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April 12, 2002

Dockets Management Branch
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, Maryland 20857

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Citizen Petition: The Labeling of Serono's REBIF Is Misleading

Dear Sir or Madam:

Biogen, Inc. hereby files this citizen petition pursuant to 21 C.F.R. § 10.33.

A. Action Requested

Biogen respectfully requests that the Commissioner of the Food and Drug Administration (the "Commissioner" or "FDA") take the following actions. First Biogen requests that the FDA assure that labeling of Serono, Inc.'s interferon beta-1a product, REBIF®, and any promotional or advertising materials for such product are neither false nor misleading by requiring that Serono supplement existing information in the label about the relative efficacy of REBIF and Biogen's AVONEX® (interferon beta-1a) product from the first 24 weeks of Serono's 48-week EVIDENCE trial with data on the relative efficacy of the two products gathered during the second 24-week period of the trial. Second, Biogen requests that FDA correct errors in the discussion on neutralizing antibodies contained in the publicly available analysis document prepared by the Center for Biologics Evaluation and Research (CBER) in connection with approval of REBIF. Finally, Biogen requests that the FDA further investigate the manner in which Serono conducted the EVIDENCE trial, particularly whether its conduct of the trial introduced bias into reporting of exacerbations in the treatment groups and further that the FDA monitor Serono's conduct of upcoming Phase IV trials.

As outlined more fully below, these actions are required to assure that REBIF's labeling complies with the law and that FDA documents relied upon by Serono, physicians, and patients are scientifically accurate. The requested actions are also essential to ensure that multiple sclerosis patients have full and complete

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information available to them about the relative benefits of REBIF and AVONEX when they make decisions about how to treat this long-term, debilitating illness.

B. Background

In May 1996, CBER approved AVONEX for treatment of relapsing forms of multiple sclerosis (MS). AVONEX was approved as an orphan product and granted seven years of market exclusivity.

On March 7, 2002, CBER approved Serono's REBIF for the same labeled indications – breaking AVONEX's exclusivity based on the results of a head to head clinical trial showing that more patients on REBIF remained relapse free during the first twenty-four weeks of therapy than patients on AVONEX. This head to head trial was entitled EVIDENCE and was conducted for a total of 48 weeks. FDA has not received full data from the final six months of the study period. It has, however, received preliminary data and used that data in a document explaining its decision to break AVONEX's exclusivity. See C. Rask, E. Unger, and M. Walton, Comparative Study of REBIF to AVONEX and Orphan Exclusivity, March 7, 2002 (“CBER Analysis Document”). This document is available on CBER's website. See <http://www.fda.gov/cber/review/ifnbser030702r1.pdf>.

As the data referenced in the CBER Analysis Document show, during the second six months of the EVIDENCE study, the relative efficacy of REBIF and AVONEX was different than in the first six months with a slightly higher percentage (83%) of the relapse-free patients remaining relapse free on AVONEX compared to REBIF (82%). Despite this data showing no advantage for REBIF during the second six months of the study, CBER did not require Serono to include the data in the REBIF label. Instead, the REBIF label and Serono's promotional materials reference only the limited data from the first 24 weeks.

C. Statement of Grounds

1. REBIF's Labeling is False and Misleading

The Federal Food, Drug and Cosmetic Act (FDCA) prohibits the sale of a misbranded drug. 21 U.S.C. § 331(a). A biological product, like REBIF, is a drug within the meaning of the FDCA. 21 U.S.C. § 321(g); 42 U.S.C. § 351(j). A drug is misbranded if the labeling or advertising fails to reveal material facts relevant to representations made in the labeling or advertising or fails to disclose material consequences which may result from the use of the drug to which the labeling or advertising relates. 21 U.S.C. § 321(n). REBIF's package insert which claims an advantage for REBIF at 24 weeks fails to reveal facts material to multiple sclerosis

patients and their physicians – that, during the second 24 weeks of treatment, the chances of a relapse-free patient remaining relapse free were just as good on AVONEX as on REBIF.

Serono's approved package insert includes a statement that "Patients treated with Rebif® 44mcg sc tiw were more likely to remain relapse-free during the 24-week treatment period than were patients treated with Avonex® 30mcg im qw (Table 2)." Table 2 specifies in this context that the "[r]isk of relapse on Rebif® relative to Avonex®" is .68. See REBIF Package Insert at 7. Although the statement from the package insert and the table accurately reflect the 24-week data, the information is incomplete. The EVIDENCE study showed that, during the second six months of treatment, there was no advantage for REBIF and in fact potentially a slight advantage in favor of AVONEX in the chance of relapse-free patients remaining relapse free.

The following table from the CBER Analysis Document shows in bold the important information missing from the REBIF label:

Tbl A1: Exacerbations by Severity						
	To week 24		To week 48		From Wk 24 to Wk 48	
	Avonex n=338	Rebif n=339	Avonex n=338	Rebif n=339	Avonex n=214	Rebif n=254
No Exacerbation	214 (63%)	254	177 (52%)	209 (62%)	177 (83%)	209 (82%)
1 or more Exac.	124 (37%)	85 (25%)	161 (48%)	130 (38%)	37 (17%)	45 (18%)
Relative Rate of at least 1 exac. (Rebif/Avonex)	0.68		.81		1.02	

In weeks 24 to 48 of the EVIDENCE study, only 37 or 17% of the AVONEX patients who were relapse free at the end of the first 24 weeks of treatment had a relapse compared to 45 or 18% of the REBIF patients. Similarly, as the following table from the CBER Analysis Document shows, patients on AVONEX and REBIF experienced a similar number of relapses in weeks 24 to 48 -- there were 80 relapses in the AVONEX group and 82 relapses in the REBIF group.

Tbl A4: Exacerbations by Severity												
	To week 24				To week 48				From Wk 24 to Wk 48			
	Avonex		Rebif		Avonex		Rebif		Avonex		Rebif	
	n	%	n	%	n	%	n	%	n	%	n	%
Total # Exac.	132		98		212		180		80		82	
Mild	40	30%	27	28%	66	31%	52	29%	26	33%	25	30%
Moderate	49	37%	39	40%	82	39%	78	43%	33	41%	39	48%
Severe	30	23%	23	23%	40	19%	34	19%	10	13%	11	13%
Grade N. Avail	13	10%	9	9%	24	11%	16	9%	11	14%	7	9%

These data establish that there is no advantage for REBIF in the second six months of treatment. In other words, after the first 24 weeks of treatment, the chance of a relapse-free patient developing a relapse is at least the same with both therapies and may in fact be slightly higher on REBIF. It is only during the first six months of treatment that a relapse-free patient taking REBIF might have a smaller risk of relapse relative to AVONEX. In fact, even REBIF's small short-term reduced risk of relapse would not be expected to extend to those patients who are switching from AVONEX therapy. For patients who have been on AVONEX for more than 24 weeks, there is no efficacy advantage that would warrant switching to REBIF because, after 24 weeks, the relative efficacy of AVONEX and REBIF on the relapse endpoint is the same or even slightly favorable to AVONEX.

In the CBER Analysis Document, CBER asserts that the "treatment effect observed during the initial 24 weeks was maintained during the succeeding 6 months." See CBER Analysis Document at 8. This statement may make a valid statistical point – that, despite the similar performance of REBIF and AVONEX in the second six months, the statistical advantage for REBIF is maintained because of the data from the first six months. However, CBER's assertions do not accurately reflect the clinical experience of MS patients. An MS patient who is relapse free at 24 weeks faces, at the very least, the same probability of relapse on either drug and in fact perhaps a slightly higher risk of relapse on REBIF. This distinction between the statistical argument and the actual clinical meaning of the data is important because Serono has repeated the statements made in the CBER Analysis Document regarding maintenance of effect and has directed the public to the REBIF approval-related materials, including the CBER Analysis Document, on the web site. See Attachment 1 at 12, 24-25. As a result, the inaccuracies are being disseminated creating misinformation among patients and physicians. Without careful

qualification and a full presentation of the 24 to 48 week data, Serono has the opportunity to mislead patients that their risk of relapse is permanently lower on REBIF.

Because interferon treatment is potentially a life-long therapy, it is vitally important for physicians and patients to be aware of the limited purported benefit of REBIF over AVONEX and to weigh that information against the information about REBIF's potential problems. These problems include (i) a greater safety risk, particularly the incidence of injection site skin necrosis seen with REBIF but not with AVONEX, (ii) a 92% rate of injection site reactions for REBIF versus a 4% rate for AVONEX, and (iii) a higher rate of neutralizing antibody formation associated with REBIF. Physicians and patients are likely to consider the 24 to 48 week data important when determining whether these additional risks are worth the benefit. The short term nature of the benefit would also likely be an important consideration to physicians and patients when assessing longer term benefits/risks of the two drugs, including the effect of the drugs on slowing the progression of disability, the gold standard in the treatment of MS. As stated in the AVONEX label, AVONEX showed a 37% reduction in the cumulative probability of disease progression over two years compared to placebo. See <http://www.fda.gov/cber/label/ifnbser030702LB.pdf>. The REBIF label indicates that REBIF showed a 30% reduction in the proportion of patients with sustained disability progression compared to placebo. See <http://www.fda.gov/cber/label/ifnbser030702LB.pdf>.

In addition, patients and physicians would likely want to weigh data showing the limited benefit against other data available including data on the effect of the two drugs on reducing the rate of brain atrophy. Data show that the rate of brain atrophy associated with 44 mcg REBIF is equal to or possibly higher than with placebo over two years as contrasted with published papers on AVONEX showing that AVONEX reduces the rate of brain atrophy over the same period.¹

Without the 24 to 48 week data in the package insert, Serono will likely continue to disseminate misleading information about the alleged

¹ Jones, C.K., et al., MRI Cerebral Atrophy in Relapsing-Remitting MS: Results from the PRISMS Trial; *Neurology* 56 (April 2001) (Supplement 3): A379; Rudick, R.A., et al., Use of the brain parenchymal fraction to measure whole brain atrophy in relapsing-remitting MS. *Neurology* 53, 1698-1704 (1999); Rudnick, R.A., et al., Brain atrophy in relapsing multiple sclerosis: relationship to relapses, EDSS, and treatment with interferon β -1a, *Multiple Sclerosis* 6, 365-372 (2000); Hardmeier, M., et al., Short and Long Term Brain Volume Changes after Initiation of Treatment with rIFN- β -1a in Multiple Sclerosis (MS), Abstract ENS, June 2002 (submitted study).

"maintenance" of Rebif's "advantage." Given that FDA already has information showing no advantage for REBIF between weeks 24 to 48, the information should be made available to patients and clinicians immediately. FDA should not await Serono's submission of additional information in June 2002. See REBIF Approval Letter, available at <http://www.fda.gov/cber/approvltr/ifnbser030702L.htm>. FDA should require immediate amendment of the REBIF labeling to include all of the 24 to 48 week data so that patients and physicians can perform a complete and accurate comparison of the two drugs, not just a comparison based on limited information which, taken out of context, favors REBIF.

2. Neutralizing Antibodies

The REBIF label highlights the comparative efficacy of REBIF and AVONEX on a single endpoint during 24 weeks in a disease requiring life long treatment. An important data point for predicting long term comparative efficacy of the two drugs is the relative rates of formation of neutralizing antibodies. The formation of neutralizing antibodies has been shown to significantly reduce clinical efficacy of interferon beta products over time.² The CBER Analysis Document contains a discussion of neutralizing antibodies. However, the discussion is incomplete and, in some cases, inaccurate. The nature of these errors and omissions is discussed below. Serono has referred the public to the REBIF approval-related materials on the FDA website which include the CBER Analysis Document. See Attachment 1. As a result, the misinformation and omissions in the discussion on neutralizing antibodies are being disseminated in the marketplace. Biogen requests that the Commissioner correct the discussion in the CBER Analysis Document and notify the MS community about those corrections.

Before FDA approved REBIF, Biogen asserted that long-term antibody formation in REBIF patients (13–25 percent according to Serono's pivotal trial) raised a serious concern about the product's long-term efficacy relative to AVONEX. When FDA approved REBIF on the basis of "greater efficacy" at 24 weeks, CBER attempted to address Biogen's concerns about antibody formation in the CBER

² The PRISMS (Prevention of Relapses and Disability by Interferon- β -1a Subcutaneously in Multiple Sclerosis) Study Group and the University of British Columbia MS/MRI Analysis Group PRISMS-4: Long-term efficacy of Interferon- β -1a in relapsing MS; *Neurology* 56, 1628-1636 (2001); The INF β Multiple Sclerosis Study Group and the University of British Columbia MS/MRI Analysis Group, Interferon beta-1b in the treatment of multiple sclerosis: Final outcome of the randomized controlled trial, *Neurology* 45, 1277-1285 (1995).

Analysis Document. See CBER Analysis Document at 9. Unfortunately, CBER's discussion of the issue is both inaccurate and incomplete.

The CBER Analysis Document shows that the REBIF group in the EVIDENCE trial had a higher rate of neutralizing antibody formation than the AVONEX group. See Table 7A, CBER Analysis Document (269 out of 294 AVONEX patients were antibody negative versus 185 out of 298 REBIF patients). However, there are several inaccuracies in the accompanying discussion. The CBER Analysis Document states:

In the Rebif group, there was no association between antibody status and the probability of remaining exacerbation-free, for either the Week 0-24 or the Week 24-48 period (Table A6). Comparisons between the 2 treatment groups with respect to antibody status and clinical outcome demonstrated that all subsets of Rebif-treated patients, categorized by antibody titer, experienced lower exacerbation rates than AVONEX-treated patients.

Analysis Document at 9. This statement is factually incorrect and misleading. It is incorrect for CBER to state that all subsets of REBIF-treated patients categorized by antibody titer experienced lower exacerbation rates than the AVONEX-treated patients. Patients on REBIF who developed antibodies were not more likely to remain exacerbation free than patients on AVONEX. The percentage of AVONEX patients (antibody positive or negative) who remained exacerbation free in weeks 24 to 48 was 83% (See Table A1 of the CBER Analysis Document included above) as opposed to 79% for the REBIF antibody positive group (see excerpt from Table A6 of the CBER Analysis Document below).

Exacerbation Free Status by Subsets based on Week 48 Neutralizing Ab Status						
Neutr. Ab Status	Weeks 25 to 48					
	Avonex			Rebif		
	#at risk	# Exac. Free	%	#at risk	# Exac. Free	%
Neg	171	139	81%	146	123	84%
Any Pos	13	12	92%	78	62	79%
+ titer < 20	7	6	86%	21	16	76%
+ titer >= 20	6	6	100%	57	46	81%
+ titer >= 100	1	1	100%	40	32	80%
+ titer >= 500	1	1	100%	14	12	86%

CBER's statement is also factually incorrect comparing antibody-positive patients, with 92% of AVONEX antibody positive patients remaining exacerbation free in weeks 24 to 48 as compared to 79% for the REBIF antibody positive group. In fact, the only subset in which there was a slight difference favoring REBIF was in comparing antibody negative patients and in that case the difference was only 3%, as shown above.

In addition to being factually incorrect, CBER's statement is also misleading. Neutralizing antibodies generally develop after 9 to 15 months of treatment. Their effect is not immediate and is not generally measurable until after 15 months of treatment. In fact, in the publication of Serono's long term study of REBIF, the authors indicated that the 4-year efficacy data demonstrated reduction in efficacy in years 3 and 4.³ As a result, the neutralizing antibodies measured in Week 48 of the EVIDENCE study are likely to have developed toward the end of the study period, and their effect would not be expected to be seen in the data until after week 48. An effect on exacerbation rates would not be measurable in week 24

³ The PRISMS (Prevention of Relapses and Disability by Interferon- β -1a Subcutaneously in Multiple Sclerosis) Study Group and the University of British Columbia MS/MR1 Analysis Group PRISMS-4: Long-term efficacy of Interferon- β -1a in relapsing MS; *Neurology* 56, 1628-1636 (2001).

(and in fact neutralizing antibodies have not developed at that point in most patients) and is not likely to be significant until after week 48. CBER's discussion fails to acknowledge the shortcomings of the 48 week time period and instead erroneously implies that, in the context of neutralizing antibodies, there is real relevance of 24 and 48 week results. This is very misleading and should be corrected.

CBER's analysis also fails to recognize the likely effect of REBIF's higher rate of neutralizing antibody formation on the long-term relative efficacies of REBIF and AVONEX. In fact, the effect of the high rate of neutralizing antibody formation associated with REBIF is evident in the data from Serono's own studies. In the publication of the four-year PRISMS-4 study results, the authors note that "an analysis of 4 year efficacy data by Nab status demonstrated reduction in both clinical (in years 3 and 4) and MRI efficacy in patients who were Nab-positive".⁴ The authors also stated that: "The implications for IFN therapy are considerable because the development of NAB may influence treatment decisions, particularly in patients who are not doing well."⁵

Even in the original two-year PRISMS study, REBIF's performance compared to placebo changed over time. In the two-year study, the reduction in mean exacerbation count per subject in the REBIF 44 mcg group compared to placebo was 40% in the first year, but decreased substantially to 25% in the second year.⁶ In fact, Figure 2 of Dr. Kaiser's review of Serono's BLA shows a steady downward trend in the differences between the groups in exacerbation count at each successive 6-month period.⁷ Serono may argue that the drop in rate of exacerbation in the placebo group accounted for the difference, however a similar drop in the placebo group occurred in year two of the AVONEX pivotal trial, but the difference between AVONEX and placebo was maintained. In the case of REBIF, the gradual reduction in efficacy is likely due to neutralizing antibodies blocking the biological activity of the drug.

⁴ Id. at 1636.

⁵ Id.

⁶ Kaiser, J. FDA's Medical Officer's clinical review, BLA 98-0261 Serono Laboratories, Inc. Interferon- β -1a (Rebif®), February 9, 1999, p17, available at <http://www.fda.gov/cber/review/ifnbser030702r4.pdf>.

⁷ Id. at 18.

The CBER Analysis Document is also inaccurate in its discussion of the comparability of the antibody formation rates for the two drugs. CBER states that "rates of antibody formation to these molecules are not directly comparable, because the assays performed by Serono measured antibodies by their ability to bind Rebif." See CBER Analysis Document at Page 9. In fact, the rates of antibody formation between REBIF and AVONEX are directly comparable. Biogen and Serono have exchanged neutralizing antibody positive samples and there is 100% concordance between the assays used by the two companies. Biogen also sent vials of AVONEX to Serono, and Serono assessed numerous neutralizing antibody samples with both AVONEX and REBIF. Again, there was 100% concordance of neutralizing antibody positivity when product was used. In addition, independent investigators have tested numerous samples with both REBIF and AVONEX and, when the neutralizing antibodies are detected with one antigen, they are always detected with the other.⁸ See also: Presentation by Schellekens, H, at *Immunogenicity of Therapeutic Biological Products*, Lister Hill Auditorium, National Institutes of Health, Bethesda, MD, Oct. 31-Nov. 2, 2001. It is clear from this data that the relative incidences of neutralizing antibody formation in the EVIDENCE study can be validly compared.

The PRISMS data provides evidence that the high rate of neutralizing antibody formation will have an effect on REBIF's efficacy. CBER's decision to ignore this and to characterize short-term EVIDENCE data as indicative of neutralizing antibody effect is simply not supported by the available scientific data. What is clear from the available data regarding AVONEX and REBIF is the following:

- REBIF has a significantly higher rate of neutralizing antibody formation (25%) as compared to AVONEX (2%).
- The PRISMS long term study of REBIF indicates that antibody formation has a negative long term effect on clinical efficacy.
- The PRISMS 2 year data shows the gap between placebo and REBIF narrowing over time. (AVONEX Phase 3 trial did not show a narrowing effect).

⁸ Berlotta, A., et. al. Interferon β neutralizing antibodies in multiple sclerosis: neutralizing activity and cross-reactivity with three different preparations *Immunopharmacology* 48, 95-100 (2000).

- Contrary to CBER's statements, the percentage of patients who remained relapse-free in weeks 24 to 48 of the EVIDENCE study is higher in the AVONEX group than the REBIF antibody positive group and is higher in the AVONEX antibody positive group than the REBIF antibody positive group.

FDA should not play a role in dissemination to physicians and patients of inaccurate and incomplete information regarding the potential effect of neutralizing antibodies. The discussion on neutralizing antibodies contained in the CBER Analysis Document is not complete and, in some respects, is inaccurate. Because Serono is referring the public to the REBIF approval documents on the FDA website and will undoubtedly use the FDA approval documents in its promotional activities, it is important that FDA ensure that the information in these documents is accurate and complete. Biogen requests that FDA review the antibody discussion in the CBER Analysis Document and clarify the discussion in its records so that it is consistent with the available scientific data.

3. Investigate Serono's Conduct of the EVIDENCE Trial and Monitor its and Phase IV Trials

Biogen requests that the Commissioner institute a full and thorough investigation of allegations of Serono misconduct during the EVIDENCE trial. Biogen understands that at least one clinical investigator participating in the EVIDENCE trial reported to FDA that each time his site reported a relapse with a REBIF patient, Serono's clinical group would insist that the determination be re-evaluated and would require more substantiation and documentation of the exacerbation. We understand that the investigator also indicated that Serono never questioned or required further documentation of any relapses he reported in the AVONEX group. This allegation raises serious concerns that bias may have been a

factor in the EVIDENCE trial. ^{9/} When it approved REBIF, CBER made no mention of this investigator's complaint or any resulting investigation, presumably because none was conducted.

It is of utmost importance that FDA take seriously all allegations of sponsor misconduct. Because CBER evidently did not fully investigate the allegations that Serono tried to influence those reporting REBIF relapses, Biogen requests that CBER undertake a thorough audit of the EVIDENCE study immediately.

Biogen also believes that Serono's conduct could affect any future studies that Serono is required to submit to CBER. The REBIF approval letter requires that Serono conduct a Phase IV clinical trial. See Approval Letter at 3, no. 6. Biogen requests that CBER regularly and thoroughly audit postmarketing trials to ensure that there are no efforts to influence study outcomes.

D. Environmental Impact.

Pursuant to 21 C.F.R. § 25.31(a), the actions requested herein are exempt from an environmental assessment or environmental impact study within the meaning of the National Environmental Policy Act of 1969.

E. Certification

^{9/} In fact, the EVIDENCE data itself may suggest bias. For example, as shown in table A2, from the CBER Analysis Document (reproduced below), there were 142 unscheduled visits by REBIF patients in the EVIDENCE trial as compared to 105 unscheduled visits by AVONEX patients, yet of these only 57 (or 40%) in the REBIF group were referred by the unblinded referring physician to the blinded assessor to determine if a relapse had occurred as compared to 65 (or 62%) in the AVONEX group.

Tbl A2: Numbers of Unscheduled Visits and Exacerbation Outcome				
	Avonex N=338		Rebif N=339	
Unscheduled visits	105		142	
No Neuro exam	40		85	
U.Visit with Neuro exam	65	62%	57	40%
U.Visit with Exacerbation Confirmed (% of Exams)	44	68%	39	68%
Steroid use at U.Visit with Exac (% of Exac)	16	36%	20	51%
Scheduled Neuro exam with Exac confirmed	35		42	

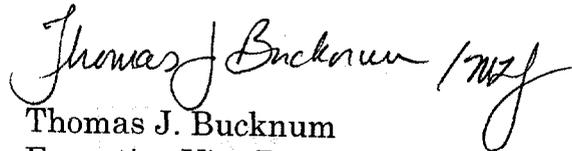
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The undersigned certifies, that to the best of his knowledge and belief, this petition includes all information and views on which the petitioner relies, and that it includes representative data and information known to the petitioner which are unfavorable to the petition.

Respectfully submitted,

A handwritten signature in cursive script that reads "Thomas J. Bucknum" followed by a stylized flourish.

Thomas J. Bucknum
Executive Vice President & General Counsel

Thank you very much and good day, ladies and gentlemen. Welcome to Serono's conference call. Today's discussion is going to focus on the very good news, which we announced on Friday last week, that the Food and Drug Administration has approved Rebif for relapsing multiple sclerosis. This has a coming drug stage of Biogen AVONEX. Today's conference call comes to you from U.S. headquarters here in Rockland, Massachusetts, and I'm very pleased to be here today with Ernesto Bertarelli. Ernesto is Serono's chief executive officer. And Dr. Gordon Francis, neurologist and head of our multiple sclerosis clinical development unit. Before I turn the call over to Ernesto, I must advise all listeners that our discussion today may contain forward looking statements that reflect management's current views, as the company's collaborative arrangements, clinical trials, product developments, ready for approvals, manufacturing scale and other future events and operations. These forward looking statements with the SEC's findings with the U.S. Securities and Exchange Commission. Including the risk factors and operating financial review and prospectus section of Serono's annual report on form 20 filed on April 23, 2001. Actual results would differ materially from the forward looking statements. Now I'd like to turn the call over to Ernesto and his comments about this very good news about Rebif - Ernesto?

Thank you, Andrew. Hello ladies and gentlemen, welcome to our conference call. You can imagine how pleased I am to report on the positive outcome of the FDA review of our BLA for Rebif relapsing. As you will recall, we originally filled our BLA for Rebif in

1998 and after much discussion with the Food and Drug Administration, we decided to perform a head to head study comparing the secrecy of Rebif with AVONEX. The objective was to confirm in a perspective study that Rebif was **clinically superior** to AVONEX. As agreed with the FDA, the primary point of the study is the proportion of relapse free patient over 24 weeks of treatment. As you know from the data presented last year at the World Congress of Neurology on June 22, the evidence study was highly positive for Rebif. It shows statistically significant results in favor of Rebif over AVONEX on the primary and all secondary end point. Clear benefits were seen within 6 months of starting treatment with Rebif, the variety of relapse, and brain lesion parameters. Based on the agency review of the results, the evidence study in the context of the orphan drug act, Rebif has been determined to be **clinically superior to AVONEX** by the Food and Drug Administration. On Friday, the FDA released a great deal of detail about their review, including in the documentation was a 48 week data from the evidence study, which had been provided by Serono during the agency review of our file.

The FDA observed that the treatment effect of Rebif in 24 weeks is maintained in 48 weeks. A patient treated with Rebif during the 48 weeks of observation, 62% remained free of relapses, as compared with 52% of those treated with AVONEX. A highly significant result with a P value of 0.006. We have seen the primary outcome of the 48 week result in our press release today. We will not be releasing more detail today since

as previously announced the 48 week result will be presented in detail by Dr. Panach (SI) on April 16 in a platform presentation at this here American Academy of Neurology meeting in Denver. We are obviously extremely pleased with the FDA's review of our data. Friday was a great day for Serono. Even more importantly, it was a great day for people in the United States suffering from multiple sclerosis.

Turning to our business, during 2001 we have seen Rebif become the market leader in MS treatment outside of the USA. As you will recall, we achieved \$380,000,000 of sales, which is a growth of 54% on the previous year. Despite being the 3rd interferon to come to market outside of the U.S., Rebif became the most prescribed therapy. Over 38,000 people were prescribed Rebif by the end of 2001. Meaning that we now have more than 38% of the world market outside of the U.S.A. Rebif has demonstrated consistently strong growth quarter after quarter compared to its competition. Rebif is now registered in 75 countries worldwide, including the U.S.

It is a little too early to give precise figures with regard to performance in the United States. However, given our excellent performance in the rest of the world, I expect Rebif to do just as well in the U.S. I expect our product to capture more than 25% of market share in the U.S.A. within the next 3-4 years. And by 2005, I expect Rebif worldwide sales to exceed \$1,000,000,000. The FDA decision is a landmark moment in the life of our company. Today we are launching Rebif, just a few days after receiving

FDA approval. This is the result of our decision late last year to invest in a significant marketing and sales infrastructure here in the United States. Today that infrastructure is in place and I'm pleased to confirm that it's ready to run with the product. Our overall business is in great shape and we continue to grow. I'm very confident about our future and the future of Rebif in the U.S. For what concerns more precise outlook for 2002, we will provide new guidances during our annual management road show at the end of March. And before we answer some of your questions, I'd like to return the call to Andrew. He will remind us of some of the highlights of Rebif's success last year. Andrew?

Thanks, Ernesto. I'm going to be very brief. On some of the excellent news of last week about our approval, I just want to remind everybody about the impressive array of regulatory milestones achieved over the last 12 months. Firstly, in the first quarter of 2001 the European Commission recognized the high dose of 44 micrograms, 3 times a week as the recommended dose of Rebif in the European Union. As anticipated in the 4th quarter, the European Commission approved the variation to expand the European labeling of Rebif to include the treatment of patients with early secondary progressive multiple sclerosis and the relevant literature was published in Neurology in June of last year. On June 22, the results of the evidence studies were presented at the world conference of neurology in London. As you know, following this the data was submitted to the FDA for review in the 3rd quarter. As many of you anticipated, 48 week data was

requested by the FDA in their review. And as I mentioned earlier this is acknowledged in the documents the agency made available on their website on Friday last week. The FDA approval last week is clearly a landmark as Ernesto said for Serono and for patients with multiple sclerosis. I'd just like to make a few final points about that. Based upon our clinical studies, **Serono has always been confident of the greater clinical effectiveness of Rebif** from the very earliest data of our program. And as you know, there were two important studies of the making of _____ First there was the PRISM study, which demonstrated Rebif's effectiveness in reducing relapses, slowing the rate of progression of disability, as well as producing marked reductions in MR disease activity and disease burden. And four years later data from this study, it was published in Neurology in June of last year.

In order to bring Rebif to the United States early, by demonstrating **greater clinical effectiveness**, Serono had to undertake a head to head study, which we now know as evidence. This is the first time in 19 years of the orphan drug act that a company has performed such a study. A recent publication, actually in the January 2002 edition of Neurology, Gooden and his colleagues classified evidence as being of the class one type in terms of its design and liability. And in the current decision by the FDA, it's the first time a new product has overcome the orphan drug status of an existing therapy based on greater efficacy or effectiveness.

In conclusion, ladies and gentlemen, this decision demonstrates **Rebif is clinically superior** and provides a significant therapeutic advantage over and above AVONEX. As we've seen from our press release this morning, it can be prescribed by physicians in the United States as of today and we look forward to its success in the future. At this stage, we'd be happy to take any questions that you have.

Excuse me, I am the conference call operator. We will now begin the question and answer session. Anyone who wants to ask a question, press star and one on their touch telephone. If you change your mind, and wish to remove yourself from the question queue, then you may press star and two. Anyone with a questions may press star and one at this time. The first question is from Andrew Fellows of Pictet & Cie..

Good afternoon, gentlemen, thank you. Congratulations very much on this success. Just a couple things. Can you give us an idea about pricing in the U.S. market for Rebif? And secondly, of those 15,000-20,000 new patients adding treatment this year, how many realistically do you think will be a reasonable assumption to Rebif itself?

Thank you for your questions. I can obviously give you a pricing now that the product is in the market. We are pricing Rebif on a monthly basis at \$1,156. And that's about a 20% markup on other products in the market today. What concerns the prediction for

the penetration of the U.S. market, I would prefer to provide those indications at a later date.

Given what you said you did to the market in Europe, would it be reasonable to assume 50% uptake of new patients?

Again it's difficult to give you any information at this point. We will prepare a more fuller and more explicit answer to a projection for the United States for our road show at the end of March.

OK. Thank you.

The next question is from Montia Serio from Brodeehay.

Good afternoon. Of course, congratulations as well. I have two questions. First of all, on your 48 week start, could it be added some time in the future the packaging as well? Will you also continue evidence trials for the next year so that we have some two year state on the evidence trial? And the second question on the earnings out of the 2nd quarter given no guidance there, is it right to assume from the first 2 quarters and the costs coming in there and not yet probably many additional meaningful, see somewhat lower earnings grow from the first 2 quarters?

OK, the evidence will not run beyond the one year point. And we will submit the 48 week for inclusion in the package to the FDA. For the guidance, we're going to wait for March. To give you an idea for costs, do you remember last year, our investment over the last 2 quarters of the year for the Rebif infrastructure in the United States was \$30,000,000. So you can expect that amount to approximately double to be around \$60,000,000 for the full year.

But does that mean for example about \$15,000,000 run up costs per quarter? Or are there some run up costs?

Yes, yes, 15 per quarter.

OK. Thank you.

The next question is from Tim Wilson of Bear Stearns.

Yeah, let me add my congratulations. My question is: at 24 weeks you referred to the 32% relative reduction and relaxation rate between the 2 groups of patients. I scoured those FDA documents hard and I can't see an equivalent figure. Do you have an equivalent figure at 48 weeks?

The 32% that you are referring to is the relative reduction in patients experiencing a first event on Rebif relative to AVONEX at 24 weeks. The primary outcome of the study was the proportion of the relapse free and that was the relative increase in the proportion of the patients who remained relapse free, and over 48 weeks, that same value was approximately 19% that remained relapse free. So it really depends on which way you look at these proportions, free or not free, which value you get there.

Look, I'm still confused. I want an equivalent to that 32%, if you can give me that. Because I can understand the 18 or 19, I can do that arithmetic as well. But I'm trying to get at what the equivalent of the 32% would be for 48 weeks.

Well that was the equivalent number for 48 weeks would be 19%.

Right, OK. Thank you very much.

It's in the document.

The next question is from Geraldine O'Keefe from Fortis

Hi, congratulations once again, great news. I just have a question regarding your launch in the U.S. You say you have a budget of about \$60,000,000. Biogen has had theirs at \$200,000,000. I'm just wondering how you're going to effectively launch the product in the U.S. with that money. Tell us about your strategy perhaps.

Well I'm not managing Biogen's budget obviously. That 60 million is plenty of money to launch the product. We'd like to remind you that we have an existing infrastructure in the United States. We already have two business units. One for practical one for growth omen. So we will use the economy of scale to establish the carry the launch of Rebif or success. 60 million is related only to the investment, related to their product. We're not sustaining the company with Rebif. We're not like Biogen, a one product company.

Will you be significantly increasing the number of sales reps in the U.S.?

Our organization is in place. We have recruited all the sales force and marketing staff to launch the product, and we're launching today.

OK, thank you.

That 60 million is just for the United States. I hope that was clear.

Yes, thank you.

The next question is from Sam Williams of Robertson Stevens.

Hi, congratulations, that obviously a great step forward. Just one question following up on an earlier one about the 6 month and 12 month data. I noticed from scanning that document that one of the conclusions of the FDA is that if the difference between the two drugs in terms of exacerbation rate in the second 6 months of the trial, there is no difference. So if you were exacerbation free on Rebif for 6 months, there's no difference in your chance of getting another or first exacerbation in the second 6 months compared to being on AVONEX. Is that of any concern in terms of trying to get some patients to switch? Assuming you in terms of hitting good numbers you will need at least some patients to switch from AVONEX to Rebif apart from picking up obviously the new patients?

I think the...I'll have to when looking at the data and the evidence, keeping in mind the most important factor of any individual patient starting on the treatment is the efficacy over time. And the evidence study has shown over the clinical course of a patient on Rebif over this one year is characterized by a greater likelihood of remaining relapse free, of having fewer brain lesions than a patient who starts on AVONEX. When this 24

week data has been reviewed, again PRISM led to the approval, but also when the FDA has received the 48 week data based on their preliminary review of that data, the conclusion being that the treatment effect observed during the initial 24 weeks was maintained during the second 6 months. I think from a patient perspective, coming onto Rebif, one doesn't look at a single epoch in time, but rather how will they do at the start of treatment into the future. The data out to the 48 weeks is supportive of the Rebif advantage over AVONEX for that patient.

If I can just add something to that. And that is, throughout the FDA documents you will see references to the treatment effects observed after 24 months...weeks was maintained during the preceding 6 months. I mean that was repeated again and again. And obviously we're limited by what we can tell you about the details because they are going to be presented out at the AAN in a field review forum. But we have to keep repeating that in their documents and I think that's extremely important. Because obviously there is a massive data here and it would be a mistake to read too much into a single data item. You have to look at the overall effect. Because I think it's face (sl) for any of us to draw conclusions, because they obviously have a very good reputation to do exhaustive reviews.

OK, that's great. Congratulations.

Thank you.

The next question is from eel siyanoff, bank serazin

Yes, gentlemen, let me add my congratulations as well. I've 2 questions. I noticed that in the package inserts, you have no claim of superiority. My question is how are you going to leverage layman in the markets? And the 2nd question is, in the response letter from the FDA, I notice the FDA is requesting an additional dose comparison study. Can you comment on that?

I'll comment on the first one, and Andrew can comment on the second one. We are permitted to promote consistent with the package inserts. And in the package inserts the evidence data are included with the mention of the P value that we see between the two products. Therefore we can claim greater efficacy of Rebif. And if any of you doubt, you can read the FDA report on the comparative study of Rebif to AVONEX, which gives an extensive review of its findings. **So it is clear that our marketing strategy will be based upon those findings and we don't see any problem in using our superiority in our marketing strategy.**

About the postscrim commitment. First off, the postscrim commitment is very common following the FDA approval. We're very pleased to do more and more studies for Rebif

in multiple sclerosis because we feel there are still questions that need to be answered. And clearly from the approval that we just got from the FDA they have recognized that, Rebif 44 micrograms, three times a week, worked better and appeared to be **superior to AVONEX in the context of this study**, and of course the real significance of that was that AVONEX had its recidity (SI) until then. The four year analysis of prisms in terms of efficacy wasn't part of the file. The safety data was in there. The four year prisms wasn't. And if you remember, the four year data from prisms which offer particularly convincing evidence that the higher of the two doses used in prisms, the 44 micrograms, 3 times a week, worked much better long term than 22 micrograms, 3 times a week. And I think if the FDA wants to look into further at the prospect of a randomized study where we compare those two doses, there is sort of a nuance about what is the optimal dose. Clearly 44 micrograms, 3 times a week, instead of the AVONEX dose. And that's what we've got to prove. But the question is, would half the dose of Rebif given on the same schedule, and we're very happy to do that study I must say. And to do it in a timely fashion. Nothing unusual about that. (inaudible) Gordon very eloquent.

I think that's correct. The original prism study was not powered to show a difference between the two doses. The dose difference was in fact demonstrated over the duration of the study. The FDA has requested us to look at that in somewhat more detail. But as you say, the prisms four data has not been formally reviewed by the FDA

as of yet, and one can't say whether that will have an impact on that commitment or not.

OK, so one could say that this study will be a follow-up on the prism study? And the FDA might be looking for signs 3 x 22 micrograms would also be more efficacious than AVONEX?

Well, I think that would be a difficult assumption. It's also not necessarily a follow-up onto the prisms. The prisms have been done, and if we go into another assessment of dose, to take it into potentially a slightly different patient group to answer some additional questions that Andrew has said related to other things that still need to be addressed in the MS population.

OK, thank you.

An advantage.

The next question is from Alexandra (inaudible) from Bear Stearns.

Good afternoon and congratulations from my part as well. Could you please comment on your current status in the U.S. You mentioned that you have recruited all the sales

force. I was wondering to what extent your patient support systems are in place, or is that something you will gradually build up as you start, as you start rolling patients under best (sl). And then secondly, the number 15,000-20,000 MS patients a year, the number comes from Biogen. It seems a bit aggressive given that (inaudible) secondary progressive market also fairly penetrated it basically you have to have your recruit early on the MS side (sl). Is that the number you're working as well in your market projection, 15-20,000 new MS patients? And lastly I do appreciate your comments on the U.S. market penetration. Biogen made a strong case on their conference call on Friday and they said this will be a battle for new patients. If you could just briefly tell us to which extent switching is actually figuring in your market attempt (sl).

That's a lot of questions, very simple answers. We're very confident that we will be successful against Biogen. Quarter after quarter I've been in a conference call with you guys, telling you what we're doing, what we're about, what we can show. I think our best vote of confidence is our success in Europe. Now the assumption of Biogen is probably based on the fact that they don't realize that we just broke off the drug on (inaudible) priority. In fact, I don't think we've been indifferent to physician or patient. What concerns the approval is you live in the U.S. for the lasting forms of the disease. So it doesn't classify or segment necessarily the market the way you present it. It talks about relapsing forms. Finally what concerns our infrastructure as I said, people probably don't realize which extent we are ready. We are launching the product today,

only physically 48 hours after the product was approved. We have a call center receiving calls as we speak. The product in the market being distributed by the Serono infrastructure. We have the sales force out there, we have the keyess (sl) out there. We're extremely confident that we are going to repeat the success that we've had in Europe here in the U.S. Considering that when we launched with this in Europe we didn't have the planes (sl) that we have today from the review of our evidence.

Thank you. Can I just come back to your...you said you have been successful, obviously you have, quarter after quarter in the market against Biogen in Europe, but you could argue that the European market has been on a different level. Have you seen in Europe a substantial switching from AVONEX into the midboys (sl)? Is your success largely because you've been successful at capturing the new patients?

We're very confident because when you ask the physician to rank or determine what is more important efficacy or convenience, all of them mention efficacy. This is very relevant. It has been relevant in Europe, and it's going to be relevant here in the U.S. as well.

Thank you.

It's been very recent that we've had such persuasive data in the shape of evidence.

And the fact that we've seen it flourish by the regulatory authority here in the U.S. So it's obviously going to be very important to our marketing strategy.

The next question is from Erica (inaudible) from Merrill Lynch.

Just a few questions. First of all, how soon will you be able to obtain reimbursement in the U.S. for rebif? Secondly I wonder if you can provide information on who your distributor or distributors are for Rebifin the U.S.? Thirdly, I was wondering if you have any idea what stocking levels might be initially? And the final question, was the label you received from the FDA negotiated at all? That's it for now.

OK. I'll start with the last question. The label is always negotiated with the FDA, it's part of the process. We're going to keep the stocks at a minimum because we want to feel the demand there and oversee the launch of the product very closely. The distribution network is in place, and it will be open to sellers. And finally, with regard to reimbursement, we have already pre-agreements with 80% of the Medicare, And 44 out of 50 states for Medicaid.

OK, so are those in place now, when you say pre-agreements? When will they be operated on?

I think you have to have the product in the market for the agreement to become final. But you can assume those pre-agreements are in place today. So 80% of the managed care and PBM are with us.

And you said how many states?

44.

If I could ask one more question. Are you...Biogen made a point of the potential label expansion in Europe on the favorable opinion on early MS with their chance data. Are you at all planning a similar label expansion using your eton (si) study data?

We're not convinced that it's really necessary to do that. The labels are generally left at the moment. The treatment guideline for neurologists to start treating MS earlier and earlier and that's all the clinical data and the preclude (si) data as well has been showing that you really need to treat it as early as possible. Although at the beginning the disease may be largely clinically silent. There's a lot of central nervous system information, and we know that today, whereas we didn't know that a few years ago. So the treatment should be as early as possible. As soon as the neurologist can competently diagnose somebody with multiple sclerosis. So now we have...it's contrary

to what Biogen said at their conference on Friday, we have a study on multiple sclerosis, it's called the eton study. And people on the core (sl) with Biogen, perhaps they should read that, it came out in May of last year. I think it's very focused (sl), it does show how (inaudible) works in multiple sclerosis. The dose that we used in that study, and that was several years ago, was 23 (sl) micrograms once a week. But we have learned from that program over the years that higher doses of (inaudible) were better than low doses. There are two reasons why we're not going to use intom (sl) to extend our labeling. For one thing, we think that's what physicians are already doing, they are treating people very early anyway. Anyway we don't want to confuse the market by trying to register a dose which doesn't fit in with the rest of our overall conclusion from our whole program. The high doses are better than the low doses.

Also, I'd like to remind everyone that the regulatory bodies both in Europe and in the U.S. (inaudible) market differencing most of the other people this year see it as relapsing versus non-relapsing, and you might recall that in Europe that we had an extension of our label to cover the relapsing form of techno-progressive (sl). So I'm very confident that early MS falls into the relapsing forms of the disease and we don't see the positioning that Biogen takes to be at all significant with regards to the use of the product in the marketplace.

OK, that's great, thanks.

The next question is from Anne Marden (sl) of JP Morgan.

Oh yes. Hello. I guess most of the things have been discussed, but I was wondering if you could just remind us what the pricing differential is in Europe between Rebif(sl) and the other two drugs. And also, in Europe you have the approval now for early use. How important will this be in the US given that many of the new patients are being diagnosed earlier and earlier, and this seems to be a big competitive thrust for Biogen AVONEX?

As I said again, the authorities don't really segment the market the same way that other people do. They really look at relapsing forms versus non-relapsing forms, and both in the US and in Europe (inaudible) this a proof for the relapsing forms of the disease, and therefore we don't see any significance of whatever claim Biogen is making on their chaff (sl) study and so forth. So it is really not an issue – it's a non-issue. Now, for what regards the pricing, as I mentioned the price in the US will be \$1,156 per month, which is about twenty percent markup on the other, about twenty percent markup on the other products. Which is similar to the markup that we have for high dose (sl) in Europe.

Since you've been using the evidence study to market the drug in Europe, how much market share have you gained against Biogen and sharing (sl), and maybe you can just add some clarity because we're getting conflicting information from Biogen.

I'm not surprised. They have done that in the past. As you remember the evidence study has been formatted and run specifically to address the orphan drug issue, specifically addressed to the FDA, and we kept it somewhat confidential from other entities until I would say Thursday, when we obtained approval. The fact that the FDA reviewed the data and made the findings that Ribif (sl) **was clinically superior to AVONEX** is very, very significant. And it is for us now the time to use this evidence study and findings more extensively in other part of the world and with other entities such as, for example, the European Commission. So, the extent and the significance of the evidence study will be felt also in Europe.

Ok, one last thing . . . sorry?

(inaudible) We need to give it some time, we need to get our peer review publication out there, and you know we need time to build a delay (sl). But I mean you've seen the histogram of how things have grown during the last twelve quarters or so; very consistent growth, and it looks like the last couple quarters probably there's been a

slight acceleration although we don't want to read too much into small changes in gradients. But clearly the gradient is much higher than that of our competitors.

Alright, and then in the US, do you have a feeling, do you sort of sense or have a knowledge you already have, you know, maybe a couple thousand patients who were using Rebif(s) in clinical trials or who were expecting issue (s) the drug who are waiting to phone you guys up today to get the drug? Or do you think it's going to be more difficult than that?

No, we're very confident that a lot of people are looking forward to using this in the US.

Ok, thank you very much.

The next question is from Tom Giarneal (s) of American Century (s).

Hi. Could you remind how many US reps you have, how many of those will detail only Rebif(s), and how many is optimal?

Thank you for the question, but we're keeping this information confidential.

Alright.

The next question is Katherine Harsberger (sl), independent.

Thank you for taking my call. I'm interested in, first of all, you didn't say anything about side effects, AVONEX (sl) Durall (sl) had side effects, and I was wondering what this one has. And also, you mentioned about clinical trial studies, is it possible to still get into these in the United States, or have you already, have your patients started on this? And do you have a telephone number that I might be able to call to find out more about this product?

Well, studies in the US, I mean the evidence study was in fact predominantly a US-based clinical trial and there's also a second study ongoing looking at the use of auto-injectors here in the United States. So there have been ongoing studies but not anything immediately planned in terms of your issue about where's the call for getting involved with studies. In terms of the safety profile, as the review doctors have shown that the two products were broadly comparable with exceptions related to injection sites, reactions not surprising based on the route of administration, as well as issues related to some of the asymptomatic laboratory abnormalities.

And just to quote from the FDA correspondence which is available on their website, the mack issues (sl) of this (inaudible) represent a significant therapeutic advantage, with

this adverse effects do not pose a serious limitation on its usage. So I think that about says it all really. I mean this is an independent view of (inaudible).

We're going to take another of couple of questions, maybe two question, then we're going to close this conference.

The next question is from Frankson Berger (sl) of JP Morgan.

Good morning, and congratulations again for your winning approval in the US. Looking at the FDA website, what are some of the highlights that you think might be useful in your marketing campaign with the sales force, and which ones of them do you think you'll be permitted to use?

(inaudible) . . . for the question, whatever is in the website of the FDA is public information, so everyone has access to this document, and I believe we could not expect a better document than the one we have at this point, because throughout the **document you can read the evaluation of the FDA and its findings, which are unequivocal mentioning the clinical superiority of our product.**

On the adequacy of the studies, I mean for ours (sl), I think we're very reassured, not reassured . . . it's very nice to read, having faced a lot of skepticism. You know they say our studies are really very good studies, and the data's very reliable.

So we're very pleased with the document because it does answer many of the questions and issues and rumors, and all sort of misleading statement made by our competition with regard to evidence study and with regard to Ribif (sl). It is a comprehensive document. I have here all of it. It's probably 50-60 pages, and obviously we're going through this document to extract the most relevant findings. **But I would say it summarizes in one conclusion which is that Ribif is clinically superior to AVONEX.**

And we're spoiled (sl) for choice, when it comes to the details, I think it's an overwhelmingly positive set of documents, and we're very pleased with them obviously.

Thank you.

The next question is from Ellen Guam (sl) of Solomon Smith Barney.

Hi, congratulations as well. Could you tell me, what is the proportion of patients in Europe who are on the high dose versus the low dose at this point?

In recent months, with regards to that really is confidential information. I mean, I can confirm that we are seeing a higher and higher proportion straight onto the high dose, which means some patients switching to high dose from the low dose. I don't what more I can say, it's over third, but I can't give you the exact details for confidential reasons. But I can't give you progress reports on that.

We'll take one last question.

The next question is from Nicolai Dunon (sl) of Suisse First Bank (sl).

Good day, gentlemen. Congratulations also from my part. During the last telephone conference for the full year results, Mr. Berterelli (sl) said that the US market is mainly convenience-driven whereas the European market is more efficacy-driven, concerning Ribif (sl). Can you say how this is going to influence your marketing strategy?

Well, obviously, the fact that the two markets are different is mainly driven by the fact that we haven't been able to promote Ribif (sl) in the United States. And it was very difficult for us to provide the marketplace the physician and patient with the bulk of the clinical data we have on beta interferon (sl). And this obviously is changing, and will

change in a significant way. And I believe the result of Thursday and this approval is clearly demonstrating this.

Ok, but what are actually the arguments you are going to use to market your product?

Is it mainly efficacy?

Absolutely.

Exclusively or . . . ?

We have many more arguments, as you know. Ribif is a convenient product to use, it's in a pre-filled (sl) syringe. It is liquid. I mean, Ribif is a great product, as it has demonstrated it's success in Europe. We have our entire marketing propaganda ready, and we're going to be marketing with (inaudible) confidence this product in the United States.

We should also mention the auto-injector which has been very popular in Europe, we think that's going to be a very important convenience argument in the United States as well. Efficacy and convenience. The (inaudible) injections can be self-administered. I'm not sure about the case for intermuscular (sl) injections.

Anyways, thank you very much for this conference call. Again, it's been a pleasure. I've had a very good time, and really looking forward to being with you on the road how, answer the many questions I haven't been able to answer over the last two conference call. You've given us a good indication of what you are interested in, and we will prepare for giving you the guidances that you are waiting from us with regard to 2002 and our performance with Ribif in the US market. And now I'd like to ask Andrew to close the conference call.

Yeah, well, it's been a pleasure to pass inspection. It's really a great landmark. For many of us this represents a decade of work (inaudible) and we're very pleased that it's the end of this chapter and the beginning of a new one. We're very pleased that our product was obviously confirmed, has been confirmed by the FDA to have greater effectiveness. In the context of these orphan drug debates that we've had versus AVONEX, so I think that's a great achievement. We're in a very good position, so I couldn't agree more about what (inaudible). Just a few events for your calendar. I'd like to remind you that we're going to be holding our annual management road show at the end of this month, starting with the (inaudible) presentation in London on Monday, March the 25th, and this event will be webcast if you can't make it to London. On Tuesday, March the 26th we'll be giving a presentation in New York, and on Wednesday March the 27th there'll be a presentation in San Francisco. The following week, on Wednesday, April the 3rd we'll be presenting a meeting in Geneva and Zurich. For those

of you who'd like to participate in the London events and have not had any details, please contact Judith Phillips or Veronica Seller at Noonan and Russo in London. For those of you who'd like to participate in the US meetings and have not heard about those details, please contact Anita Marquis (sl) at Monk's Ridge (sl) and her contact details are at the end of our press release today. We'll be announcing our first quarter results on Tuesday, April the 23rd, and our annual general meeting will be held in Mozam (sl) on Wednesday, May the 22nd. And on that happy note, we'd like to say, thanks very much on behalf of Serono management for your participation and wish you all a very good day.