, that the two doses of 30mg and 300mg were not different from placebo, and that the 100mg of saredutant was quite similar to 20mg of fluoxetine, and that we got similar results you can see when we use the Hamilton Anxiety Rating Scale.

What about percentage of patients with sustained response? As you can see here, we got roughly 44% of responders in the saredutant in the 100mg group, and concerning the remitters that is to say the patients with Hamilton Depression scores less than eight, we got roughly the same results with saredutant 100mg than with Fluoxetine 20mg.

### c. Safety Profile

What about the side effects? As you can see, saredutant is very well-tolerated, possibly with a better tolerance than fluoxetine; especially concerning the classical side effects of fluoxetine, which are GI disorders, mainly nausea which are most of the time mild and transient and concerning the CNS side effects, this is mainly dizziness.

So, we all know that depression is quite complicated. Keep in mind what happened with the NK1 receptor antagonist. However, we do hope that after the beta 3 receptor antagonist which is currently in Phase III in depression right now in our portfolio, we'll start by the end of this year a

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new compound in Phase III – an NK2 receptor antagonist. So we don't put the eggs in the same basket and do hope that at least one of these compounds will have positive results in Phase III.

I just also would like to add that we have three other new targets and three other compounds which are currently in development for depression. This is the V1 receptor antagonist, the CRF1 receptor antagonist, and an inhibitor of the enzyme fat. So, in other words, we strongly believe that one day we'll have at least one year that we'll be able to launch in depression with a very new mechanism of action. For sure, all of these compounds have nothing to do with the classical mechanism of action of SSRI.

## **6. Acomplia (Rimonabant) Phase III Programme**

### *a. Overview*

So right now, a few words about Acomplia (rimonabant). We have a very large Phase III programme: seven studies, including more 13,000 patients – roughly half in obesity and half of the patients in smoking cessation. You all know that obesity is the only area where FDA asks for a two-year follow-up, so I just will present to you the first Phase III we have right now. After one year treatment, this is RIO-Lipids; that is to say, obese patients with hyperlipemia as morbidity. Moreover, I will present to you the first Phase III study we have in smoking cessation, the so-called STRATUS US, which is a 10-week treatment.

### *b. STRATUS US*

So, let's start with STRATUS US. You can see here that it is a rather large and pivotal study for the smoking cessation versus placebo. Two doses close to 800 patients, 10-week treatment, but maybe the primary efficacy criterion is from week seven to 10. But maybe the most important fact here is that the abstinence is not only measured on clinical parameters, but also on biological parameters; that is to say, CO levels and cotinine levels – cotinine is a metabolite of nicotine. We all know that in fact, I would say both smokers and even all these patients are really liars, so we just need to be sure that when they say, "Okay, I stopped smoking," that it was true. That's why we use another parameter, which is a biological one.

So here you have the results of the primary end point, which is the prolonged abstinence rate during the last four weeks of treatment. Here you have the results: ITT population, meaning all the patients. In placebo group the abstinence rate is 16%, but close to 28% in 20mg group of Acomplia. When we consider the completers; that is to say, the patients which finish the 10-week treatment, we got roughly 20% abstinence rates with placebo and above 36% in the 20mg Acomplia group. You can see that everything is very significant.

### *c. Side effects*

It is well known that when you stop smoking, one very important side effect is that you have an increased body weight. Knowing the mechanism of action of Acomplia (rimonabant), for sure we just wanted to measure the body weight change from the baseline. You can see here, in the whole ITT population, we have an increase of 1.1kg in this population and a decrease of 0.3kg in the 20mg Acomplia group. But even more important, when we use the non-obese patient with prolonged abstinence – that is to say, for the placebo respondent – we got an increase of 3kg body weight and only 0.7kg in the 20mg Acomplia. One more time, this is very significant.

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A few words about side effects, because side effects are very important. First of all, the dropout rates in the placebo group in this clinical trial is 28%, 30% in the 5mg Acomplia, and 28% in the 20mg Acomplia. No difference versus placebo. You can see that this compound is very well tolerated, and look for a sense of the serious adverse events: no difference versus placebo. The only subject who discontinued due to adverse events, the only increase we got was as expected because we only got such side effects in the Phase IIb mild in terms of GI disorders, which might be close to what happened with Prozac, as I mentioned to you previously.

Also, some very atypical side effects that we can't distinguish from a kind of withdrawal syndrome. In other words, it is when you stop smoking you are a little bit irritable, a little bit anxious. In fact, what we got a little bit with rimonabant in this study. However, keep in mind we got a 1.5% side effect of this kind in the placebo group and only 2.3% in the 20mg group. In other words, this compound is very well tolerated.

*d. Impact on mood and anxiety*

Because of the past of both the compounds which are already on the market in smoking cessation, and even more on depression, we were told by the health authorities, especially the FDA, to look for possible effects of these compounds in mood and anxiety. In all the patients we used the HAD (Hospital Anxiety-Depression) Scale, and as you can see here, we got no difference versus placebo in the depression sub-score in this study, and no study in the anxiety sub-score. So, there were no side effects on mood and anxiety, as expected.

We have also been told to be very careful with the cardiovascular safety profile of this compound. One more time, you can see here there is no difference on the systolic blood pressure versus placebo, no difference on the diastolic blood pressure, no difference in heart rate, and no difference in the QTc. We have a compound which is very efficient versus placebo for smoking cessation and with a very safe profile.

*e. Obesity profiles*

Now, a few words right now with the first Phase III study we have with this compound in obesity. This is, as I mentioned to you, RIO-Lipids, so it is randomised, double-blind, placebo-controlled, and we compared one more time placebo to two doses of Acomplia and we got roughly 1,000 patients in this clinical trial of one-year treatments.

At the beginning, the mean body weight index is 34 and the mean body weight is 96kg. Here, you have the primary endpoint. First of all, the weight. You have a decrease in body weight of close to 9kg; in fact it is 8.7kg from a one-year treatment of Acomplia in clinical trials. A little bit more than 4kg after 5mg and a little bit more than 2kg in the placebo group. This is very, very significant for patients under 30.

We got roughly the same profile for the waist. It is well-known that visceral fat is the main risk factor for cardiovascular side effects. Again, one more time, we got a decrease in waist circumference of more than 9cm in the 20mg Acomplia group; close to 5cm in 5mg; and between 3-4cm in the placebo group. Again, this is very significant.

One more parameter: what about the number of patients with a weight loss of more than 5%? We were told by the authorities to measure this population of patients. In ITT population, you can see that we have less than 20% with a decrease of body weight above 5%, and we roughly tripled it after 20mg of Acomplia; we got 58% of patients. For the completers, we roughly tripled versus

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placebo. In other words, 73% of patients have a body weight loss of above 5% after a one-year treatment of 20mg Acomplia.

But even more important, when we measure the percentage of patients with a weight loss above 10%, you can see here, in the ITT in the total population, is more than four times the placebo effect, from 7% to more than 32%, concerning the completers from 10% to 44% of patients. This is really a huge effect.

*f. Impact to cholesterol levels*

You know, all the patients in the study but with a co-morbidity, which is hyperlipemia. So for sure, we measured the lipid parameters in the blood of these patients. This compound has no effect on the total cholesterol levels. This compound does not decrease the LDL levels. This is not an inhibitor of polycoelocentesis. However, as you can see here, this compound very significantly induces an increase in the HDL cholesterol, the so-called good cholesterol. This effect is more than 20% with the 20mg group. This is very significant. We also got a very large decrease in triglyceride level in the 20mg levels, which is, one more time, very significant.

Maybe more importantly, when we tried to correlate these effects on lipid parameters with a decrease in body weight, 50% of both effects are linked to the decrease in body weight; 50% are totally indefinite. In other words, apart from the decrease of the full intake, there is a specific peripheral effect, possibly likely in the adipose tissue of this compound, which could explain the increase in HDL cholesterol and the decrease in triglycerides.

*g. Impact to glucose levels*

What about sensitivity to the oral glucose tolerance test? It is well known that this kind of obese patient is of pre-diabetic status, and you can see here that after a one-year treatment, there is a decrease on the glucose level after the OGTT. This decrease of blood level glucose is explained by the sensitivity to insulin of these patients. It might also be explained by this peripheral effect, which is independent of the body weight. Both effects are very significant.

*h. Metabolic syndrome*

You know from the last few years that the so-called metabolic syndrome is considered a very high risk factor for cardiovascular side effects. So, if we consider the definition of the metabolic syndrome, you might have at least three among the following criteria: abdominal obesity (I mentioned to you the effect of Acomplia in this area); hypertension; hypertriglyceridemia; low HDL cholesterol; and abnormal fasting glucose, that is to say, not to be a good responder to a neural tolerance test of glucose. In all the patients, we have roughly 50% of our patients who suffer from metabolic syndrome. After a one-year treatment with 20mg Acomplia, there is roughly a 50% decrease of the rate of the person with metabolic syndrome.

*i. Safety profile*

One more time, a few words about the side effects. First of all, dropout rate: 38% in the placebo group, 40% in the 5mg group, and 36% in the 20mg group. There is no difference versus side effects. You can see here one more time that the compound is very well tolerated. Just keep in mind that we are in the very, let's say, atypical population. They are not very compliant, and it is a one-year treatment. You can see, concerning the serious adverse events, that it is from 2.3-4%. And in fact, we got roughly the same side-effect profile that we got in smokers. That is to say, GI

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disorders, mainly nausea, which are mild and transient, and if we want to explain this effect, it is about 0.3% in the placebo group and 2.6% in the 20mg group.

Talking about the so-called psychotropic effect, the so-called withdrawal syndrome effect, concerning mood: that is 0.6% in the placebo group, only 2.9% in the 20mg Acomplia group. Concerning anxiety: 0.6% in the placebo group and 1.7% in the 20mg group. In other words, one more time, this compound is very, very well tolerated.

Again, as I mentioned to you because of the past, I don't have to mention to you the Fen-Phen story of what happened with all the obesity drugs. We were told to be very cautious about possible psychotropic side effects. We use, as we did in the smoking cessation study, we use the HAD scales. We got no difference versus placebo on the depression sub-score, no difference on the anxiety sub-score. For the same reason, we were told to be very careful of the so-called cardiovascular safety profile. One more time, we got no effect either on systolic or diastolic blood pressure; in fact, maybe some decrease in hypertensive patients. In any case, no important effect. No effect on heart rate, and no effect on QTc.

*j. Summary*

One more time in this study, roughly 1,000 patients, a one-year treatment, very good efficacy, and a very good safety profile. So to conclude, in fact, we demonstrate that this compound has a dual mechanism of action, certainly the central one I already mentioned to you: the so-called effects of this compound on the reward system. But there is no doubt there is also a peripheral effect, possibly linked to an effect in adipose tissue. I just would like to say that you will have more results on both studies at the next ACC at the beginning of March, and you will have very new results possibly on the so-called adipokins. In the past, adipose tissue was considered as a storage organ for fat. Now, it is well known that adipose tissue is also able to stimulate the excretion of hormones that might explain some of the effects of Acomplia on the lipid and glycedic profile. In any case, this compound is the first CB1 receptor antagonist. Because of its effect both on obesity and the so-called glycol-lipidic profile and smoking cessation, it might be, if we can reproduce the effect of this compound, a cornerstone in the management of patients with cardiovascular risk factors.

Maybe I was too long, so if you don't mind I will stop now. I would just like to say in conclusion that I am lucky enough to have the opportunity to present to you so many positive results. Keep in mind, five positive at risk studies out of six. I am an old guy, doing this job for more than 30 years; this is the first time that I have the opportunity to present such good results. I would like to say it is because I have a wonderful team and I just would like to thank them for that, and to thank you for your attention.

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## Conclusion

**Jean-François DEHECQ**  
Chairman and CEO

### **I. A Productive R&D**

Just to conclude this presentation, I wanted to make a short conclusion. I think that these results are outstanding results, and that is not the first year. That is not only 2003. I think the last years, and especially the last five years in Sanofi has created a very strong platform for strong, sustainable, profitable growth, which I said before. I think that everybody recognises – and perhaps after the new results of Gérard, which are just the new results of the last six months; they don't include all the results of 2003 – yes, we have a strong and very productive R&D.

### **II. An Efficient, Market-Oriented Organisation**

What is perhaps also very important to say is that if we have a growth of our sales between 15-20% per year, when we look at the market, when we look at the competitors, I think that we are also an efficient, market-oriented organisation. I think that the sales and marketing in this company is not theoretical, it is a very strong one; it is marketing in the field, and that is something which is very, very important. That is another way to say that we have a very strong respect of the cultures. We have to be in each country, in front of the culture of the country if we are to succeed.

So, yes, we are ready to progress further. You know the story: I will go very quickly on that. You know the story; we know the offer: creating the number one in Europe, creating the number three worldwide with a strong presence in Europe, especially in France and Germany yes, but building a rapid growth in North America. I read a certain number of things in the last weeks saying it would be a mistake because the decrease in North America. When we are growing at 40% more than where we are now in North America, I think the new company will be very efficient in this region. As I said before, I think that the other countries are also very important and very important for the future.

### **III. Making Progress**

#### **1. Combining Resources**

Let me say, I always speak about strong growth. The first line is what is important, and to succeed it is necessary to have a specific strategy for each country, for each product. That is the reason why we have succeeded in the past and are successful now in terms of sales: a specific strategy for each country and for each product. Yes, putting together the resources of marketing and commercial assure that we will accelerate the growth of major products and, more than that, prepare to optimise the launch of future products of the two companies.

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## **2. Research**

Yes, sustainable growth. You know as well as or better than me that research is not only a problem of money; it is not only a problem of expenses. But, I think that focusing the combined resources on the best of projects, really innovative projects because we make something important in this industry as soon as you have very innovative products. Me too products could be interesting, but it is not the same as to make a break as you have done in the past with some products. The most innovative projects, the most advanced projects, because that is very well to say that we have a very good pre-clinical portfolio of Phase I or IIa products, but what is important is to have the products for the next years. That is why to focus on the most advanced product is so important and the most promising. To list the number of products is interesting, but you know better than me that all the products are not the same. There are very small products, there are middle-sized products, and very big products. What we need is to focus on innovative, advanced and promising products.

## **3. Profitable Growth**

To say that the growth has to be profitable is normal. To say that it is serving the interests of all the shareholders is true. The interests of both companies, because yes, it is impossible to invest in research, to invest in manufacturing and marketing, to build a company without very good profitable growth. I think that for the employees it is the same because yes, we have to continue this process of optimisation; that is where we have to do that. We have to do that all the year, all the day. But what is most important for the people and the employees, and to be sure we progress, is to have a very strong development and growth. The growth and development are the motivation of the people. To have people running in place of sitting is a question of growth and development. I think also that it is in the interests of the patient to continue to have strong research.

I do not spend too much time on that. Yes, we need a rapid implementation because I think that in the world today, it is not possible to spend two or three years to make the harmonisation between two companies. I think that we need to have a clear-cut project, to have the motivation of the people, and to go as quickly as possible and not to lose time.

## **IV. An Attractive Offer**

The risk behind the organisation is a long story. I think that you know that. To say again that we have in mind that this offer is attractive for the Aventis shareholders, for Sanofi shareholders, and for the future of the new group, I think that it is better for us to answer your questions. I will stop here.

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**Question and Answer Session**

**Jean-François Dehecq**

Okay, so now questions.

**Jo WALTON, Lehman Brothers**

A few questions please. I wonder whether you could tell us whether you have made any progress in increasing the average length of prescription for Plavix. We hear a lot about new drugs but growth in that still seems to be key.

Secondly, regarding dronedarone do you think that the FDA will require a mortality study? One failed. When you said that you were going to be talking to the FDA I assumed that you were not assuming to file it.

When it comes to rimonabant, I wonder if you could explain page 65 in the handout, where you have this last observation carried forwards of weight and waist measurement and there seems to be a rebound of people getting fatter and heavier again. I do not quite understand what that is and wonder if you could explain that. Could you also talk a little bit about how you think this would be acceptable to managed care, and any work that you have done to try and ensure that this product would be reimbursed, either for smoking cessation or obesity treatment.

**Jean-François Dehecq**

Okay, perhaps first on Plavix. Hanspeter?

**Hanspeter Spek**

On the length of treatment we conveniently improved on all markets. We had one in the last year, in 2003, and between approximately ten and twenty days in the region of treatment. This is in terms of the SAP indications as well as from a geographical standpoint.

Answering right away for the managed care issue, I think it is a little bit early to say how we will handle rimonabant in managed care, because it was not clear that those results you just saw, which I have known for a couple of days, would come up. Of course I feel very much encouraged by the metabolic parameters which should give us significant edge in our upcoming conversations, of 2005 and 2006, with managed care organisations.

**Gérard Le Fur**

Concerning rimonabant, I am sorry Jo, but we do not like to talk, we never like to comment, before we talk with the health authority because you know they do not like that too much. In other words,

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we will go in the next few weeks or months, and discuss both with the FDA and the EMEA and we will see what we will do. It is too early to say, so frankly we do not know.

Concerning what you mentioned on LOCF this is not a rebound at all. With LOCF you consider all the patients, that the curve you have are only the completers, in other words, some of the patients in all of the groups stop far before, some of them after only one week or two weeks, so there is apparently no effect. This is not a rebound at all. Opposite to maybe some people I saw on other reports, or maybe I am losing my mind, but there is no rebound effect at all after one year of treatment. For sure, we will know after two years of treatment, because the guidelines of the FDA are for follow-up after two years.

**Kristen MANN, Cardew**

I understand from this morning's webcast, that, regarding the offer for Aventis, that you have not got any details with regards to the Aventis litigation with regards to your offer. Apparently, that is quite key to the timetable. Would you have any comments or tactics, an understanding of what they are litigating against?

**Jean-François Dehecq**

Yes, we have read that an appeal has been made by Aventis challenging the receivability of our offer. We find it strange to try to attempt to delay the story, but that is another problem. We do not know today the content of the appeal or its motivation. We are very confident of our offer being successful and we do not see any reason today to change our expectation of closing the transaction before the end of the first half of '04. That is my answer on that. After, we have to see the content of the appeal and its motivation. We are very confident.

**Alexandra HOLBER, Bersteins**

A couple of questions on rimonabant and saredutant. First, is the fact that you use biological markets in this smoking cessation study, does this explain the lower quit rate compared to other comparatives, for example, Zyban? Could you just explain why these biological markets are superior when measuring carbon monoxide? Also, what was the weight loss in the initial four-week lead in? Can you confirm that that was definitely excluded from the nine kilos that we saw on the slide?

**Gérard Le Fur**

I do not understand this question.

**Marc Cluzel**

When you are treating patients for obesity you need to be absolutely sure that they are on a diet and that they are following the diet. You have one month before randomisation, so what you have seen here is after this one year. If you had linked the totals, I think we made the calculation that it is more than twelve kilos for the completers for rimonabant 20mg.

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**Alexandra HOLBER**

I just wanted to confirm that it was in line with other studies which have seen this three kilos usually. Also, the timelines seem to have slipped a bit. It used to be fourth quarter: fourth quarter this year, early quarter next year. Can you just tell us why there is a little delay. I think you said this morning, I am not sure whether you said second quarter or second half, for filing for the rimonabant. Then, on the diabetes...

**Gérard Le Fur**

No, I can answer very quickly. We will have the results by the end of this year of all the 13 000 patients, so we need two or three months, maybe a little bit more. That is why we are saying second quarter 2005. Nothing has changed from the very beginning.

**Alexandra HOLBER**

Okay, I was just comparing to your September presentation. Then, on the diabetes study, could you just tell us what the end points are, just on renal diabetes.

**Gérard Le Fur**

On renal diabetes we have the same end points. The one we presented to you. For sure, diabetes, that is to say the old tolerance effect of rimonabant and glucose is more important in diabetes than it was in hyperlipidemia, but keep in mind that both, in all the studies we have, the pre-diabetic status, most of them have hyperlipidemia, and all of them are obese.

**Alexandra HOLBER**

Can I just clarify that. That means that renal diabetes, these are people with impaired glucose tolerance rather than hyperlipidemia

**Gérard Le Fur**

Some of them will have hyperlipidemia all of them will suffer from diabetes.

**Alexandra HOLBER**

So they are not pre-diabetic, they have full-blown diabetes?

**Gérard Le Fur**

Yes.

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**Alexandra HOLBER**

Okay. And you are not looking specifically at HDA1C?

**Panel Member**

No.

**Alexandra HOLBER**

Okay. Good. And then just for me to understand, you said that 50% can be attributed to the weight loss, and 50% can be attributed to the, whatever those CB1 receptors do peripherally. Does that mean that if you look at the non-responders, you still get about half of the lipid effects? Is that what you wanted to say?

**Panel Member**

No. Please, be a little bit patient. Wait for a couple of weeks and you will have all the answers at the ACC. We just presented quite a lot of data. Quite a lot of data. Please let our PI, our Principal Investigator, present all the data. Just wait a couple of weeks, the ACC is at the very beginning of March.

**Alexandra HOLBER**

You know this audience is not famous for patience. Just one final question on saredutant. The lack of this response curve shouldn't this be an alarm signal because we know that all the depression was not very good, so if you see something like that you might actually have no efficacy?

**Gérard Le Fur**

You know, each time you perform those response curves, sometimes it is a U curve, but depression is quite complicated, we all know that. One more time, we are only confident, because we left two compounds in Phase III, with two mechanisms of action in depression. This action was only to select the dose. There's no doubt, if active, as it appears to be, the active dose is 100mg a day with saredutant.

**Hanspeter Spek**

What made you choose a biological marker in the smoking cessations as compared to Zyban?

**Gérard Le Fur**

Have a look at previous studies. We are not so sure that they are very sophisticated studies. Again, as I mentioned, it is when smokers are liars, like obese patients, they are not very compliant. So we

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prefer to reconfirm the clinical effect by a biological marker, in this case by carbon monoxide and continin.

**From the floor**

Just on accounting. If you had had expense stocks, as new accounting rules might enforce, what impact would it have had on your 2003 earnings and would it have any impact on 2004 earnings, do you think? On rimonabant, how clinically meaningful do you think your results are? Do you think you will be looking at cardiovascular events and mortality in further studies going forward?

**Gérard Le Fur**

It will depend slightly, first we would like to wait for new data. As we mentioned to you, we have seven clinical trials going ahead, which is quite a lot of trials in one area. If we reconfirm, possibly for sure some day, later, we will perform some cardiovascular risk and mortality, but it is too early to say.

**From the floor**

Would you file beforehand?

**Panel Member**

For sure we would file beforehand.

**Marie-Hélène Laimay**

Concerning the accounting points, you are referring to the Black and Scholes method we use, for example, for the US GAAP. We have already made that kind of thing. It is not completely charges for the stock option plan, but part is the evaluation following this Black and Scholes method. We will conduct some plans, million euros in terms of charges, which were already made last year, so I would say there is no major, or significant, impact in terms of P&L.

**From the floor**

And that would be true for 2004 as well?

Marie-Hélène Laimay It is at quite the same level. It is not significant for us today.

**From the floor**

Thanks.

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**Mark LASSAL, Deutsch Bank**

I have three questions. On dronedarone given the comparable efficacy, should we be comparing this to Tambacor and Covert, rather than to Cordarone. On rimonabant, two questions. Could you tell us the HDL impact? Clearly, if it is having an insulin sensitising effect, the insulin sensitizers cause an increase in nausea. I just wondered if it was the same for this compound.

Secondly, the 15% discontinuation rate versus 7%, clearly it is quite significant. I think with Zanaco it was 9% versus 5%. Can you talk about when patients discontinued. Was it in the first few weeks or was it progressively over the first few months? Also, how do you anticipate the patients to be compliant in the real world? Only about 75% of patients only took one or two scripts on Zanaco and then discontinued. I was just wondering what you think the discontinuation profile will be in the real world?

**Gérard Le Fur**

Discontinuation was, all these patients are not so compliant. It is not very easy to have them continue for one year treatment. You know, they say they have side-effects and would like to stop. It is not so easy to work with such patients. That is why we decided to have such a powerful study. Really, this component is definitely very safe, but it is very difficult to have a follow-up with such patients.

**Hanspeter Spek**

Then there was a question on insulin-synthesising I think.

**Gérard Le Fur**

Yes, as we mentioned to you, please wait a little bit. In a couple of weeks you will have much more results. I do not want to disclose results that will be presented by our Principal Investigator. In any case, we think that both the effect on the lipidic profile and the insulin sensitisation is linked certainly to a peripheral effect which has nothing to do with the decrease in body weight.

**From the floor**

Have you seen any impacts on LDL at all?

**Hanspeter Spek**

Could you repeat the question?

**From the floor**

Do you have any impacts on LDL cholesterol?

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**Gérard Le Fur**

No, I mentioned to you no effect on total cholesterol, no effects on LDL cholesterol. No effect at all. This is not an inhibitor of the synthesis of cholesterol, it has nothing to do with that.

**Hanspeter Spek**

Dronedarone has the profile of Flecanide or Amiodarone.

**Gérard Le Fur**

No doubt. First of all, Dronedarone is chemically related to Amiodarone. You know we looked for such compounds for more than twenty years, maybe thirty years, and I can tell you for sure without revealing any secrets, that it is very complicated. Once you have a compound, which, in animals, appears to be as effective as Amiodarone, you have plenty of side-effects. You know, as I mentioned to you, that for the first time we are very close, and maybe this is an understatement, to have an Amiodarone-like compound, chemically related to Amiodarone, with the same mechanism of action but a very safe profile. And nothing to do with Flecanide, nothing to do with this compound, both chemically and in terms of mechanism of action.

**Andy PLAYSON, UBS**

Regarding other operating income, the increase of H2 on H1 seems very dramatic and quite hard to reconcile with the performance of the Bristol-Myers Squibb products in Europe and the US. Is there any sort of colour you can give on how things have phased there. It just seems like a big change. And then, I am afraid, back to the pipeline again, and to the 15% drop-out rate on 15mgs and Rimonabant. You explained that it was not cardio-vascular or psychiatric side-effects that were the problem here. Could you tell us what it actually was? Was it anything to do with the renal system for example? Finally, on Ambien CR, you looked at WASO for six hours. Was there any reason you did not look beyond six hours on that end point?

**Gérard Le Fur**

Concerning AmbienCR, the effect on WASO was significant, as expected, until six hours, and not more. That is to say, on WASO, the compound is only active during six hours.

**Marc Cluzel**

Just on the drop-out rate there is a misinterpretation. The drop-out rate in rimonabant studies as given by Gérard, is exactly the same in the rimonabant group as in the placebo group, even a little lower in the rimonabant group.

**Gérard Le Fur**

Thirty-eight percent in placebo, 36% in 20mg rimonabant.

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**Marc Cluzel**

And what you are taking as a number, is just the patients who drop for side-effect. There is a kind of compensation likely efficacy seeing as the product is more effective, patients are staying longer for treatment, so the drop-out rate is exactly the same, even a little bit less, on rimonabant. There is just a little bit more side-effect, mainly gastrointestinal side-effects, nausea in fact.

**Marie-Hélène Laimay**

On the line of the income and operating expense I give you the detail of this line. The increase in this line, with this 30% in 2003, is mainly due to the success of both Plavix and Aprovel-Apravo in the United States, and to the productivity of the sales force during the year 2003. You can see that the share profit coming from the US, and generated by the US, increased by close to 100 million euros in 2003. By the same time, the increase in terms of profits coming from Europe increased by, I would say, half, and that is why we have that increase. The success of Plavix and Avapro is a real worldwide success.

In 2002, the evolution of this line was limited by all the stocking effects coming from Bristol-Myers Squibb. We talked about that a number of times in 2002 and 2003. Now, as the evolution of Plavix and others in the United States are much more in line with the evolution of the prescription in the United States, the evolution of this line is very significant and will be very significant.

**Matthew WESTON, Lehman Brothers**

Two questions if I may. One quick one for Gérard, and then a strategic one for M. Dehecq.

Gérard, you gave us the data for the aquaretique in SIADH. Is there any potential for that compound in hyper-tension, which I imagine would be a much bigger indication?

Then, for M. Dehecq, the one take-home message for me today, is that you presented some fantastic data and some fantastic new potential compounds, but if I am to refer to some of the things you said as a company in the past, you have said that salesmen, particularly in the US, want to sell exciting products, you have said yourself that they are very easy to hire. I seem to remember that you hired a thousand reps over the internet within a month, which was seen as a great success at the time, so the thing I am confused about, is why you want to dilute your future earnings growth potential by buying Aventis. As far as I can tell, you can get an awful lot of reps for \$50 billion, the market will be very happy for you to invest future in R&D if we see how fantastic the pipeline is, but when I run my model, the earnings growth going forward is basically slowed by buying Aventis, and I do not see why you need them, so why are you hunting them down?

**Gérard Le Fur**

A quick answer concerning hyper-tension: the answer is possibly, but only in a sub-group of patients, which might have an increase in hyper-tension, so I am not so sure. Unfortunately, it will be an anti-hypertension compound for all hyper-tension patients.

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**Jean-François Dehecq**

I think that I have answered this question many many times during the last three weeks. First of all, I agree with you that perhaps that you are ready to accept that we increase our sales force and our expenses to launch a new product. I agree perhaps that you agree also that we increase dramatically our research expenses to continue to push the new compounds that are going from Phase IIa, IIb to Phase III. But I am sure also that if at the end of the day I give you my final answer which would be to have 20% less profit at the end of the year, even if it is to launch new products or even if it is to continue to develop new compounds, I am sure that you would be very unhappy. The question is that the world is changing very rapidly. We need more effort in our research, we are exactly in the same situation where we were some years ago when we had the opportunity, the talent, the chance, to develop Avapro and Plavix. At that moment we had no way to develop that product except by making a joint venture and sharing the development and sharing the co-promotion, and sharing, at the end of the day, also the profits. So what we decided last year, thinking around that, because we will be in the same situation around the end of the year, we decided to try to be alone, so we do not always have to share the future with another party. The reason why we decided that putting together these two companies, it is a big opportunity, because they have a lot of expenses in terms of research, and you have to remember our story when we bought Sterling in the past. The research of Sterling was exactly the same level as us, there were not a lot of big compounds in the research of Sterling, but Gérard put inside, through the research centre and the people of Sterling, very strong projects and he succeeded. The success of our research in the States comes from that. When we bought Synthélabo five years ago, the story of Synthélabo is the story of a research, of 60% of our research. There are not a lot of big compounds inside, but now all the research centres of Synthélabo are working on Gérard's new compounds and making a very fantastic job. I think, that to build the story of the future, and to build that keeping the results, keeping the future, the best way is to find this kind of solution. We have in mind that we could make better today in terms of sales, that is what we tried to explain, and in terms of profit, what could be done, and that is the reason why we have decided to make this story. Not only for the sales force.

**Allan GEORGE, Freelance Journalist**

I read a report that you have gone so far with your proposals as to notify the Brussels Merger Taskforce about the disposals you would be prepared to make to gain acceptance by the European Commission. I presume therefore that you have very detailed plans about this potential merger. I also see, on page 82, in serving the interests of employees, the expression "Brussels optimisation is a continuous process". That seems to me to mean job losses, and I am wondering on what scale those are envisaged, and where.

**Jean-François Dehecq**

I will give the floor to the architect of the story today. I will continue if you want.

**Jean-Claude Leroy**

Okay, on the process with Brussels. I would say that Brussels, as with the FTC, we have contacts before the launch of the offer, with these two institutions and the process is, obviously, not over yet. They are still studying the dossier and we are still providing information, and it will take some weeks and a few months to come up with the decision. Now, we knew from day one, because as

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you can imagine, we studied and studied with the Merger Taskforce, because we knew that we would have some problems, both in the US and in Europe, with Brussels. We decided from day one to make clear that, in the areas where there were clear overlaps, in terms of over 80 or 90% of market share, we would begin the disposal process with all the means that were necessary to run the business, and that is the reason for which we decided from day one to announce the decision to dispose of our extra worldwide and Fraxiparin in Europe, as Fraxiparin has never been present in the US. The reason for which we have set up the process for the rest, the dossier is under implementation and we do not know exactly the result. It is too early to say. But we can add that we are rather confident on the issue of those dossiers as we do anticipate anything larger than 2.5% to 3% of the global sales of the new group.

**Jean-François Dehecq**

Going back to page 82, I think that in this point there are two different points. The first is why the resource optimisation is a continuous process, and yes we have the same prime/problem? It is not exactly the same when you have growth of around 15 or 20% and when you have growth of around 5%. I read in the newspapers at the end of last year that there is a lot of cost-cutting to do, closing one plant in two, and I heard also last week that the carve-out story is something that is in the pipe for a long time, because they say that they expected to launch this story in May this year. I think that the optimisation of the process is something that we have to do clearly, and with the consequences that you say.

The second point is totally different. When I say that only growth and strong development is the motivation of the people, I think that the motivation of the people inside Sanofi, and the story of Sanofi is one of mergers throughout its thirty years of its existence. I think that we succeed to have the motivation of the people, because we have always built as we were making optimisations, and I think that it is the only way to obtain the motivation of the people and maintain good growth.

**Vikram SAHA, Goldman Sachs**

A question for M. Le Fur, and also for Hanspeter. CHARISMA, I have seen that the patient enrolment for CHARISMA seems to have been completed. Can you tell me when we will get the results from the trial?

**Jean-François Dehecq**

2006.

**Vikram SAHA**

Would it justify greater resource allocation to Plavix and if it would, how would it change the structure of your deal with Bristol-Myers Squibb in the States. Would it change it in any way, shape or form?

Finally, how does it alter your assessment of the six billion forecast for Plavix?

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**Hanspeter Spek**

Do I understand your question properly: if CHARISMA were positive, would we need a larger field for resources?

**Vikram SAHA**

Yes.

**Hanspeter Spek**

The answer is little . It is an indication for cardiologists, and we see cardiologists in high-frequency. I would say insignificant.

**Vikram SAHA**

Thank you.

**From the floor**

I just have a question about the Plavix-Asprin combination. We have always known that you have it there, and now I see it is on the list to be filed this year. Can we have an indication of the timing of filing. Is it early this year or late this year?

**Gérard Le Fur**

Late this year.

**From the floor**

Can you give us an indication of the number of years of marketing exclusivity, any patents we have not heard of on the compound, and to what extent you think it can take over from just Plavix on its own?

**Gérard Le Fur**

We have no special patents on it on this association.

**From the floor**

It is not really part of any major defence strategy? Is it just a new product, or is it something that you are rolling out this year because...

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**Hanspeter Spek**

It is out of convenience for our patients. If I remember rightly, about forty percent of our Plavix patients are, at the same time, on aspirin, so it is a convenience issue and, consequently, it is a compliance issue, which is, in fact, of very dramatic importance for the product for managed care. Besides, there is no additional protection on it.

**From the floor**

There is no additional patent on it?

**Hanspeter Spek**

No.

**Kevin SCOTCHER, SG Cowan**

A quick question. Relative to the current net present value of your R&D pipeline, what would be increase in the net present value by putting Sanofi's pipeline together with Aventis's resources?

**Jean-François Dehecq**

I think that we have no answer in terms of calculation. But I can speak about the premium, because what is interesting is the fact that, travelling around the world during the last few weeks, I saw a lot of investors. Some of them are very invested in Sanofi, and they have told me that 15% is too much. When I met some people who are very into Aventis, they have said that 15% is not enough. You know that some people say that you need a lot of increase. I think that what is important for me, is to ensure that the right weight is on the table. What was important? For one year, the market put the two companies at the same level in terms of market capitalisation. That is the first point. They will put 15.2% as a premium to take this company. I read a certain number of papers saying that it is not enough, and that the Sanofi paper is not interesting. I think that after these figures perhaps it could be different. What I said to the people is that they will see, at the end of February, the results and the updates of the research of Aventis. You will see, on the 16th February, the results of Sanofi, how these results are built, without cutting research and making capital gains by selling products and so forth. These will be pure results. You will see what could be the update of the research. I think that today, all of you have all the figures to make the choice and to look at what is the situation. If I made the calculation, and gave you the calculation, some people would ask about Plavix or I could ask about Allegra, or other products, but I think that that is not the true way to make the deal. I think that we put a certain number of things on the table and shareholders have to see what they think. The calculations and the comparisons between the NPV and the research, I saw that they have a great number of blockbusters but not for today or tomorrow. You will make this calculation. I am very confident in this company and the reason why I think that this is a fair proposal and a fair offer.

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**Ruchlee PADIA, Merill Lynch**

I had a few R&D questions. The first was on the V2 receptor antagonist. You spoke about SIADH and cirrhotic SITs but you omitted congestive heart failure, and I wondered whether you could expand on what is going on there or whether the programme has been terminated. Also, regarding thirst as a side-effect, is this constant over time or does it fluctuate?

**Gérard Le Fur**

It fluctuates.

**Ruchlee PADIA**

Then I had a question on Dronedarone. Does it have specific activity in the atrium? Is that the reason why you are not getting these pro-rhythmic effects?

**Gérard Le Fur**

No, this compound, like Amiodarone, works at both the ventricular level and the atrial level. There is the same mechanism of action on both areas.

**Ruchlee PADIA**

So how do you explain the lack of pro-arrhythmic effects?

**Gérard Le Fur**

Because this compound, like Amiodarone, is very very safe in terms of pro-arrhythmic activity. It processes the same mechanism of activity as Amiodarone.

**Ruchlee PADIA**

Finally, about tirapazamine. Could you confirm whether survival is the primary end point with the study?

**Gérard Le Fur**

For head-and-neck or for non-small cell lung cancer?

**Ruchlee PADIA**

For head-and-neck.

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**Gérard Le Fur**

For head-and-neck the answer is yes. That is why it takes a long time.

**Ruchlee PADIA**

What is your level of confidence regarding the success of the study considering non-small cell lung cancer has been terminated?

**Gérard Le Fur**

You know, because of the mechanism of action of tirapazamine, this compound, it is well known, is more active in hypo conditions, which is to say that, theoretically, it is certainly a better sensitizer of radio-therapy than to be more active in association with chemotherapy. That is why we strongly believe that such a compound might be, should be, and will be, active in head-and-neck and was not active enough in non non-small cell cancer compared to quite a lot of other compounds.

**Ruchlee PADIA**

If you could go back to the aquaretique question now on CHF.

**Gérard Le Fur**

On CHF, we do not have the data right now. What we know, is that when you have hypo-natrenia in CHF, the compound seems to be active one more time. That is why we will develop the compound in all types of hypo-natrenia, including SIADH, or cirrhotic patients, or whatever the cause of the water-retention that you can have. Clearly we do not have the data yet.

**Ruchlee PADIA**

Thank you.

**Jean-François Dehecq**

Are there any final questions?

**From the floor**

Aventis has pointed out that it has various change of control clauses in its agreements with its various joint-venture partners, and that these would be negatively affected if they were acquired by you. Can you comment on that? Does this concern you?

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**Hanspeter Spek**

We think that this is a big argument. First, we feel that somebody who has given a licence or another business in a company, has little reason to destroy this business, when the respective company gets stronger, which definitely would be the case. Secondly, in line with this, Genta has already given rather an important licence, and has made a statement that they would not be at all bothered by a fusion or merger of both companies. Thirdly, if you have such change of control clauses, and you make a careful negotiation, you usually negotiate it with a compensation clause, so if the business or the product should be withdrawn, you have to be compensated. This is a nice effect, and raises the level to restore the product. Last but not least, if Aventis feels that this is such a dramatic issue, it is up to Aventis to declare which products are concerned. With the ongoing process, we will know within the next couple of days if products are concerned and to what extent they are concerned. We estimate it, overall, as a minor effect and more a tactical argument than a business reason. To tell you one thing, we have not one clause of this kind in our portfolio.

**Jean-François Dehecq**

A last question?

**From the floor**

A couple of questions. Can you be more specific in where exactly you expect the 1.6 billion euros in synergies will come from? Secondly, based on your comments this morning in Paris, should our expectations for Ambien be that, for the 20-25% of patients who would like one or two more hours of sleep would be paying a branded price and the other three-quarters of the market would be paying a generic price? Third, can you talk a little bit more about the rimonabant, about the long-term safety that you have so far, and a little more detail on adverse events?

**Hanspeter Spek**

Perhaps I will start with the price issue. This really will remain a secret until the very last minute. Everything is possible. One of the strengths of CR, of Ambien CR, is that we have a prolonged protection, which means that product will be patent protected, which should, if the current situation is being maintained, lead to a higher price. We, of course, have the opportunity to look at the upcoming competition from Astra and Pfizer, and then anything is possible. We could also sell the better Ambien CR at the same price as the old product, or we could even sell it at a lower price. This is one of the tactical cards we can play, and we will not take a decision before 2005 or even 2006.

**Gérard Le Fur**

So, concerning the safety of Rimonabant, as we mentioned to you, the drop-out rate in both studies is equal, or even lower, than the placebo. Secondly, the side-effect profiles are finally, the one we got in Phase IIb, so that is mainly GI disorders, the kind of nausea which are mild and transient and, let us say, Prozac-like. We also got some CNS effects, that we can distinguish from a withdrawal syndrome, although, as I have shown, by using HAD we got nothing on depression and anxiety sub-scores. In other words, the compound is very well-tolerated.

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**Jean-François Dehecq**

The other question about the synergies. I said this morning, that the 1.6 billion will be around one third in positive synergies and around two thirds in cost-cutting. What I also said, is that I do not think it is possible to put on the table and in the newspapers, before discussions with employees and unions, the numbers of employees. What is sure, is that from my experience of the last mergers that we had, is that we find a number of things. First step, we have a number of headquarters around the world. We had two, we will have one. One thing is also very important in my mind. I always found a lot of consultants inside the companies that I have bought. I do not understand why it is necessary to have so many large expenses. I also saw a lot of partnerships. We spoke about the partners in terms of products on the market, but you could also find a lot of partnerships and I am not sure that each contract has to be continued, because when you need products you can put a lot of contracts to have products on the file, but I am not sure that all that is necessary. We will have to discuss with the people, and find the best way to optimise the headquarters, the sales force, manufacturing and so on. We have always done that. During the last merger we closed more than ten plants around the world, but with good, open discussions with the people, we found the best solution. We will continue like that. Perhaps what surprised me, is that the countries and regions where we have the most important job to do in this way, is perhaps not exactly what the guys on the other side said. When you are totally involved in terms of research and manufacturing and developing a sales force, we are strong in Europe, like US companies are strong in the States, because they have their headquarters and the most important of their research centres and manufacturing plants and so forth. Yes, we prefer to discuss with the unions and the representatives and the workers' councils. Say, the second day after the announcement we arrived in Frankfurt and closed the research centre and the plant - clearly, this is impossible to do. It is impossible to close a plant, it is a very interesting plant, and the research centre for us is a big chance, because even if we think that it is interesting to do research in the States, the researchers there are not researching in the States in the same way as in Europe. This famous 'pluralism', which is one of the biggest parts of the success of Sanofi, we have to keep this spirit. We will do what we have to do, and look at what we have to sell. We said that we would have to sell Fraxiparine and Arixtra. We were, the first or second day, in the plant at the Notre-Dame-de-Bondeville, explaining that we will sell this plant because it is a prime of competition, so we are not anxious about how to manage the social story. I think that the social story of Sanofi is not such a bad one, and I prefer to explain what I have to do, than to explain how to make a carve-out of 9% of the business. It is easier.

Thank you very much for your time.

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