NIHS Notification no. 2677
17 July 2000

To: Director of Drug Safety Division, Ministry of Health and Welfare

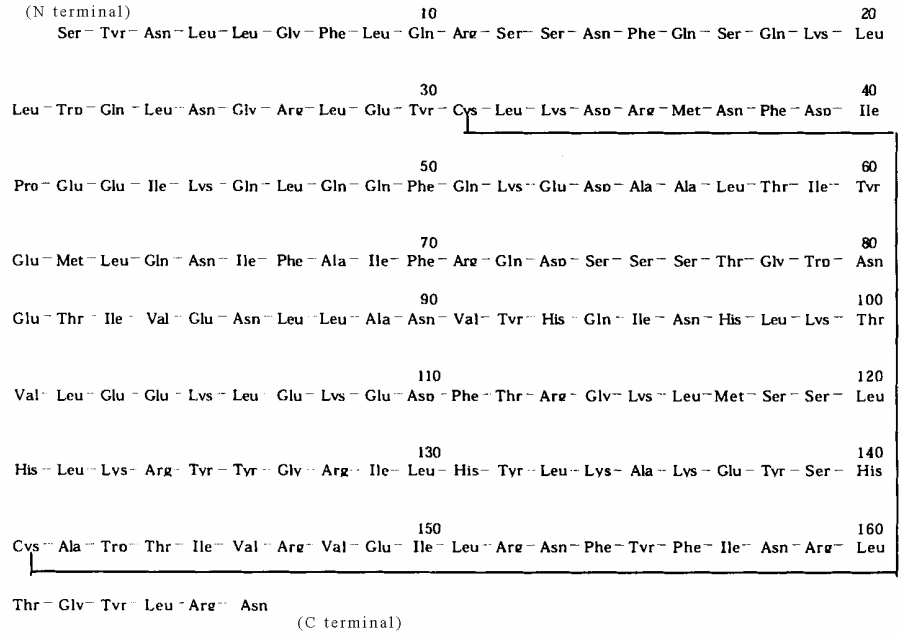
Director of the NIHS

Evaluation Report

The following report is presented as a result of review by the Pharmaceutical and Medical Devices Evaluation Center of the pharmaceutical product etc. noted in the schedule for which an application for approval has been submitted.

[Product name]	Betaferon
[Generic name]	Interferon beta-1b (recombinant)
[Applicant]	Nihon Schering Co. Ltd
[Date of submission]	10 September 1999
[Form of preparation, content]	Lyophilized injection containing 9,600,000 IU of Interferon beta-1b per vial
[Class of application]	Medicinal drug for therapeutic use (1)
[Chemical structure]	See appendix
[Designation]	Orphan drug ((6A) 47, designated 1 July 1994)
[Evaluated by]	Evaluation Division 2

Appendix



Chemical name (English)

Protein consisting of 165 amino acid residues (C903H1397N245O252S5; molecular weight; 19,877.57), produced in a recombinant cell by expression of a derivative human interferon βcDNA which codes cysteine substituted for serine at the seventeenth residue

Evaluation Result

17 July 2000

[Product name]	Betaferon
[Generic name]	Interferon beta-1b (recombinant)
[Applicant]	Nihon Schering Co. Ltd
[Date of submission]	10 September 1999 (date of orphan drug designation 1 July 1994)

[Result of Evaluation]

From the application data submitted, we judge that the efficacy and safety of this interferon preparation in preventing relapse and controlling progression in multiple sclerosis has been demonstrated. Although the neuropsychiatric symptoms common to interferon preparations have been seen in clinical studies, the results obtained indicate that with the application posology and method of administration, the relapse rate is reduced and, albeit in the overseas studies, that disease progression is controlled. Thus following evaluation by the Pharmaceutical and Medical Devices Evaluation Center, we judge that there is no obstacle to approving the following uses, posology and method of administration for this product.

[Uses] To prevent relapse and control progression in multiple sclerosis
[Posology and method of administration] The usual adult dose is 8 million international units given subcutaneously on alternate days.

Evaluation Report (1)

16 June 2000

1. Application product

[Proprietary name] Betaferon
[Generic name] Interferon beta-1b (recombinant)
[Applicant] Nihon Schering Co. Ltd
[Date of application] 10 September 1999
[Form of preparation, content] Lyophilized injection containing 9,600,000 IU of Interferon beta-1b per vial
[Uses at time of application] Multiple sclerosis
[Posology and Administration at time of application]
The usual adult dose is 8 million international units given subcutaneously on alternate days.

2. Outline of submitted data and summary of evaluation by Evaluation Center

i. Origin or course of discovery and overseas usage situation

Interferon (IFN) is a form of glycoprotein produced by cells at times of viral infection and has been developed as a drug for viral hepatitis or malignancy in view of its diverse biological activity. It mainly is classed as α, β and γ but Betaferon has biological properties similar to natural IFN-β and a more stable three-dimensional structure than recombinant forms with the same amino acid sequence as the natural type. It is a novel active ingredient developed in the US by Cetus and Triton (by Chiron and Berlex via take-over) and by Nihon Schering Co. Ltd in Japan. On 1 July 1994, it received designation as an orphan drug for multiple sclerosis as (6 Yaku A) No. 47.

Multiple sclerosis is a disease causing demyelination of the white matter of the central nervous system and is characterized by repeated relapse (temporal multiplicity) and the development of damaged sites in various parts of the central nervous system (spatial multiplicity). Its etiology has not yet been satisfactorily explained but as it is often triggered by infections and stress etc., it is considered to be an autoimmune disease. Pathologically, perivascular mononuclear cell infiltration is noted in the central nervous white matter and these cells are considered to be lymphocytes or macrophages etc. which recognize diverse peptide regions in the proteins of the myelin sheath, in particular,

myelin basic protein (MBP), proteolipid protein (PLP) and myelin-oligodendrocyte glycoprotein (MOG). These cells act directly to damage the myelin sheath and cytokines such as TNF-α or IFN-γ released from these cells are believed to cause the demyelination. There are also reports of autoantibodies to myelin structural proteins or glycolipids present in myelin and the involvement of humoral immunity has also been indicated. As a result of all this, the central nervous white matter where inflammation has occurred develops lesions involving demyelination, axon degeneration and gliosis known as plaques. Local neurological symptoms appear corresponding to the anatomic sites of these and when investigated by MRI, are detected as high signal regions in T2 enhanced imaging. These plaques usually persist and never fully disappear.

The clinical symptoms involve repeated attacks of visual disturbance, paraplegia, quadriplegia, sensory disturbance and bladder or rectal dysfunction etc. (relapsing-remitting MS) and there are also cases in whom the dysfunction gradually comes to persist and proceeds irrespective of any clear clinical relapse (secondary progressive type). Multiple sclerosis is designated as a special disease by the Ministry of Health and Welfare and at the end of 1997, 6881 patients were receiving treatment for it, representing a low prevalence in Japan of 6-7 cases per 100,000 populations. There is much higher prevalence in Europe and America however, with 30-80 cases per 100,000 and in particular, there are known to be regions at high latitudes around 40-65 degrees north and south where it exceeds 100 per 100,000. Even in Japan, the prevalence is known to be higher in Hokkaido. Environmental and genetic factors are therefore inferred to be involved in this disease and differences between genetic groups as regards immune response beginning with histocompatibility antigen analysis have been studied but the details are still unclear.

It is also known that whereas the type common in Japan has long been the so-called Devic type in which involving recurrent lesions of the optic nerve and spinal cord (optic neuritis-spinal cord type), in the US and Europe, the 'usual' type involving lesions mainly seated in the cerebrum, brain stem and cerebellum was more common. In recent years however the usual type has been confirmed to have become more common amongst

young multiple sclerosis patients in Japan too, suggesting a possible connection with dietary and environmental changes.

To treat multiple sclerosis, treatment seeking to reduce inflammation with a cornerstone of pulse steroid therapy is given, or lymphocyte purging procedures to remove pathogenic clones and immunoadsorption therapy to remove inflammatory cytokines and improve Th1 dominance are undertaken during acute phases to try and minimise demyelinatation. However, each time there is relapse, sequelae remain little by little and as the dysfunction worsens, so visual disturbance, motor paralysis, physical numbness and bladder and rectal dysfunction come constantly to be present. These require symptomatic treatment such as rehabilitation and the use of analgesics or antispasmodics etc. To control relapse, the most important aim of treatment is to prevent the worsening of dysfunction due to the disease and to prevent the appearance of new dysfunction, but the continuous administration of steroids is known to be ineffective for controlling relapse and the efficacy of the various immunosuppressants in controlling relapse has also not been confirmed.

In a double blind study in North America in 1993 (conducted by Berlex Inc.), Betaferon was the first drug found to be effective for controlling relapse in multiple sclerosis and it has been approved in 63 countries world-wide such as the UK and Germany as well as the US (as of May 2000). Subsequently a recombinant interferon-β-1a using CHO cells and a polypeptide preparation glatiramer-acetate used in desentization treatment were confirmed to reduce the number of relapses in double blind placebo-controlled trials and were approved in Europe and the US.

ii. Data on physicochemical properties and data on specifications and test methods etc.

Betaferon is an injectable produced by DNA recombination techniques and is reconstituted when required. It is a highly pure protein with molecular weight of about 18,500 daltons which has lost the N terminal methionine of natural IFN-β and comprises 165 amino acids wherein the cysteine at the seventeenth residue has been substituted by

serine. As it is produced in E. coli however, it does not have the sugar chain possessed by natural IFN-β.

E. coli was transformed by a plasmid into which the target gene had been integrated by genetic engineering to give seed cells and a master cell bank (MCB) was established from these seed cells. The product is produced by culturing from this MCB via a working cell bank. After being cultured, the cells are deactivated and the target protein recovered, whereupon it undergoes ** by way of isolation and purification processes and the eluent of the ** is pooled and stored as the bulk. This is ** with ** to prepare the formulation and following filtration sterilization, is divided into vials and lyophilized to give the product. Manufacturing process control and quality control are undertaken using an in-house reference standard (reference standard) and international reference standard.

For structural determination, amino acid compositional analysis, N-terminal amino acid sequencing and peptide mapping analysis are conducted using** and ** etc. to determine the primary structure. To analyze the physicochemical properties, the UV absorption spectrum, SDS-polyacrylamide gel electrophoresis (SDS-PAGE) and high performance liquid chromatography are used and the higher structure has been inferred by circular dichroism. Its immunochemical properties have been confirmed in comparison with the natural type using ** and also investigating ** as an indicator.

The Specifications and Test Methods at the time of application had been set using **. This had also been done using the ** from the tests on the formulation. That is to say, specifications had been set for ** in**, for ** etc. in ** and for **, **, ** and ** etc. in **. In accordance with guidance from the Evaluation Center, ** has been added for ** and ** for the preparation.

When the Evaluation Center asked for the yields in the purification process and for SDS-PAGE data etc. on the protein in each of the purification processes, yields of ** were demonstrated and data were also submitted. Moreover, upon requesting clarification of the international and Japanese reference standards, it was shown that the international reference standard is the WHO standard and that this had been supplied from the NIH.

When they asked why so many minor peaks could be seen in the HPLC charts for the final preparation, it was demonstrated that the product had peaks deriving from **. When they asked for explanation about its **, efficacy and safety, the reply was given that content has been confirmed to be constant, and also that no problems of efficacy and safety have been demonstrated in the animal and clinical studies.

In the light of these responses, the Evaluation Center further enquired whether there was any need to match the ** specification values to the observed values and about the specification for ** etc. Regarding **, the reply was given that the current specification levels were 1/80 to 1/110 of the toxic doses in the animal studies and could be considered to be no problem, and as regards **, that the specification was for the preparation. The Evaluation Center judged these responses to be broadly reasonable. As additional points, they enquired regarding the validity of process control the reasons for having the bulk solution as ** and whether a specification item should be set for **. In response, the applicant replied that because the bulk solution has been **, not all the tests can be conducted but ** is the bulk and that E. coli tests will be set as purity tests for ** and ** for the preparation. The Evaluation Center accepted this. When they asked about the determining of the properties of the first reference standard for the in-house reference standard and the setting of revised specifications for the next reference standard, the applicant replied that specifications and test methods for the standard product had been shown and that as only limited data were available at the point when the first in-house reference standard had been produced, new tests had been added subsequently.

The Evaluation Center considers that the Expert Committee needs to be consulted regarding how to set the reference standard appropriately.

iii. Data regarding stability

As tests on stability, the bulk ** has been subjected to long term storage tests and the preparation to long term storage tests, stress tests (temperature, light) and stability tests

following dissolution in the 0.54% saline provided as the solvent. Long term storage and thermally accelerated tests were also conducted on the solvent provided.

The results indicated that the respective storage periods should be 18 months at -20°C or 6 months at 4°C for the bulk, and for the preparation, not more than 30°C in hermetically sealed containers but, as the long term storage study is still ongoing, the expiration period has been tentatively set at one year. As the attached solvent was also confirmed to be stable in the tests, no storage conditions have been set.

The Evaluation Center asked for the HPLC chromatograms for the various stability tests on the ** preparation and mannitol-containing preparation to be shown and confirmed that they were stable from the charts submitted. When they also enquired whether or not stability had been evaluated in biological activity tests, they were shown that titer had been determined by ** in order to evaluate stability.

iv. Data regarding toxicity

The acute toxicity study had been conducted by subcutaneous dosing using mice. Although transient weight loss was noted with the administration of 85.8 and 171.6 million international units per kilogram (MIU/kg), as no deaths were noted and no changes in general condition observed either, the approximate lethal dose was inferred to be 171.6 MIU/kg or over.

The multiple dose toxicity study was conducted by intravenous and subcutaneous dosing using rats, rabbits and monkeys. With dosing for two weeks to rats (maximum dose 17.8 MIU/kg/day), for four weeks to rabbits (maximum dose 1.8 MIU/kg/day) and for four weeks to monkeys (maximum dose 8.9 MIU/kg/day), no toxic findings attributable to the effects of the drug were found and the non-toxic dose levels were therefore estimated to be respectively not less than 17.8 MIU/kg/day, 1.8 MIU/kg/day and 8.9 MIU/kg/day. The neutropenia, increased lymphocyte ratio, thrombocytopenia and reticulocytosis observed with four weeks dosing in monkeys were considered to have been caused by IFN (secondary response) and so were not taken to be toxic findings. The decreases in

total protein and albumin seen in the 8.9 MIU/kg/day intravenous groups were variations with the normal range.

No long-term multiple dose toxicity study has been conducted because antibody production against the drug was noted with four weeks administration to monkeys.

The reproductive and developmental toxicity studies were conducted by subcutaneous administration using rats and monkeys. In the fertility study, no toxic signs attributable to the drug were found for parental toxicity and reproductive performance and in the fetuses even in the 7.2 MIU/kg/day (maximum dose) group, and the non-toxic dose was therefore inferred to be not less than 7.2 MIU/kg/day for both general toxicity and reproductive performance in the dams and for fetuses. In the monkey organogenesis study, decreases in red blood cells, hematocrit and hemoglobin and associated deterioration in general condition were seen as general toxicity in the dams at 13.4 MIU/kg/day and over, and absorption or increased fetal mortality for reproductive performance and fetuses at 13.4 MIU/kg/day and over. The non-toxic dose was thus estimated to be 8 MIU/kg/day for dam general toxicity and reproductive performance and for fetuses. In the studies on rat prenatal and postnatal development and dam function, no toxic signs attributable to the effects of the drug were found at 7.2 MIU/kg/day (maximum dose) for parental general toxicity and reproductive performance and for F_1 and F_2 offspring and the non-toxic dose was therefore estimated to be not less than 7.2 MIU/kg/day in both cases. Moreover, upon subcutaneous administration of the drug over three cycles (about 100 days) to female cynomolgus monkeys to observe any effects on the estral cycle in monkeys, no toxic signs attributable to the effects of the drug were found in the 10.7 MIU/kg/day (maximum dose) group and the non-toxic dose was therefore estimated to be not less than 10.7 MIU/kg/day.

Mutagenicity was studied through reverse mutation tests using bacteria, chromosomal aberration tests using human lymphocytes and transformation tests using mouse fetal blast cells but as all the results were negative, the possibility that Betaferon would manifest mutagenicity *in vivo* was considered remote.

No carcinogenicity study was conducted for the same reason as for a long term multiple dose toxicity study.

In the local irritation study, persistent reddening was noted in the non-washed group when testing for irritation of the ocular mucosa but no irritation by the drug was found in the other irritation tests (intramuscular injection, primary skin irritation tests etc.). However local skin reactions at the injection site have been noted in clinical use and so it was decided to mention this in the Precautions and Warnings.

As other toxicity tests, pyrogenesis and antigenicity/immunogenicity were investigated in a 4-week multiple dose toxicity study in monkeys. The drug was considered to show the rising body temperature pattern common to IFN, with the fever seen in the early stages of administration lessening as administration continued. As regards its antigenicity and immunotoxicity, the findings for antibody measurements and blepharal and abdominal wall intracutaneous reactions did indicate that IFN-β-1b produced antibodies, but there was considered to be little possibility that it would induce delayed hypersensitivity reactions. As no morphological changes were observed in immune system-related organs and tissues (spleen, lymph nodes, thymus, bone marrow) either, the possibility of IFN-β-1b being immunotoxic was considered unlikely. The safety of ** was monitored as regards the toxicity of residues but there was considered to be little possibility that toxicity would be manifested by ** at the specification level.
No dependency study has been conducted because there have been no reports suggesting the development of dependency in foreign usage data.

The Evaluation Center asked the applicant for explanations concerning 1) the validity of the dose levels for the fertility study in rats and studies on rat prenatal and postnatal development and dam function given that no toxicity had been observed in the parent animals even at the maximum dose (7.2 MIU/kg/day) and 2) the possibility that the fetal ventricular septum defect seen in the rat fertility study could be manifested in man.

The applicant replied that 1) as the susceptibility of rats to IFN-β-1b is low, it may be considered that toxicity would be difficult to detect even at dose levels far removed from

the clinical dose level, and because up to about 5-40 times the clinical dose was administered in this study, safety at the clinical dose has been confirmed, and 2) the ventricular septum defects seen in rats were within the range of variation in the background data. Moreover, upon surveying adverse events etc. in the world-wide usage results for this drug in man to date, the findings have failed to reveal any reports of ventricular septum defects in newborns and so there is no possibility of this being manifested in man.

v. Data on pharmacology

The following investigations and explanations about the mode of action of the drug have been provided.

IFN-β-1b (10-1,000 IU/mL) inhibited the release of IFN-γ due to phytohemagglutinin (PHA) in human peripheral blood mononuclear cells (PBMCs) in a concentration-dependent manner. As it has been demonstrated that IFN-β-1b (1.8-180 IU/mL) inhibited HLA-DR expression due to IFN-γ in human glioma cells in a concentration-dependent manner, that IFN-β-1b (100, 200 IU/mL) significantly inhibited T-cell proliferation due to IFN-γ treated allo glioma astrocytes and microglia cells and that IFN-β-1b (100, 1000 IU/mL) significant inhibited T cell proliferation from B cells due to antigen presentation. In that IFN-β-1b thus inhibits IFN-γ production and HLC class II expression, it was considered that it would control the exacerbated immune response in multiple sclerosis.

IFN-β-1b (180 IU/mL) improved the lowered Con A-induced suppressor T cell activity in PBMCs derived from multiple sclerosis patients to the levels seen in PBMCs derived from healthy subjects. TGF-β1 rose significantly compared to the baseline in the serum of multiple sclerosis subjects three hours following subcutaneous administration of IFN-β-1b (8 MIU). IL-10 production increased significantly upon applying IFN-β-1b (160 IU/mL) to monocytes derived from healthy subjects and multiple sclerosis patients. In view of these observations, IFN-β-1b is considered to control the exacerbated immune response in multiple sclerosis by improving the diminished T cell suppressor activity

function seen in multiple sclerosis patients and potentiating the production of inhibitory cytokines such as TGF-β1 and IL-10 etc (reference data).

Regarding the effect of the drug on the tissue infiltration of inflammatory cells, IFN-β-1b (1000 IU/mL) significantly inhibited rises in the fibronectin (FB) barrier crossing capacity of PBMCs due to regulated upon activation, normal T expressed, and presumably secreted (RANTES) macrophage inflammatory protein-1α (MIP-1α) and macrophage chemoattractant protein-1 (MCP-1), inhibited the production of matrix metalloproteinase-9 (MMP-9) from PBMCs by MCP-1 at the protein and mRNA levels, is known to inhibit FN barrier crossing capacity and increased MMP-9 production due to IL-2 and is reported to reduce the number of new active lesions identified by MRI. IFN-β-1b is therefore considered to inhibit the adhesion of peripheral blood mononuclear cells to vascular endothelial cells by inhibiting the expression of very late antigen-4 (VLA-4) and increasing soluble vascular cell adhesion molecule-1 (VCAM-1) release. It is also thought to inhibit the migration of inflammatory cells from peripheral blood into the central nervous system (reference data).

As the effects of Betaferon on factors which damage oligodendroglia which are the myelin-producing cells, IFN-β-1b (0.3-300 IU/mL) and natural IFN-β (0.3-300 IU/mL) inhibited the release of TNF-α due to PHA stimulation of human PBMCs in a concentration-dependent fashion; IFN-β-1b (180 IU/ml) inhibited lymphotoxin (LT) release due to PHA stimulation of human PBMCs (reference data) and IFN-β-1b (10-500 IU/mL) inhibited NO production from the human astrocyte cell line A172 due to the concomitant addition of IFN-γ, TNF-α and IL-1β in a concentration-dependent fashion (reference data). This demonstrated that IFN-β-1b inhibits the production of TNF-α, LT and NO which damage oligodendroglia.

The action of Betaferon was investigated in a model of experimental autoimmune encephalomyelitis (EAE) as a model of multiple sclerosis. Guinea pigs were chosen as the species for investigation as Betaferon exhibited the same inhibitory activity against the proliferation of PBMCs by PHA as in man and their susceptibility is relatively good. In the control group in the guinea pig EAE model, all the animals developed symptoms

of EAE, with 9 out of 10 progressing as far as quadriplegia and 8 dying. Whilst presentation of the disease was not completely suppressed in any individual treated subcutaneously with IFN-β-1b (1.2 MIU/kg, once daily for 20 days), the progression of the disease was significantly inhibited in terms of mean cumulative disease scores compared to the non-treated group. Although there was no significant difference from the control group in the 12 MIU/kg group, virtually the same suppression of disease progression as in the 1.2 MIU/kg group was seen and onset of the disease was inhibited in 2 of the 10 animals. This suggested that the immunoregulatory and anti-inflammatory actions of Betaferon contribute to delaying the progression in multiple sclerosis as an autoimmune disease and to the frequency of relapse.

As other pharmacological activities, Betaferon is held to have antiviral activity, cell proliferation-inhibiting activity, NK cell activity and reactivity to anti-natural IFN-β antibodies similar to natural IFN-β.

When receptor binding tests were conducted with lymphoblasts (Daudi cells) as reference data, the dissociation constant with ^{125}I-IFN-β-1b was 0.24nM. In binding substitution tests, IFN-β-1b, natural IFN-β and recombinant IFN-β displaced the bonds of ^{125}I-IFN-β-1b (175 U/mL) in a concentration dependent manner and IFN-β-1b and natural IFN-β did so almost totally at 1000 U/mL, from which it was interpreted that IFN-β-1b has IFN-β receptor binding capacity.

In general pharmacology studies, a rise in rectal temperature was noted in rabbits when injected subcutaneously with 0.89 and 8.9 MIU/kg of IFN-β-1b (about 5 and 50 times the clinical dose), the maximum rise being 0.30 and 0.39°C after 7 hours. With intravenous administration, no effects were noted at 0.89 MIU/kg and although there was a rise of 0.86°C after 3 hours, this had virtually returned to normal after 4 hours.

In anesthetized rabbits, an increased respiratory rate was noted 5 minutes following intravenous injection of 8.9 MIU/kg of IFN-β-1b and a decrease in blood pressure after 90 minutes, but these were minor and transient.

When guinea pigs were given intraperitoneal injections of 8 and 40 MIU of the IFN-β-1b ** preparation (approximately 140 and 710 times the clinical dose), erythema and edema of the ear, blepharal region and foot pads were observed but these had virtually disappeared after 10 days. Skin reactions were also observed 9 days after the dose with intraperitoneal administration of 8.9 MIU/kg. The results of passive cutaneous anaphylaxis (PCA) tests on serum obtained from guinea pigs which had manifested symptoms suggested the possibility that the skin reactions observed upon intraperitoneal administration were allergic responses to the human serum albumin incorporated in the preparation and it was suggested that IFN-β-1b potentiates such allergic responses. In view of the fact that the guinea pigs manifesting the skin reactions had produced IgG antibodies to the human serum albumin but not to IFN-β-1b and those similar skin reactions have also been reported with natural IFN-β as well, it was considered that they were not a reaction peculiar to recombinant IFN-β.

The Evaluation Center asked the applicant about the following points.

As neopterin has been determined as the biological response marker in the clinical studies, an enquiry was made as to whether neopterin has physiological roles other than pharmacological activity pertaining to IFN and whether the blood level thereof can rise for reasons other than the administration of IFN. It was explained that whilst the physiological role of neopterin itself is not clear, the fact that serum neopterin rises during microbial and viral infections, in cancer, autoimmune disease and transplantation etc. may be interpreted as meaning that IFN-γ, TNF-α and IL-2 etc. are endogenous factors inducing neopterin.

An explanation was sought for the immunoregulatory and anti-inflammatory actions of IFN-β-1b compared with natural IFN in experimental systems etc. The explanation given was that natural IFN-β inhibits TNF-α and IFN-γ production at the same titers as IFN-β-1b. IFN-β-1b and natural IFN-β inhibit the passage of melanoma cells through matrigel-coated polycarbonate filters under conditions at which cell proliferation is not inhibited, and IFN-β-1b and IFN-β-1a inhibit T cell proliferation and LT production due

to antigens at the same titers in human myelin base protein (MBP)-specific T cells. The action of IFN-β-1b is thus similar to natural IFN-β in terms of its immunoregulatory and anti-inflammatory actions also.

Clarification was sought for the facts that whilst the action of the drug in the guinea pig EAE model had been investigated, no efficacy correlated to dose was found, that it is difficult to claim that basic investigations such as the times and period of treatment had been properly investigated and that drug potency has been backed up with the findings of only one study. It was explained that in this model, the immunity abnormality in response to the immune hyperfunction and autoantigens is considered to begin immediately after the administration of MBP and that this process resembles the transition period from remission to relapse in multiple sclerosis. In the clinical setting, IFN-β-1b provides activity by being given not only throughout relapse periods but also in periods of remission, and so in the guinea pig EAE model too, IFN-β-1b was given from immediately after starting the administration of MBP until the end of the study. The results of preliminary studies have indicated that because complete inhibition was noted in the high dose group but not in the low dose group, that high doses provide more potent control.

When asked to re-examine the mechanism of onset for multiple sclerosis and of the point of action of IFN-β-1b based on a discussion of how these contribute to clinical efficacy, the explanation was given that multiple sclerosis is a disease controlled by diverse and overlapping cytokines and if IFN-β-1b is considered to be a cytokine with diverse functions, then it will be difficult to specify the mechanisms mainly involved in the manifestation of its clinical effect. This is reflected in the *Gaiyo* (Summary Basis of Approval).

An answer was requested regarding the different results from natural interferon at low concentrations in the receptor binding tests using Daudi cells. The explanation was given that natural IFN-β replaced the binding of ^{125}I-IFN-β-1b in a concentration-dependent manner and did so almost completely at the same concentration as IFN-β-1b

(1000 U/mL) and that looking at the published literature etc., the difference at 100 U/mL was within the range of experimental variation.

The Evaluation Center considers that further investigation within the Expert Committee etc. will be needed to establish whether or not the potency of Betaferon can be explained or not simply from test results based on a guinea pig EAE model.

vi. Data on absorption, distribution, metabolism and excretion

(1) Findings in animals

The pharmacokinetics of Betaferon was investigated by administering IFN-β-1b and ^{125}I-labelled IFN-β-1b to rats and monkeys.

When monkeys were given a single intravenous dose of IFN-β-1b (0.18 MIU/kg), serum IFN disappeared with a half life of 1.9 hours. The serum IFN levels with a single subcutaneous dose indicated that it was absorbed more slowly than by intramuscular injection and Cmax and AUC_{0-24} increased with rises in the dose level over the range 0.18-0.72 MIU/kg. When IFN-β-1b 0.18 MIU/kg was given twice daily for ten days by multiple intravenous, intramuscular and subcutaneous injection, serum IFN was higher than after the first dose whatever the route of administration, and AUC on day 10 of intravenous injection was about three times higher than for the first dose.

When male rats were given a single intravenous injection of ^{125}I IFN-β-1b and IFN-β-1b (0.72 MIU/kg), total serum radioactivity, precipitate radioactivity following trichloroacetic acid treatment (TCA precipitate) and the serum IFN concentration showed elimination half lives of respectively 7.6, 1.8 and 0.4 hours. With a single subcutaneous injection, Tmax for total radioactivity and TCA precipitate radioactivity was respectively 6 and 4 hours and serum IFN was below the quantitation limit. No gender difference was noted in radioactivity levels following single intravenous and subcutaneous doses of ^{125}I IFN-β-1b. When male rats were given a single subcutaneous injection of ^{125}I IFN-β-1b (0.72 MIU/kg), total organ and tissue radioactivity except in

the thyroid and TCA precipitate radioactivity peaked 6 hours after the dose and then disappeared following a course similar to the serum concentration. Radioactivity in the thyroid peaked 24 hours after the dose at much higher concentration than in the serum, but the level of IFN in the thyroid was below the quantitation limit after 7 days. In the serum and urine, peaks for radioactivity were detected only at the positions corresponding to the elution times for Na ^{125}I and the molecular weight marker (1355.4) and in the thyroid, only at the position corresponding to the elution time for the molecular weight marker (29,000). Upon giving male rats a single subcutaneous dose (0.72 MIU/kg), 85.3% of the radioactivity had been excreted in the urine and 5.5% in the feces by 7 days. When pregnant rats were given a single subcutaneous dose of ^{125}I IFN-β-1b (0.72 MIU/kg), radioactivity concentrations in the fetuses and amniotic fluid were lower than in dam serum. With a single subcutaneous dose of ^{125}I IFN-β-1b (0.72 MIU/kg) to lactating rats, TCA precipitate and total radioactivity in the milk peaked 6 hours after the dose and Cmax was respectively 32 and 17 times the serum concentration. TCA precipitate radioactivity in the milk accounted for 65-80% of total radioactivity, a higher proportion than in the serum.

(2) Findings in man

The pharmacokinetics of IFN-β-1b in man were investigated in healthy subjects, relapsing-remitting multiple sclerosis patients and cancer patients.

In the Phase I clinical study in Japan, multiple sclerosis patients given a single subcutaneous dose of 1.6 and 8 MIU showed serum IFN concentrations below the quantitation limit at most points of measurement. When healthy subjects were given repeated subcutaneous doses of 16 MIU once daily for 8 days in a study conducted in the US, about half the blood samples were below the quantitation limit and even in the samples in which it was detected, the levels ran at no more than 10 IU/mL. When cancer patients were given a single intravenous dose of 0.54-54 MIU in a clinical study conducted in the US, the half life of IFN in the serum was 0.44-2.59 hours and AUC rose with increases in dose.

Upon investigating the pharmacokinetics of a single 8 MIU subcutaneous dose in healthy Caucasian and Japanese subjects taking serum neopterin as the indicator amongst the biological response markers induced by the administration of IFN-β-1b, the mean baseline values were respectively 4.86 and 4.46 nmol/L. They then peaked about 36 hours after the dose and had fallen to virtually the baseline level at 168 hours. $AUC_{0\text{-}168}$ was respectively 1717.9 and 1661.5 nmol¥hr/L.

As a result of investigating the bioequivalence of the ** preparation and mannitol-containing preparation taking serum neopterin pharmacokinetics upon administration of 8 MIU to healthy subjects as the indicator, AUC satisfied the criteria for equivalence but Cmax was held slightly to have exceeded the criterion for the 90% confidence interval.

As drug interactions, a clinical study conducted in the US had indicated a lengthening of antipyrine half life depending on IFN-β-1b dose when antipyrine had been given concomitantly during a period of repeated intravenous or intramuscular treatment with 0.9-72 MIU in three cancer patients.

The Evaluation Center had investigated mainly the following points.

An explanation was requested concerning the validity of using serum neopterin concentration as the biological response marker for IFN-β-1b. The response given by the applicant stated that serum β2-microglobulin, neopterin, tryptophan and cellular 2', 5'-oligoadenylate synthetase had been determined in the US clinical pharmacology study in healthy adults and a correlation with IFN-β-1b dose had been confirmed. In view of literature reports about the clinical usefulness of IFN dose levels set on the basis of neopterin concentration and its usefulness as a biological marker in patients undergoing treatment, they believe that measuring serum neopterin is useful as a biological response marker for IFN.

The Evaluation Center also asked for the pharmacokinetics of IFN-β-1b to be compared with the natural form. The applicant explained that the course of serum IFN concentrations following a single intravenous dose in animals indicated that the serum

pharmacokinetics of this drug and the natural form could be considered almost the same. No direct comparison of tissue distribution could be made because the routes of administration and measured substances had been different but the concentration in each tissue had been less than in serum. Also, both were almost fully metabolized following administration and the intact form was not excreted in the urine etc.

As regards drug interactions, the Evaluation Center asked for results for the various molecular species of P450 and also for some discussion of the literature. The applicant replied that based on a survey of the literature, the various IFNs reduce the levels of CYP1A1, 1A2, 2B1, 2C11, 2E1 and 3A2 in mice and rats and IFN-γ the levels of CYP1A2 and 3A4 in man. In man moreover, IFNs hamper enzyme activity related to CYP1A1, 1A2, 3A4 and 2B. The applicant also said that the grounds for the statement in the package insert that it 'may potentiate the action of anti-convulsive drugs' were based on a report that in animals, IFN inhibits the metabolism of drugs in which the 2C family is involved.

The Evaluation Center further asked for some discussion about why Cmax had failed to meet the criteria in the bioequivalence study. The applicant replied that there had been a fairly large interval between sampling near the Tmax for neopterin (36 hours approx), suggesting the possibility that the true Cmax might not have been evaluated in some subjects. However, they believed that the simulation results showed that such variations in Cmax would have no major effect on the administration method for Betaferon (alternate day administration). Antiviral activity measurement had been used to determine the serum concentrations of IFN and when the Evaluation Center asked for findings about the quantification method including investigations by other methods to be provided, additional text was included in the data summary regarding data illustrating the validity of the analysis method and results by ELISA. When asked to explain the evaluation method for pharmacokinetics including the existence of any serum IFN measurements beyond 6 hours after the dose in subcutaneous and intramuscular administration to monkeys, an investigation of the calculation methods for the pharmacokinetic parameters was undertaken and the text in the *Gaiyo* suitably amended.

The Evaluation Center accepted the above responses.

vii. Data on clinical studies

(1) Japanese clinical study findings

1) Phase I study (vii-9)

Orphan drug designation was granted in Japan in July 1994 and a Phase I study in multiple sclerosis subjects (relapsing-remitting) was commenced in December of that year. Pharmacokinetics and safety were investigated administering 1.6 MIU or 8 MIU by subcutaneous injection on alternate days for one month to 8 patients. No randomized comparative clinical study has been conducted.

Adverse events were encountered in all cases but were the same as reported in the overseas studies, such as flu-like symptoms. Adverse events were classified into grades 1-4 in accordance with the NCI Common Toxicity Criteria (CTC Ver.2.0) and the protocol for the North American Phase III study. The abnormal laboratory values found included two cases each of Grade 2 leucopenia (2,000-2,999/mm^3) and neutropenia (750-1,499/mm^3) in the 8 MIU and 1.6 MIU groups. Lymphocytopenia of Grade 3 (500-999/mm^3) was noted in two cases from the 8 MIU group and 3 from the 1.6 MIU group and of Grade 4 (less than 500/mm^3) in 2 cases from the 8 MIU group. Hepatic dysfunction was found as a Grade 2 rise in GPT (5.1-10 times the baseline value) and rise in γ-GTP (2.6-5.0 times the upper limit of normal). One case from the 8 MIU group was temporarily taken off Betaferon due to thrombocytopenia then switched to half dose but all cases completed the course of subcutaneous administration.

2) Phase II study (Suppl. vii-9)

In order to investigate the efficacy and safety of the long term use of IFN-β-1b in multiple sclerosis (relapsing-remitting) in Japan, a Phase II randomized comparative study was commenced from July 1995. No placebo group was established in this study

and the 194 cases were compared in two groups treated subcutaneously with 1.6 MIU or 8 MIU on alternate days. The treatment period was set at two years, with the primary endpoint being the annual relapse rate and the second endpoints being MRI lesion area, days to initial relapse, non-relapsed cases ratio, severity upon relapse EDSS (Kurtzke Expanded Disability Status Scale), relapse duration, NRS (modification of Scripps Neurological Rating Scale), IS (Incapacity Status; degree of inhibition to usual activities). Safety endpoints were also set.

The interim analysis had not been completed at the time of the application and an analysis combining the two groups under blinding was presented as reference data but the key code was broken following application and the analysis results were presented as an attachment (December 1999).

For the interim analysis set, the date when the final case to be started on the treatment had been treated for one year (2 July 1998) was established as the base and the interim analysis took data up to 24 months for cases started up to 2 July 1996, data up to 18 months for those started up to 2 January 1997 and data up to 12 months for later cases. 205 cases were enrolled but due to withdrawal of consent etc., 194 cases were actually treated with Betaferon and there were 34 complete cases in the 1.6 MIU group and 28 in the 8 MIU group, making a total of 62 cases (32%). There were 20 mid-term drop outs in the 1.6 MIU group and 24 in the 8 MIU group, making a total of 44 cases (23%). The main reasons were adverse reactions (abnormal laboratory values) (1.6 MIU: 5 cases, 8 MIU: 13 cases) and symptom deterioration (1.6 MIU: 8 cases, 8 MIU: 2 cases). At the time of the interim analysis, 44 cases in the 1.6 MIU group and 44 in the 8 MIU group (total 88 cases, 45%) were still being treated. There was no difference between the two groups in terms of patient background, that is sex, age, primary site and primary symptoms, nor was any difference found by diagnostic classification, with the optic neuritis-spinal cord type being found in 19% in the 1.6 MIU group and 23% in the 8 MIU group. There was likewise no difference in the number of relapses over the past two years, this being 3.4 episodes in the 1.6 MIU group and 3.2 episodes in the 8 MIU group.

The primary endpoint of annual relapse rate was 1.169 in the 1.6 MIU group and 0.801 in the 8 MIU group, and was significantly lower in the 8 MIU group (p=0.032, one-sided). As second endpoints, change in the MRI lesion area was 0% in the 1.6 MIU group and –0.8% in the 8 MIU group (median values) but no significant difference was identified. The number of days to first relapse (median value) was 360 days in the 1.6 MIU group and 462 days in the 8 MIU group (NS, survival time analysis). The non-relapse rate was 36.3% in the 1.6 MIU group and 48.4% in the 8 MIU group and no significant difference was found. Severity upon relapse was investigated in terms of the EDSS at the relapse peak relative to the pre-relapse score and the change in NRS, but no significant difference was found. The change in final EDSS scores relative to the initial scores was zero in both groups. Relapse duration during the year was 19.3 days in the 1.6 MIU group and 5.1 days in the 8 MIU group, significantly shorter in the 8 MIU group (p=0.021, 2 sample Wilcoxon test, one-sided). NRS and IS showed no change compared to the baseline in either group, and no significant difference was noted.

In this study, dynamic balance randomization had been used to allocate patients to the two groups taking the factors of 1) number of relapses prior to commencing administration, 2) initial EDSS and 3) initial lesion area by MRI and analysis stratified into these factors was undertaken. For reference, an analysis was also shown arranged for the items showing inequality, namely illness duration and total number of relapses prior to the start of administration. As a result, when arranged by all except total number of relapses prior to the start of administration, the annual relapse rate in the 8 MIU group was significantly lower than in the 1.6 MIU group, as in the main analysis. When arranged by total number of relapses prior to the start of administration (2-5 and 6 and over), although there was no significant difference between the two doses, the relapse-inhibiting effect was larger in the 8 MIU group in both classes. No significant difference was found between the two groups for the final change in lesion area by MRI relative to the initial area nor for the size of change in EDSS score (2-compartment Wilcoxon test).

In the analysis of partial sets, whereas the annual relapse rate in ‘males’ was 0.689 in the 1.6 MIU group and 0.609 in the 8 MIU group, in ‘females’ it was 1.430 in the 1.6 MIU group and 0.882 in the 8 MIU group, and the anti-relapse effect appeared greater in

females. Efficacy against relapse by age and by illness duration was greater in the 8 MIU group in both. By lesion site, annual relapse in the optic neuritis-spinal cord type was 1.699 in the 1.6 MIU group and 1.138 in the 8 MIU group and in other types (usual type) was 1.044 in the 1.6 MIU group and 0.714 in the 8 MIU group and no difference in efficacy depending on illness type was identified.

Safety as the incidence of adverse events was 94.8% (91 cases) in the 1.6 MIU group and 96.9% (93 cases) in the 8 MIU group. Serious adverse events amongst these were evaluated looking not only at the target data for the interim analysis but at all events throughout the study period and were encountered in 10 cases in the 1.6 MIU group and 18 cases in the 8 MIU group. The adverse events judged to be severe in the 1.6 MIU group comprised one case each of decubitus ulcer, arthralgia, tremor, depressive state, memory impairment, dehydration, urinary tract infection, fever and miscarriage and in the 8 MIU group, one case each of head of femur necrosis, dizziness, suicidal ideation, nausea, vomiting, hematemesis, hepatic dysfunction, jaundice, thrombotic phlebitis, cerebral infarction, bronchitis, pneumonia, respiratory failure, pneumochysis, lymphocytopenia, disseminated intravascular coagulation syndrome, acute renal failure, (feelings of) malaise, disease deterioration, septicemia and infection and 7 cases of fever (7.3%), two cases each of flu-like symptom complex and urinary tract infection (2.1%) and three cases of headache (3.1%). There were no deaths in either group.

Seven cases withdrew due to adverse events other than deterioration in the underlying disease (7.3%) in the 1.6 MIU group and 13 cases (13.5%) in the 8 MIU group. The main adverse events cited as reasons for withdrawal were symptoms at the injection site (6 cases), hepatic dysfunction (4 cases), depression (3 cases), feelings of malaise (3 cases) etc. The cases who withdrew due to feelings of malaise (3 cases), fever (2 cases) and myalgia (1 case) were found only in the 8 MIU group.

Adverse events as mental symptoms with an incidence of 5% or more comprised depressive state (1.6 MIU group: 8.3% (8 cases), 8 MIU group: 5.2% (5 cases)) and insomnia (1.6 MIU group: 1.0% (1 case), 8 MIU group: 9.4% (9 cases); significantly higher in 8 MIU group). Additionally, 0-2 episodes of irritability, anxiety, excitation,

drowsiness, impaired memory, neurosis and delirium were noted. The one case of suicidal ideation mentioned previously was a serious adverse event.

The incidence of fever in the 1.6 and the 8 MIU groups was respectively 58.3% (56 cases) and 78.1% (75 cases), of headache 35.4% (34 cases) and 39.6% (38 cases), of flu-like symptom complex 32.3% (31 cases) and 32.3% (31 cases), of (feelings of) malaise 13.5% (13 cases) and 29.2% (28 cases), of arthralgia 8.3% (8 cases) and 16.7% (16 cases), and of chill 1.0% (1 case) and 9.4% (9 cases). Fever, (feelings of) malaise and chill were significantly higher in the 8 MIU group. The incidence of reddening at the injection site was 43.8□" in both groups. Necrosis at the injection site judged to be severe was found in 2 cases in the 1.6 MIU group and 6 cases in the 8 MIU group.

Laboratory value abnormalities for which causality by the study drug could not be ruled out were noted as GOT elevation in 17 cases (17.7%) in the 1.6 MIU group and 22 cases (22.9%) in the 8 MIU group. Amongst these, no Grade 2 cases were seen in either group. GPT elevation was noted in 22 cases (22.9%) in the 1.6 MIU group and 26 cases (27.1%) in the 8 MIU group, of which Grade 2 change (5.1-10.0 times the baseline value) was found in 18 cases (19.0%) in the 1.6 MIU group and 13 cases (13.5%) in the 8 MIU group, Grade 3 change (10.1-20.0 times the baseline value) in two cases (2.1%) from both the 1.6 and 8 MIU groups and Grade 4 change in 1 case (1.1%) in the 1.6 MIU group and 3 cases (3.1%) in the 8 MIU group. γ-GPT elevation was noted in 14 cases (14.6%) in the 1.6 MIU group and 20 cases (20.8%) in the 8 MIU group. Amongst these, Grade 2 change (2.6-5.0 times the upper limit of normal) was present in 14 cases (14.6%) in the 1.6 MIU group and 13 cases (13.5%) in the 8 MIU group, Grade 3 change (5.1-20.0 times the upper limit of normal) in 4 cases (4.2%) in the 1.6 MIU group and 8 cases (8.3%) in the 8 MIU group and Grade 4 change (20.1 times or more the upper limit of normal) in 1 case (1.0%) in the 8 MIU group. One case of jaundice was seen in the 8 MIU group.

Leukopenia was seen at Grade 2 (2,000-2,999/mm^3) in 8 cases (8.3%) in the 1.6 MIU group and 23 cases (24.0%) in the 8 MIU group and at Grade 3 (1,000-1,999/mm^3) in 1 case (1.0%) in the 8 MIU group, but in none in the 1.6 MIU group. Lymphocytopenia

was seen at Grade 2 (1,000-21,499/mm^3) in 26 cases (27.1%) in the 1.6 MIU group and 19 cases (19.8%) in the 8 MIU group, at Grade 3 (500-999/mm^3) in 45 cases (46.9%) in the 1.6 MIU group and 45 cases (46.9%) in the 8 MIU group and at Grade 4 (less than 500/mm^3) in 14 cases (14.6%) in the 1.6 MIU group and 19 cases (19.8%) in the 8 MIU group. Neutropenia was seen at Grade 2 (750-1,499/mm^3) in 12 cases (12.5%) in the 1.6 MIU group and 25 cases (26.0%) in the 8 MIU group, and at Grade 3 (500-749/mm^3) in 1 case (1.0%) in the 1.6 MIU group and 2 cases (2.1%) in the 8 MIU group and at Grade 4 (less than 500/mm^3) in 1 case (1.0%) in the 8 MIU group but in none in the 1.6 MIU group.

A rise in blood glucose was noted at Grade 2 (161-250mg/dL) in 10 cases (10.6%) in the 8 MIU group and in 7 cases (7.4%) in the 1.6 MIU group and at Grade 3 (251-500mg/dL) in 4 cases (4.2%) in the 1.6 MIU group, but in none in the 8 MIU group.

(2) Foreign clinical study findings

1) Phase I / Pilot Study (US) (vii-1,2)

The clinical development of IFN-β-1b in multiple sclerosis began with a Phase I/Pilot Study in a few multiple sclerosis patients in June 1986. In this study, patients with multiple sclerosis (relapsing-remitting type) were given three subcutaneous doses per week of 0.8, 4, 8 and 16 MIU of the drug or a placebo under blind conditions and mainly safety was investigated.

Six cases were enrolled in the IFN-β-1b group and 7 in the placebo group, and interim analysis conducted 24 weeks after commencing administration to the last case to be enrolled (a point when at least 30 cases had completed six weeks treatment) indicated that 4 of the 5 cases who had required their dose to be reduced by that time were in the 16 MIU group, suggesting that the dose level of IFN-β-1b permitting continuous administration was 8 MIU. Rises in serum neopterin measured as a biological response marker in the groups treated with 4 MIU and over were also noted. The dose to the subsequent IFN-β-1b groups was therefore changed to 8 MIU under blind conditions

and treatment was continued for three years, during which efficacy was also investigated. Treatment was not withdrawn from any patient beyond 24 weeks due to adverse events but one case required a reduction in dose.

2) Phase III Study (US/Canada) (vii-3,4)

In a Phase III study conducted from June 1988 in the US and Canada, 338 multiple sclerosis patients (relapsing-remitting types) were given subcutaneous doses of 1.6 MIU or 8 MIU of IFN-β-1b subcutaneously on alternate days for 104 weeks.

Consequently, the annual relapse rate which formed one of the primary endpoints was 0.84 in the 8 MIU groups, significantly lower than the 1.27 seen with placebo and the 1.17 seen in the 1.6 MIU group. The proportion of cases failing to relapse during the trial period which formed another primary endpoint was significantly greater in the 8 MIU group at 31% than the 16% with placebo and 21% in the 1.6 MIU group. The time to first relapse (median value), at 153 days with placebo, 180 days in the 1.6 MIU group and 295 days in the 8 MIU group, was significantly longer in the 8 MIU group. There was a significant reduction in cases showing moderate and severe relapse in terms of NRS score at 30% in the 8 MIU group as against 45% with placebo. Furthermore, whereas increases in mean total lesion area were found by MRI in the placebo and 1.6 MIU groups, a decrease was noted in the 8 MIU group.

The adverse events generally known with IFN preparations, that is flu like symptoms such as fever, chill, feelings of malaise, myalgia and sweating etc. were noted with significantly higher frequency in the Betaferon groups. Symptoms at the injection site such as inflammation, pain and hypersensitivity etc. were also noted at significantly higher incidences in the Betaferon groups. Necrosis at the injection site was found at 4% in the 1.6 MIU group and 5% in the 8 MIU group. Serious adverse events occurred in 33.9% in the placebo group, 21.6% in the 1.6 MIU group and 25.2% in the8 MIU group (total 91 cases, 145 episodes), and 142 of the 145 adverse events in all involved hospitalization, but of these, 104 episodes (73%) were admissions caused by the underlying disease for steroid pulse therapy. There were no significant differences in any

of the groups in the incidence of serious adverse events not due to the underlying disease. Suicidal ideation was noted in one case from the 1.6 MIU group and two from the 8 MIU group but there were no deaths. As regards laboratory values, there were many cases of decreased lymphocytes prior to treatment in all groups including the placebo group, and the decrease in the mean values during the treatment period was significantly larger in the Betaferon groups. Apart from the decreases in lymphocytes, the falls in mean hemoglobin, platelets, white blood cells and neutrophils were significant larger in the Betaferon groups (at time of final tests). In the hepatic function tests, GOT and GPT (mean values) at the time of the final tests in the 8 MIU group had risen respectively 3.5 IU/L and 11.1 IU/L. Grade 2 elevation in GOT (5.1-10.0 times the baseline) during the trial period was noted in 4 cases in the 8 MIU group but no elevation of Grade 3 or over was found in any treated group. Grade 2 elevations in GPT (5.1-10.0 times the baseline) was found in 5 cases with placebo, 7 cases in the 1.6 MIU group and 14 cases in the 8 MIU group. Grade 3 GPT elevation (10.1-20.0 times the baseline) was found in 5 cases in the 8 MIU group. No elevation of Grade 4 or over (20.1 times the baseline or more) was seen in any group. One case from the 8 MIU group withdrew due to hepatic dysfunction. Effects on prolactin, progesterone, estradiol and the thyroid hormones (T3, T4) were investigated in 12 female patients but no particular problems were seen. Upon investigating the course of serum neopterin every six weeks, the level gradually decreased in the 1.6 MIU group in a manner similar to the placebo group but higher values were maintained for a long period in the 8 MIU group.

Administration under blind conditions was continued following completion of the two year treatment period in subjects who gave fresh consent (maximum five years) and neutralizing antibodies to Betaferon were expressed in about 40-50% of the cases in the Betaferon groups throughout the period as a whole. The possibility was suggested that the relapse-controlling effect of Betaferon might be attenuated following the expression of neutralizing antibodies.

3) Phase III Study (secondary progressive type, Europe) (Document vii-1)

A double blind study in secondary progressive multiple sclerosis was conducted in Europe from September 1994 to March 1998 with 358 cases in the placebo group and 360 in the IFN-β-1b group. The time until the progression of symptoms, which formed the primary endpoint, was taken to be the time when the EDSS score had deteriorated by one or more points relative to the start of treatment.

Covariance analysis using ranked data indicated significant difference in the time until symptom progression between the placebo group and Betaferon group (taking longer in the Betaferon group; p=0.0046). In the survival time analysis, this difference became obvious from 9 months and continued throughout the trial period. The one year symptom progression fraction was 30% with placebo but 19% with Betaferon. Significant lengthening was found in the Betaferon group in the time until patients became wheelchair-bound (p=0.0045; log-rank test). Whereas the annual relapse rate was 0.57 in the placebo group, it was significantly less in the Betaferon group at 0.42 (p=0.0045; covariance analysis using ranked data). The adverse events encountered at a higher incidence than with placebo were flu-like symptoms (61.1%), fever (40.3%), chill (22.8%), upper abdominal pain (11.1%), ulcer (4.4%), chill/fever (3.3%), decreased white blood cells (10.3%), hypertension (4.4%), injection site reaction (45.8%), injection site inflammation (48.1%), injection site necrosis (4.7%), myalgia (23.3%), exacerbated muscle tone (40.8%) and skin eruption (20.3%). 19 placebo cases (4.9%) and 41 Betaferon cases (11.4%) withdrew due to adverse events (excluding deaths). No difference was found between the two groups for depressive impairment and suicidal ideation was expressed by 5 cases in the placebo group and 3 in the Betaferon group. There was one death during the trial period in the placebo group (suicide) and 3 in the Betaferon group (one case each of suicide, pulmonary embolism, bronchitis associated with acute pneumochysis). The treatment period in this study had been three years but in the interim analysis conducted at the point giving a two-year treatment period for the last-enrolled case, it was clear that Betaferon was effective in secondary progressive multiple sclerosis. The study was therefore stopped at that point based on advice from the external advisory committee and an application for additional use approval was made

to the EMEA in May 1998. Approval for secondary progressive multiple sclerosis was granted in January 1999.

4) Other studies (clinical pharmacology studies in healthy subjects etc.)

Single and multiple dose clinical pharmacology studies in healthy subjects found responses in biological markers such as serum neopterin, β_2-microglobulin, IL-10 and serum MxA protein etc. It was observed that responses by these markers required the administration of 1.6 MIU and over, that dose-dependence was present over the range 2-12 MIU and that the response was maintained by subcutaneous doses on alternate days. In the light of the above results, the existence of ethnic differences was investigated in healthy Japanese and Caucasians living in Germany giving a single subcutaneous dose of 8 MIU, the approved dose in Europe and the US, as indicated by the course of serum neopterin which is considered to be a useful pharmacokinetic and pharmacodynamic marker. No difference in the biological response of Japanese and Caucasians was consequently found.

(3) Evaluation of efficacy

1) Comparative investigation of Japanese and foreign study findings

The applicant had emphasized that data from mainly the US Phase I study (Documents vii-1,2) and North American Phase III study (Documents vii-3,4) could be extrapolated to Japanese subjects using serum neopterin, which is considered to be based on the activation of type I IFN receptors. However because neopterin has not be satisfactorily established as a substitute indicator of efficacy and the correlation between Betaferon dose and serum neopterin has not been proved in Japanese subjects, the Evaluation Center advised the applicant to submit Phase II study results for Japan with clinical relapse as the primary endpoint as additional information and to construct data taking this study as the main evaluation data.

As it had been considered desirable in planning the said study to confirm the efficacy and safety in Japanese patients as soon as possible because no effective drug was available in the country, the draft protocol provided for interim analysis taking data up to the point when the last-enrolled patient would have been treated for one year. Although the study findings are based on the results of the interim analysis, upon breaking the code on 25 November 1999, it was judged that a study in which sufficient detection power could be guaranteed had taken place, that the conditions for interim analysis at the planning stage had been satisfied and that as data corresponding to 80% of the whole had been assembled, these constituted representative data for the study findings set.

The Evaluation Center scrutinized the study results for Japan closely and concluded that there were no major problems to the evaluation of drug potency and that efficacy had been demonstrated in Japanese patients in the application dosage group (8 MIU). In order to examine whether the findings for Japan were similar to the foreign findings, a comparison was made with the North American Phase III study (hereafter called the North American study).

The primary endpoint in the study was the decrease in relapse rate and was about the same as in the North American study. In the Japanese Phase II study, the annual relapse rate was 0.80 in the 8 MIU group and 1.17 in the 1.6 MIU group, whereas in the North American study, this had been 0.84 in the 8 MIU group and 1.17 in the 1.6 MIU group. These figures were very similar and it was judged that similar efficacy had been demonstrated in the Japanese and North American studies.

As regards differences in the pathophysiology of multiple sclerosis in Japan and America or Europe, although disease prevalence is much lower in Japan, the same criteria are used for its clinical diagnosis, diagnostic imaging centred on MRI, and laboratory tests on myelin basic protein in cerebrospinal fluid and oligoclonal banding in diagnosis are the same, and as in Europe and America, prevalence in Japan is higher in the high latitude regions including Hokkaido. They therefore judged that multiple sclerosis in Japan is comparable with Europe and America.

The fact that conventionally the optic neuritis-spinal cord type has apparently been more common in the diagnostic classification of multiple sclerosis in Japan than in Europe and America was also investigated. Reports from three centres (Hokkaido, Tohoku University and Kyushu University) have also indicated that even without allowing for diagnostic imaging by MRI, the usual type seated mainly in the cerebrum, brain stem and cerebellum seen more commonly in Europe and America than the optic neuritis-spinal cord type is on the increase (Neuroimmunology 7:175-196, 1999). In the Phase III study in North America, there were 137 cases of optic neuritis-spinal cord type as against 201 cases of the usual type, and the ratio was similar to that in the Japanese Phase II study. The pathophysiology of multiple sclerosis in Europe and America and Japan was therefore judged to be similar.

It was considered from the above investigations that the foreign findings would support the findings in Japan. Nevertheless, the Evaluation Center does not judge that the possibility of extrapolation in the strict sense has been demonstrated in the present application for reasons such as doubts over the suitability of the bridging target endpoints.

2) Validity of secondary progressive multiple sclerosis as an indication

The application uses of Betaferon are 'to prevent relapse and control progression in multiple sclerosis' and, in that the target patients in the Japanese Phase II study were in relapse or remission, the applicant was asked whether it is also indicated for secondary progressive multiple sclerosis.

In response, the applicant presented the findings of a Phase III double blind study conducted in secondary progressive multiple sclerosis in Europe. They replied that in Japan, multiple sclerosis itself is a rare disease and generally is not classified by its clinical course. Nevertheless, the pathophysiology in patient groups classed as showing 'chronic progression accompanied by relapse and remission' in recent epidemiological surveys is essentially the same as the pathophysiology classed as 'secondary progressive multiple sclerosis' in Europe and America and the 1992 survey by the Ministry of Health and

Welfare considered that the group corresponding to the secondary progressive group in Europe and America accounted for 26.1% (J. Tropical and Geographical Neurology 2:73-82, 1992). They stated that the frequency of the secondary progressive type of multiple sclerosis in Europe and America has also been reported to be 27% in Canada (Brain 112:133-146, 1989) and 35% in Sweden (Brain 116:117-134, 1993) and that the proportion of the secondary progressive multiple sclerosis in Japan may be considered to be slightly lower or not much difference from Europe and America. The Evaluation Center accepted this.

The applicant was also asked about the application situation for secondary progressive multiple sclerosis in the US. The reply was given that in North America, an approval application for the uses had been made to the FDA in June 1998 based on the results of studies in Europe but findings from the ongoing study in North America had also been requested. In the North American study, 939 cases had been enrolled for a placebo group, 8 MIU fixed dose group and 5 MIU/m^2 group (upper limit 12 MIU). As a result of data review by the External Advisory Committee every six months following the start of the study, it was held that the data needed to evaluate the study findings were already sufficient and they advised that the trials be stopped and all the cases enrolled for the study be switched to subcutaneous injection of 8 MIU on alternate days, and so the study was stopped in November 1999. At the present time, the study findings are being assembled and will gradually be submitted to the FDA.

The Evaluation Center enquired whether Betaferon has a mechanism of action which inhibits chronically progressing pathophysiology as well as a mechanism to control clear relapse in the secondary progressive type. The applicant stated that there are reports showing that the activation of macrophage-like cells beginning with microglia is observed in chronically active multiple sclerosis lesions. These cells are considered to be involved in the progression of demyelination by releasing myelin-damaging inflammatory cytokines or NO, and on the other hand, Betaferon not only inhibits the production of TNF-α and lymphotoxins from human peripheral mononuclear cells, but also the production of TNF-α from human microglia and furthermore of NO from astrocytes. It may therefore be considered to inhibit the production of myelin-damaging factors not

only from mononuclear cells infiltrating from the periphery but also from macrophage-like cells resident in the central nervous system and so control the progression of demyelination. It may thus be thought to be effective not only in relapsing-remitting multiple sclerosis but also in secondary progressive multiple sclerosis. The Evaluation Center therefore judged that there would be no objection to approving the drug for secondary progressive cases in Japan.

The application uses for Betaferon were altered to 'to prevent relapse and control progression in multiple sclerosis'.

3) Relationship between multiple sclerosis relapse-inhibitory effect of Betaferon and the appearance of neutralizing antibodies

Given that the relapse rate had not been significantly different from placebo beyond three years in the North American study, the Evaluation Center enquired about any relationship of this to the appearance of neutralizing antibodies. The reasons given by the applicant in response were that basically, treatment had been for two years and no account had been taken of the smaller number of target patients due to mid-term dropouts beyond three years or the decrease in relapse rate associated with the natural course of the disease. Statistically sufficient detection power could not be guaranteed and at the point when the external advisory committee advised study termination, only five cases had completed five years treatment. They replied moreover that effects due to the significantly higher annual relapse rate in mid-term drop-outs from the placebo group than in the Betaferon-treated patients who had completed the course or stopped taking Betaferon were also a factor. As regards any connection with neutralizing antibodies, no difference in annual relapse rate was found before and after becoming positive in those patients who once became positive for neutralizing antibodies during the trial. However, many of the patients who once became positive for neutralizing antibodies again reverted to being negative. Upon conducting an analysis regarding the period when they reverted to being negative as negative periods, the relapse rate during positive periods did appear higher than in the negative periods at 29% in the 1.6 MIU group and 18% in the 8 MIU group (both $p=0.05$). The possibility that neutralizing antibodies affect the annual

relapse rate cannot therefore be ruled out. The 8 cases in the Phase I study in Japan had been treated for a short period of just one month and no neutralizing antibodies had been seen to appear. Although neutralizing antibodies had been assayed in the Japanese Phase II study at different points from the North American Phase III study, the level of neutralizing antibody-positive cases in the Japanese Phase II study had been 33% (8/24) in the 1.6 MIU group and 17% (4/23) in the 8 MIU group, very similar to the results in North America and no correlation between the antibody-positive ratio and dose level was demonstrated.

In view of these matters, the Evaluation Center asked about the validity of using Betaferon beyond three years. The applicant replied that the annual relapse rate with administration of 8 MIU versus the placebo group in the first year had been 33% (number of cases, relapse rate respectively 8 MIU group124 cases, 0.96, placebo group123 cases, 1.44) and in the fifth year 30% (8 MIU 58 cases, 0.57, placebo group 56 cases, 0.81) and that those who continued on Betaferon had maintained about he same level of decrease in annual relapse rate beyond three years. It was therefore desirable to continue treatment even beyond three years in patients who were progressing well. The applicant also replied that whilst there was a possibility that becoming positive for neutralizing antibodies might attenuate the relapse-inhibiting effect of Betaferon, reports state that no effects have been found on the inhibition of symptom progression or changes in lesion area by MRI. The guidance proposed by the US Specialist Neurologists Group is therefore that in cases being treated continuously with Betaferon for one year or more, neutralizing antibodies should be determined if the clinical course is at all suspect and used for reference when investigating whether or not to continue treatment.

4) The absence of significant difference in lesion area by MRI in the Japanese Phase II study

Given that decreases in demyelination by MRI as a second endpoint had been found significantly and dose-dependently in the North American Phase III double blind study and the European double blind study in secondary progressive multiple sclerosis, the Evaluation

Center enquired why no significant decrease in demyelination foci had been found by MRI in the Japanese study.

The applicant stated that in the North American Phase III study, mean lesion area by MRI at the time of the final evaluation versus the baseline had increased 7.3% in the 1.6 MIU group as against a 4.2% decrease in the 8 MIU group, and that even in the Japanese Phase II study, there had been decreases of 1.7% at 1.6 MIU and 16.8% at 8 MIU, so that although there was no significant difference between the two groups in the Japanese Phase II study (Wilcoxon test: one sided $p<0.10$), the dose-response relationships in the 1.6 and 8 MIU groups in the two studies were similar. The Evaluation Center accepted this.

(4) Evaluation of safety

1) Adverse events of the mental and nervous system

Safety was investigated in the Japanese Phase II study as regards suicide, suicidal ideation and also mental symptoms as other adverse events. Mental symptoms were reported in the interim analysis in 34 cases and suicidal ideation was noted in one. The trial was stopped in this patient. The applicant stated that the incidence and details for these 34 cases of mental symptoms were similar to those found in Europe and America and that patients with mental and nervous impairment and patients with a history thereof had been added to the section on cautious administration in the Precautions and Warnings.

Convulsions and epilepsy seen in the Japanese clinical studies were investigated for any causal relationship to Betaferon. One case had undergone partial right frontal lobotomy three years earlier when convulsions had appeared and was on 200 mg of phenytoin. Upon suffering flu-like symptoms such as fever for 2-3 days, he had presented pneumonia, septicemia, cerebral infarction, acute renal failure and disseminated intravascular coagulation syndrome and had suffered convulsions with these. One case had a history of epilepsy and one had none. In epidemiological surveys in Japan, amongst the neurological signs recognized in the clinical course of multiple sclerosis, the

frequency of 'convulsions' was put at 17% (of which 8% were pain-induced convulsions) (Neurology 25:845-851, 1975) and a frequency of 6% has been reported overseas. Convulsions, confusion, detachment, emotional anxiety and heightened muscular tension are listed as 'major adverse reactions' in the package insert. The Evaluation Center accepted these responses.

2) Hepatic dysfunction

Cases of elevated GOT and GPT had been prominent in the Japanese Phase II study and so safety as regards hepatic function was investigated. The most severely affected patient was one from the 8 MIU groups who presented on day 320 of study drug administration showing rises in γ-GTP to 1,157, total bilirubin to 4.9mg/dL, GOT to 167 and GPT to 226. The treatment was stopped in this patient. Serious hepatic dysfunction caused by IFN was found in three cases in the North American Phase III study and European secondary progressive Phase III study. As the serious hepatic dysfunction seen in Japan was encountered after about one year, enquiry was made about appropriate precautions to prevent the development of hepatic dysfunction.

The applicant stated that the whilst the appearance of Grade 4 GPT change was rather greater in the Japanese Phase II study than in Europe and America, the frequency of other abnormal hepatic function values differed little from those regions. It is also recommended that regular checks be done during the treatment period 'after 4-6 weeks and 12 weeks, and thereafter every 12 weeks' or 'monthly until three months after the start of treatment, then three monthly' etc. The applicant replied that in the Japanese Phase II study, four cases had been withdrawn due to hepatic dysfunction, of whom two had shown hepatic dysfunction and two had not prior to administration. The latter two required withdrawal relatively early on (day 9, day 23) and taking these results into account, it would seem desirable for regular checks basically to be done every 1-3 months and after 1-2 weeks in cases showing any pre-administrative hepatic dysfunction. Severe hepatic dysfunction is included in the 'Major adverse reactions' in the package insert which states in the 'other adverse reactions' that the incidence of elevated GOT, GPT and γ-GTP is >5%.

3) Leukopenia, thrombocytopenia

As serious leukopenia and neutropenia had been found in three cases in Japan, of whom the leukopenia was possibly related to a urinary tract infection in one case and one case had developed convulsions, pneumochysis, pneumonia, respiratory failure, septicemia, disseminated intravascular coagulation syndrome and acute renal failure consequent to fever, the applicant was asked about the use of Betaferon if leukopenia and neutropenia develop.

The applicant was of the view that as a benchmark when using Betaferon or IFN-β preparations in multiple sclerosis, 'if granulocytes fall below 1500/mm^3, the dose should be temporarily reduced and if there is marked fall, discontinuation of treatment is recommended' or that 'if neutrophils fall below 750/mm^3, the drug should be halted and administration restarted at half dose after the level has recovered'. However, with what degree of leukopenia (granulocytopenia) administration of Betaferon can continue or with what degree it should be halted or withdrawn in the current situation when no effective alternatives to prevent relapse and control progression in multiple sclerosis are available must be determined taking account of therapeutic risk and safety for the individual case based on factors such as patient background and clinical course. In the 'Major adverse reactions' in the package insert, specific figures have been given for severe leukopenia (less than 2000 mm^3) and granulocytopenia (less than 50,000 mm^3). The Evaluation Center accepted this response.

4) Injection site necrosis

The Evaluation Center enquired about the treatment of skin necrosis at the injection site. The applicant stated that in the Japanese Phase II study, injection site necrosis had been found in 6 cases (6.3%) from the 1.6 MIU group and 11 cases (11.5%) from the 8 MIU group. These had mainly be treated by a combination of wound disinfection, topical antimicrobials and ulcer medication and four had required excision of the necrotic tissue. Healing was seen without treatment in 3 cases and the drug was withdrawn due to

injection site necrosis in 3 cases. Alleviation and healing had been confirmed in all cases. The applicant would also properly include reports about the onset and treatment of injection site necrosis in the application data. The Evaluation Center accepted this response.

5) Drug interactions

Enquiries were made about drug interactions in respect of the points to note when combining drugs clinically as regards the effects of IFN on CYP activity. The applicant stated that that various types of IFN are reported to reduce CYP levels and CYP activity. When cancer patients had concomitantly used IFN-α with theophylline, antipyrine and hexobarbitone, the clearance of theophylline and antipyrine from the blood had fallen 33% and 20% respectively but that of hexobarbitone had been unaffected. Theophylline and antipyrine are metabolized by CYP1A2 and hexobarbitone by the CYP2C family. CYP1A2 is inhibited by Betaferon but no other types of molecule have been investigated. Moreover in measurements using an erythromycin substrate in chronic hepatitis C patients, IFN-α had reduced CYP3A activity and in *in vitro* tests, the activity of CYP3A4 had been reduced by IFN-γ. On the other hand, the action of anti-epileptic drugs has been reported to be potentiated in animal tests. In view of the foregoing explanations, additional text will be provided concerning the grounds for citing interactions with anti-epileptic drugs in the package insert (draft). The Precautions and Warnings for concomitant drug usage also will state that in man, the activity of CYP1A2 is reduced as a mechanism of interaction with warfarin and theophylline as well as antipyrine. The Evaluation Center accepted this.

6) Interstitial pneumonia

As there are reports that interstitial pneumonia can arise with the concomitant use of IFN-α preparations and *shosaikoto* (Chinese herbal medicine), the Evaluation Center asked whether this should be mentioned in the Precautions and Warnings. The reply was given that as well as prohibiting its concomitant use, it would be added to the major adverse reaction section. This was accepted.

7) Relationship between infection and Betaferon

According to recent reports, *Chlamydia Pneumonie* is detected at a high frequency in the CSF of multiple sclerosis patients (Sriram S. et al. Ann Neurol 46, 6-14 (1999)) and so the Center enquired whether there is a risk of Betaferon having adverse effects on infection. The applicant replied that to date there had been several reports about the relationship of multiple sclerosis and viral infections but that interferon has been demonstrated *in vitro* to suppress the proliferation of *Chlamydia* and the mechanism involved seems not to be any action on *Chlamydia* itself but a suppression of intracellular *Chlamydia* proliferation. As very few patients had been using Betaferon amongst those reported by Sriram and the clinical symptoms in these patients were not seen to be any worse than in other multiple sclerosis patients, the Evaluation Center accepted this response.

(5) Uses

In order to reflect the findings of the clinical studies conducted in Japan and overseas more appropriately, the response was received from the applicant that the uses for this product would be 'to prevent relapse and control progression in multiple sclerosis'.

(6) Postmarketing surveillance

In view of the efficacy and safety profile of Betaferon, the following programme of postmarketing surveillance is considered necessary.

1) As the target patients in the submitted Japanese Phase II and North American Phase III studies were cases in relapse or remission who were able to walk, the inhibition of relapse and progression in chronic progressive patients and severely impaired patients with EDSS exceeding 7.0 must be monitored.
2) The appearance of neutralizing antibodies and attenuation of drug efficacy must be monitored (because ultimately no clear answer has been obtained at the present time)

3) As there was a high incidence of injection site necrosis as a serious adverse event and of hepatic dysfunction, leukopenia and thrombocytopenia as laboratory value abnormalities, the frequency and degree of these must be monitored closely.

3. Result of data compliance survey by Kiko and decision of Evaluation Center

(1) Decision of Evaluation Center on documentation compliance

It was judged that there were no major problems in relation to conducting the approval evaluation.

(2) Decision of Evaluation Center on GCP compliance

No major deviations from the standards were found and the material was judged to be GCP compliant.

4. Overall evaluation by Evaluation Center

We judge that the efficacy and safety of Betaferon in multiple sclerosis has been demonstrated from the data submitted. In handling of the clinical study findings, we have taken account of the facts that Betaferon is an orphan drug and that no effective drugs are yet available for this disease in Japan. We undertook the main evaluation on the basis of the findings up to the interim analysis of the Phase II study conducted in Japan and evaluated the foreign Phase III findings etc. as material complementing the domestic findings.

The Evaluation Center believes that if no particular problems emerge upon reference to the opinion of the Expert Committee, then there is no objection to the uses for Betaferon being set as 'to prevent relapse and control progression in multiple sclerosis' and to this product being approved having properly adjusted the Precautions and Warnings etc.

Evaluation Report (2)

17 July 2000

Subsequent to expert consultation, mainly the following points were investigated.

vii. Data on clinical studies

1. Study methods etc.

An application was made with the interim analysis data from the Japanese Phase II study at the point when the last patient to be treated had been followed for one year. The Evaluation Center thus asked the applicant why, despite efficacy being confirmed by the interim analysis, the trial had been continued for a further year and if efficacy had been confirmed by the interim analysis, why the trial had not been stopped at that stage. In response, the applicant stated that at the time of the proposal, they had planned to investigate the propriety of continuing with the trial upon the interim analysis but because case enrolment and all the checks took time, administration to all the cases had been completed by the time of the interim analysis. They had also checked whether or not the evaluation had been properly conducted in functional terms and said that the evaluation by EDSS used on this occasion is the core approach in this field.

Studies using placebo had been conducted overseas, but due to the risk that blinding might not be maintained with drugs like Betaferon which have a high incidence of adverse reactions, the applicant was asked about the validity of using a placebo with such drugs. The applicant replied that in order to maintain blinding from adverse reactions to the drug, the efficacy and safety had been evaluated in the individual patients by different doctors, and so there had been no problem. The Evaluation Center accepted these responses.

2. Safety

As there is a risk of the potency of Betaferon being reduced by the expression of neutralizing antibodies, the Evaluation Center considered that the production of neutralizing antibodies needs to be monitored during the postmarketing surveillance and asked the opinion of the Expert Committee about the need for postmarketing surveillance as regards neutralizing antibodies. The Expert Committee took the view that postmarketing surveillance was needed as regards neutralizing antibodies and upon instructing the applicant to present an outline for this, an outline scheme was presented.

The Expert Committee was of the opinion that although adverse events such as hepatic dysfunction and hematopoietic dysfunction etc. had been noted, appropriate attention had been drawn to these in the package insert and there was no particular problem.

3. Uses

The use for control of disease progression had been based on foreign data but the Expert Committee expressed the view that given the absence of dose-response, even allowing for the small number of target cases in Japan, is it really valid to indicate Betaferon for the control of disease progression. When this was checked out with the applicant, the response was given that in the final analysis of the Japanese Phase II study, a difference in percentage change in lesion area by MRI had been found between the 1.6 MIU and 8 MIU groups, that control of disease progression had been found in the European Phase III study and that no difference in the disease or biological responsivity is seen between Japanese and foreign patients (see Evaluation Report (1)). The Evaluation Center accepted this.

In the light of the foregoing evaluation, the Evaluation Center judged that there is no objection to approving the drug based on a change in the application uses to 'to prevent relapse and control progression in multiple sclerosis'.

Moreover, in that the present application is for an orphan drug and that it would be difficult to claim that efficacy and safety had been evaluated in a sufficient number of cases by the time of approval, it was judged valid to set the re-evaluation period at ten years and for this drug to be discussed in the First Special Subcommittee on Drugs.

We believe that Betaferon should be classed as a powerful drug.

Change of Product Name

An application was received from the applicant on 21 July 2000 to change the proprietary name of the drug from 'Betaferon' to 'Betaferon Subcutaneous Injection'.