European Medicines Agency
Pre-authorisation Evaluation of Medicines for Human Use

London, 25 September 2008
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WITHDRAWAL ASSESSMENT REPORT
FOR

CYLATRON

International Nonproprietary Name:

(Peginterferon alfa-2b Schering-Plough)
(Peginterferon alfa-2b)

Procedure No. EMEA/H/C/921

Day 180 Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted.

This should be read in conjunction with the "Question and Answer" document on the withdrawal of the application: the Assessment Report may not include all available information on the product if the CHMP assessment of the latest submitted information was still ongoing at the time of the withdrawal of the application.

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LIST OF ABBREVIATIONS

AE	adverse event
AJCC	American Joint Committee on Cancer
cfu	colony forming units
CHC	chronic hepatitis C
CHMP	Committee for Medicinal Product for Human Use
CML	Chronic myelogenous leukemia
CPMP	Committee for Proprietary Medicinal Products (known as CHMP)
CT	Computed axial tomography
cys	Cysteine
DMFS	distant metastasis free survival
DNA	deoxyribonucleic acid
DM	distant metastasis
DMFS	distant metastasis-free survival
ECL	electrochemiluminescent
EIA	enzyme immunoassay
ELISA	Enzyme-linked immunosorbent assay
EMC	encephalomyocarditis
EORTC	European Organisation for Research and Treatment of Cancer
EU	European Union
ECL	electrochemiluminescent
EIA	enzyme immunoassay
ELISA	enzyme-linked immunosorbent assay
EMC	encephalomyocarditis
EORTC	European Organisation for Research and Treatment of Cancer
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HDI	high-dose interferon
ICH	International Conference on Harmonisation
IFN	Interferon alfa-2b
IU	International units
Lyo	Lyophilised
Lys	Lysine
mg	Milligram
ml	Millilitre
MPA	Medical Products Agency
MW	molecular weight
OS	overall survival
PEG	polyethylene glycol
Peg-IFN alfa-2b	pegylated interferon alfa-2b; SCH 54031
Ph Eur	European Pharmacopoeia
SC	Subcutaneous
TCA	trichloroacetic acid
µg	microgram; mcg
US	United States
USP	United States Pharmacopeia
WHO	World Health Organisation

I. RECOMMENDATION

Based on the review of the data and the Applicant's response to the CHMP LoQ on quality, safety and efficacy, the CHMP consider that the application for Cylatron in the adjuvant treatment of malignant melanoma

is not approvable since major objections still remain, which preclude a recommendation for marketing authorisation at the present time.

Proposal for Questions to be posed to SAG oncology

- Due to the toxicity and tolerability problems related to five years of moderately high intensity interferon therapy, would any other outcome measure in terms of efficacy than improved survival or increased cure rate be clinically meaningful?

Inspection issues

None

II. EXECUTIVE SUMMARY

II.1 Problem statement

High dose IntronA (interferon alfa-2b) is licensed for the adjuvant treatment of patients with malignant melanoma who have no evidence of disease but are at high risk of recurrence. The treatment regimen consists of IntronA administered at 20 million international units (MIU)/m^2/daily for 5 days intravenously (IV) for 4 weeks and 10 MIU/m^2 TIW SC for 48 weeks.

The basis for regulatory approval was the landmark study by John Kirkwood and collaborators from the Eastern Cooperative Oncology Group (Study ECOG 1684). A survival benefit was initially reported and led to regulatory approval, but was lost over time and further studies with this high dose regimen have not shown an increased cure rate or survival benefit.

Roferon (interferon alfa-2a) is currently licensed in a dose of 3 MIU/m^2 TIW SC for 18 months in patients with relatively good prognosis AJCC stage II (see below). A disease-free survival benefit has been demonstrated in this population.

At least 14 randomised, mainly observation-controlled studies have been conducted exploring the activity of alfa interferons (IFN) in the adjuvant setting. The use of IFN as adjuvant therapy varies within Europe, however, and a favourable benefit – risk as judged by clinical uptake cannot be seen as firmly established throughout the EU.

II.2 About the product

Peginterferon alfa-2b is licensed as PegIntron/ViraferonPeg for the treatment of chronic hepatitis C in strengths ranging from 50µg to 150µg. In this application, Schering-Plough proposes to use three new strengths (200µg, 300µg and 600µg) of the same drug substance in vials.

II.3 The development programme/Compliance with CHMP Guidance/Scientific Advice

The pivotal study was sponsored and designed by the EORTC. Schering Corporation supported the trial with study medication and an educational grant, but was not responsible for study design and execution. Schering-Plough received a delegation of partial responsibility from EORTC, the study

sponsor, with respect to data validation and summarization for the purpose of this application. EORTC retained the ultimate responsibility for the integrity of the study data.

II.4 General comments on compliance with GMP, GLP, GCP

The pivotal clinical study was conducted in compliance of the International Conference for Harmonisation (ICH), Good Clinical Practice (GCP) Consolidated Guidance.

The manufacturer responsible for batch release in the EEA is Schering-Plough Labo N.V., Industriepark 30, Heist-op-den-Berg, Belgium. This is also the site for manufacture of the solvent. Manufacture of the active substance and of the finished product (powder) takes place at Schering-Plough (Brinny) Company, Innishannon, Co. Cork, Ireland. Other sites involved in manufacture, quality control testing, labelling and secondary packaging are: S-P Farma Lda, Portugal, S-P S.p.A Italy, S-P SA Spain, S-P SA France.

Checking of the current status of valid Manufacturing authorisations has been made by EMEA. There are no objections as regards the GMP compliance.

II.5 Type of application and other comments on the submitted dossier

The application for Peginterferon alfa-2b Schering Plough was submitted via the centralised procedure following confirmation (19-22 March 2007) by the CHMP of eligibility in accordance to Article 3(1) of Council Regulation 726/2004. Therefore a complete/full and independent application (i.e. dossier with administrative, quality, non-clinical and clinical data) according to Article 8(3) of Council Directive 2001/83/EC as amended, was submitted in September 2007. Tomas Salmonson and Ian Hudson were appointed as Rapporteur and as Co-Rapporteur, respectively.

The present application concerns three new strengths of Peg-IFN alfa-2b (200, 300 and 600 µg per vial). The drug substance (SCH 54031) is the same as that used to manufacture PegIntron (EU/1/00/131), which CPMP gave a positive opinion 15 February 2000. PegIntron is currently marketed in Europe for the treatment of hepatitis C.

III. SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 Quality aspects

PegIntron (Peginterferon alfa-2b) was approved in year 2000 through the centralised procedure (EMEA/H/C/280) in strengths ranging from 50µg to 150µg (vial presentations: EU/1/00/131/1-30). In this application, Schering-Plough proposes to use three new strengths (200µg, 300µg and 600µg) of the same drug substance in vials. The applicant states that the dossier content is essentially identical to that of PegIntron, except for the higher strengths now applied for. The present dossier is, in contrast to that of PegIntron, submitted in a CTD format.

Active substance

The active substance used to manufacture Peginterferon alfa-2b Schering-Plough is a pegylation conjugate of interferon alfa-2b.

Interferon alfa-2b

The interferon alfa-2b is the same active substance as used for Intron A (EU/1/99/127), i.e. recombinant human interferon alfa-2b (IFN) produced in *E. coli*. IFN consists of 165 amino acids with a molecular weight of approximately 19,265 Daltons. The molecule exists as a monomer with two intramolecular disulphide bonds at positions Cys1 - Cys98 and Cys29 - Cys138. Extensive characterization studies had been performed to elucidate the physicochemical and biological properties of Interferon alfa-2b drug substance. Characterization studies on the primary and secondary structures of Interferon alfa-2b and various isoforms of Interferon alfa-2b are provided, in addition to biological activity. Product and process-related impurities are described and controlled.

In the response to the D120 List of Question (LoQ), clarifications as regards the manufacture and control of Interferon alfa-2b, including a confirmation of compliance with the analytical control as stated in the current Ph.Eur monograph, were given. Furthermore, the company has committed to have a review of the IFN drug substance specification limits completed, together with an assessment of the impact on the Intron drug product presentations, by Quarter 2, 2009.

PEG-interferon alfa 2b

PEG-interferon alfa 2b (Peg-IFN alfa 2b, SCH 54031) is prepared by reacting interferon alfa-2b (SCH 30500) with methoxypoly(ethylene glycol) succinimidyl carbonate, with a molecular mass of 12000 Da. The reaction forms a bond between the mPEG and an amino group (N-terminal cysteine or the ε-amino group of lysine) or the imidazole group of histidine of the interferon alfa-2b molecule. Monopegylated species are predominant, but a few percent of di-Peg-IFN alfa 2b as well as of free Interferon are also present. The manufacture is described in sufficient detail and control of materials and critical process controls are, after a few clarifications in the response to D120 LoQ, acceptable.

The monopegylated species has been shown to consist of a population of positional isomers of varying biological activities. Of the species identified, the His^{34} conjugate was shown to account for the major part of the biological activity. On the contrary, several lysine isomers exerted a lower or almost extinguished activity. The activity is assessed using an anti-viral assay based on inhibition of virus induced cytopathic effect (CPE), in turn monitored by MTT staining. The anti-viral biological activities of Peg-IFN alfa 2b and IFN are equivalent, although Peg-IFN alfa 2b requires a 4 fold higher protein concentration than IFN for equivalent biological activity. Additional studies using an anti-proliferation assay also demonstrated equivalent biological activity between Peg-IFN alfa 2b and IFN, using higher doses than usually required for antiviral activity. Equivalent biological activity was also observed in three immunological activity assays (LAK assay, NK activity and MHC Class 1 expression on human peripheral blood mononuclear cells). On average, the biological activity was lowered to about one quarter compared to that of the non-pegylated substance.

The consistency of the isomer distribution, as assembled into 6 groups and "others", is controlled in the drug substance specifications. The His conjugate was found less stable than normally found with lysine derivatives. This principal isomer may exert its activity, partly, by dissociation of mPEG from His^{34} *in vivo*.

Characterisation of product and process-related impurities are acceptable, when taking the responses to the D120 LoQ into account. Clarifications have been made as regards the bioassay method, and the analytical procedure has been harmonised in line with the amended method to be introduced for PegIntron, following the positive opinion for variation EMEA/H/C/280/II/77 that was granted in May 2008. In conjunction with this Pegintron variation, the company committed to a follow-up measure on calibration activities. These further data should be filed also to the Cylatron dossier. As concerns certain physico-chemical test attributes, the release limits have been tightened, as based on a statistical analysis of accumulated batch data. A corresponding revision will be filed to the Pegintron dossier, as committed. Thereby, the routine quality control release and stability specifications, as a whole, are considered acceptable and well described.

Stability data has been provided to support the storage of Peg-IFN alfa 2b Drug Substance in a freezer at -80°C for up to 36 months.

Finished Product

Powder

Peg-IFN alfa-2b drug product is a white to off-white powder and a clear, colourless solution when reconstituted with diluent (Water for Injection). There are three vial strengths of Peg-IFN alfa-2b drug product, 200, 300 and 600µg. As requested in the comments on the SPC, the strength should be expressed in terms of µg/ml, because dosing is made as per kg body weight. The Peg-IFN alfa-2b drug product vial will be accompanied with Sterilised Water for Injections (Ph Eur) of 0.7mL, packed in a glass ampoule for reconstitution. The label dose is contained in 0.5 ml of the reconstituted solution. Peg-IFN alfa-2b drug product is supplied in Type I flint glass vials (Ph Eur), 2mL nominal volume, fitted with gray butyl rubber stoppers (D713) 13mm lyo shape (Type I stoppers, Ph Eur) and sealed with a crimped-on 13mm flip-off aluminum seal with a polypropylene bonnet.

The development of the formulation and method of manufacture for PegIntron, a unit-dose lyophilized powder for injection of a long-acting form of interferon alfa-2b intended for once-a-week dosing, has been provided. Initially the product was developed between 50µg - 150µg strength (100µg/ml to 300µg/ml of protein) for Hepatitis-C treatment. Three new strengths of 200, 300 and 600µg (400µg/ml, 600µg/ml and 1.2mg/ml of protein, respectively) were developed subsequently for oncology treatment (Peg-IFN alfa-2b). The Hepatitis-C and Oncology product have an identical composition and manufacturing processes, other than the concentration of the PEG-IFN. The development history, highlighting key changes in formulation and manufacturing process from pilot-scale to commercial-scale batches is summarised in the dossier.

Excipients are: Sodium Phosphate Dibasic Anhydrous, Sodium Phosphate Monobasic Dihydrate, Sucrose, and Polysorbate 80, the latter of vegetable origin. No excipients of human or animal origin are used in the manufacture of Peg-IFN alfa-2b and there are no novel excipients used to manufacture Peg-IFN alfa-2b. The strength is defined by weight, referring to the protein moiety of the molecule.

Peg-IFN alfa-2b drug product is manufactured by Schering-Plough (Brinny) Co., Innishannon, Ireland, using standard aseptic processing manufacturing techniques. The manufacture is described in sufficient detail and sufficient process validation studies have been performed to demonstrate that the process used to manufacture Peg-IFN alfa-2b Powder for Injection is controlled in order to consistently manufacture a product that meets the predetermined specifications. Upon request, the applicant has provided the simulated shipping data to support the proposed shipping times and conditions for the Drug Product.

The current approved specifications for PegIntron Powder for Injection 50µg to 150µg strengths (Hepatitis-C) are proposed to be applied to Peg-IFN alfa-2b 200µg to 600µg high strength vials (Oncology). Details of the analytical methods for quality, identity, potency, purity and safety are given. The release limits have been reviewed based on batches produced, as recommended in the primary round assessment. Limits have been tightened for certain physico-chemical test attributes. Although not part of the labelled strength, the bioactivity of Peginterferon alfa-2b Schering-Plough is controlled, using the MTT-CPE assay, as part of the product specifications. The analytical test results, for all test attributes, obtained for Peg-IFN alfa-2b drug product batches manufactured from 1998 to 2006 (which were used in clinical studies) are provided and demonstrate that all batches met the specifications and the results were consistent.

Stability data supplied as well as the approved 36 month shelf-life for the Hepatitis C strengths (50-150µg) support the proposed 36 month shelf-life at refrigerated (5°C ± 3°C) storage condition for the Peg-IFN alfa-2b vials. The physical/chemical integrity of the product is maintained when stored at refrigeration temperatures for up to 24 hours after reconstitution.

Solvent
Water For Injection (Ph.Eur.) is manufactured (filled, sterilised and packed), tested and released by Schering-Plough Labo NV, Industriepark 30, 2220 Heist-Op-Den-Berg, Belgium. As requested, data from process validation studies has been provided and is acceptable.

Conclusion on the Quality part

Cylatron is recommended for approval from a pharmaceutical point of view with two post authorisation follow-up measures. However, as indicated in the comments on the SPC, the strength should be expressed in terms of micrograms/ml.

III.2 Non clinical aspects

Pharmacology
The rationale for using peginterferon alfa-2b for the treatment of melanoma is supported by literature data. The growth suppressive and pro-apoptotic effects of IFN alfa-2b on melanoma cells appear to stem from the activation of cellular signalling pathways followed by transcriptional activation and regulation of translation. Induction of genes like the cdk inhibitor p27 may be particularly important for inhibition of melanoma cell growth and survival. IFN alfa-2b is also active in xenograft melanoma

models, suggesting that this cytokine has direct anti-tumour effects in this disease. Other models, for example those using STAT1 knockout mice, have highlighted the importance of the immune system in understanding the activity of IFN alfa-2b in melanoma.

Cardiovascular, gastrointestinal, CNS and renal effects were studied in rats and cynomolgus monkeys. In monkeys a significant sustained increase (doubling) of the heart rate was recorded in animals treated with a high dose, with a concomitant rise in body temperature. The tachycardia was attributed as a secondary effect of the hyperthermia, which is a recognized effect of IFN-alfa-2b administration. No other significant effects were found on electrocardiographic parameters.

Pharmacokinetics

The bioavailability after subcutaneous injections was 60-90 % in monkeys. The plasma half-life was 13-25 hours. Subcutaneous injection resulted in peak plasma concentrations after 4 hours. Distribution studies in rats indicated no localization to any specific organ or tissue, elimination (as low molecular weight radioactivity) was primarily through the kidneys. Depegylation was not detected in monkeys, which is in contrast to the situation in man, where most of the plasma bioactivity was derived from non-pegylated interferon.

Toxicology

Single dose toxicity studies in mice, rats and monkeys using up to several hundred times the intended clinical dose of Peg-IFN alfa-2b, indicated a low order of toxicity in these animals. However, two of four monkeys given a single dose of 117721 µg/m^2 (more than 500 times the intended clinical dose) either died or were sacrificed in moribund condition. One death was the result of myocarditis and pleural effusion that was most likely present prior to dosing. The cause of death in the other monkey was not determined. Adverse events noted in survivors at the high-dose included loss of appetite, lower body temperature and reduction of blood pressure.

Repeated dose toxicity studies were performed in cynomolgus monkeys treated with subcutaneous doses of Peg-IFN alfa-2b every other day for one month.

Peg-IFN alfa-2b was well tolerated when administered to cynomolgus monkeys at the low and mid doses of 1414 and 4239 µg/m^2. Peg-IFN alfa-2b was *not* well tolerated at the high dose of 14126 µg/m^2 based on severe reductions in food consumption, leading in some cases to dehydration.

Important findings included dose-related decreases in all types of blood cells, serum proteins, calcium phosphorus and potassium. The findings observed in Peg-IFN alfa-2b-dosed monkeys were similar in nature to those produced by Intron A. There was thus no unique toxicity due to the pegylation. Greater incidence and/or severity of the findings were noted in the high-dosed monkeys compared to Intron A -dosed monkeys, which is in accordance with the prolonged exposure and higher AUC values.

Reversal of the findings were observed after several weeks of dosing, possibly due to the appearance of neutralising activity to interferon alfa in monkeys.

Reproduction studies were not performed. Interferon alfa-2b has been shown to be abortifacient in primates. Peg-IFN alfa-2b can be assumed to also have this effect, as expressed adequately in the SPC. (The present application contained an additional study showing that peginterferon alfa-2b prolonged the menstrual cycle and disturbed estradiol and progesteron levels in Cynomolgus monkeys.)

Genotoxicity was studied using a standard battery of tests. All findings were negative. The dosing was limited to 175 µg/plate in the Ames test, and 35 µg/ml in the chromosome aberration study, which, although below the guideline recommendations, is considered acceptable due to the (protein) nature of the test article.

Carcinogenicity studies were not performed, which is acceptable since human interferon alfa has no apparent effect in rodents, and since antibodies are rapidly formed after administration of the pegylated product.

Local tolerance. Subcutaneous injection of Peg-IFN alfa-2b and placebo to rats, both produced mild irritation, as did intramuscular injection of Peg-IFN alfa-2b to rabbits.

In addition, the present application contains an acceptable justification for not conducting an Environmental Risk Assessment, since the peginterferon alfa-2b is composed of a protein and a carbohydrate moiety.

III.3 Clinical aspects

Pharmacokinetics

Fourteen Phase 1 and three Phase 2/3 trials contributed pharmacokinetic data for this application. Included are studies which define the pharmacokinetic characteristics of Peg-IFN alfa-2b in oncology subjects, healthy volunteers, and subjects with hepatitis C, and define the effect of intrinsic factors (age and renal insufficiency) on the pharmacokinetics of Peg-IFN alfa-2b. Studies which define the effect of single and multiple doses of Peg-IFN alfa-2b on various drug metabolizing enzymes are also included. The majority of these studies were conducted in support of the previous registrations of Peg-IFN alfa-2b for the treatment of chronic hepatitis C. These studies have been submitted to health authorities as part of previously approved applications or as post-approval commitments.

Data submitted include pharmacokinetic data in subjects with chronic myelogenous leukaemia (CML) (C97-187, C/I97-275, and C/I98-026) and solid tumours (C/I97-188), as well as Peg-IFN alfa-2b trough concentration data from a subset of subjects enrolled in the pivotal Phase 3 trial, P00435 (EORTC 18991).

The applicant has provided a sufficient amount of pharmacokinetic data in support of the extension of the dose range from the doses used for treatment of hepatitis C, 0.5 µg/kg to 1.5 µg/kg administered subcutaneously once weekly for one year, to the dose recommended for melanoma treatment, 6 µg/kg/wk subcutaneously for 8 weeks (induction) followed by 3 µg/kg/wk subcutaneously (maintenance) for an intended total treatment duration of 5 years. The data in subjects with melanoma is limited and difficult to compare with data from subjects with CML and solid tumours, however, there is no trend towards a difference in pharmacokinetics between these groups.

Regarding subjects with renal impairment, there are no exposure data at the doses proposed in this submission (ie, 6.0 µg/kg for induction and 3.0 µg/kg for maintenance therapy). However, the applicant has justified the proposed recommendations for subjects with renal impairment.

The pharmacokinetics of peginterferon alpha-2b has not been studied in subjects with hepatic dysfunction. Treatment is contraindicated in subjects with severe hepatic dysfunction, including autoimmune hepatitis, cirrhosis and decompensated liver disease.

There are no data regarding the magnitude of potential changes in the activity of drug metabolizing enzymes CYP450 1A2, 2D6, 3A4, 2C8/9, and N-acetyl transferase at the Peg-IFN alfa-2b doses proposed in this submission. However, as the interaction potential was characterised for PegIntron, no further studies are warranted.

Age, gender and weight do not seem to affect the pharmacokinetics of Peg-IFN alfa-2b.

Pharmacokinetic summary of Peg-IFN alfa-2b

Peg-IFN alfa-2b is a well characterized polyethylene glycol-modified (“pegylated”) derivative of interferon alfa-2b and is predominantly composed of monopegylated species. The plasma half-life of Peg-IFN alfa-2b is prolonged compared with non-pegylated interferon alfa-2b. Peg-IFN alfa-2b has a potential to depegylate to free interferon alfa-2b. The biologic activity of the pegylated isomers is qualitatively similar, but weaker than free interferon alfa-2b.

Peg-IFN alfa-2b is slowly absorbed following subcutaneous administration with the maximal serum concentrations attained within 15-44 h, which are sustained for up to 48 to 72 h post-dose. CL/F ranged from 11 to 33 ml/h/kg, which is about one-tenth of the CL/F of Intron A.

Peg-IFN alfa-2b Cmax and AUC measurements increase in a dose-related manner. Mean apparent volume of distribution is about 1 l/kg.

Mean Peg-IFN alfa-2b elimination half-life is approximately 30.7 hours (range 27-33 hours), with apparent clearance of 22.0 ml/hr·kg. The mechanisms involved in clearance of interferons in man have not yet been fully elucidated. However, renal elimination may account for a minority (approximately 30 %) of Peg-IFN alfa-2b apparent clearance. It has been shown that serum interferon concentrations increase over time following multiple dosing. This has been reported for Peg-IFN alfa-2b, for non-pegylated interferon- alfa 2b and for interferon beta-1a. The reason for the accumulation of any of the interferons is unknown.

Peg-IFN alfa-2b does not affect the activity of cytochrome (CY) P1A2, CYP2C8/9, CYP2D6, and hepatic CYP3A4 or N-acetyl transferase. Caution should be advised in the interpretation of these results as the use of other forms of interferon alpha result in a 50% reduction in the clearance and thus a doubling of plasma concentrations of theophylline, a substrate of CYP1A2.

Renal function: Renal clearance appears to account for 30 % of total clearance of Peg-IFN alfa-2b. In a single dose study (1.0 microgram/kg) in subjects with impaired renal function, Cmax, AUC, and halflife increased in relation to the degree of renal impairment. Following multiple dosing of Peg-IFN alfa-2b (1.0 microgram/kg subcutaneously administered every week for four weeks) the clearance of Peg-IFN alfa-2b is reduced by a mean of 17 % in subjects with moderate renal impairment (creatinine clearance 30-49 ml/minute) and by a mean of 44 % in subjects with severe renal impairment (creatinine clearance 15-29 ml/minute) compared to subjects with normal renal function. Based on single dose data, clearance was similar in subjects with severe renal impairment not on dialysis and in subjects who were receiving hemodialysis.

Hepatic function: The pharmacokinetics of Peg-IFN alfa-2b has not been evaluated in subjects with severe hepatic dysfunction.

Elderly subjects ≥65 years of age: The pharmacokinetics of Peg-IFN alfa-2b following a single subcutaneous dose of 1.0 microgram/kg was not affected by age.

Subjects under the age of 18 years: Specific pharmacokinetic evaluations have not been performed in these subjects.

Pharmacodynamics

No pharmacodynamic information has been generated in support of the current application.

Clinical efficacy

A single pivotal trial has been submitted in support of this submission, but this trial should be assessed in the light of available studies conducted with alfa interferons for the adjuvant treatment of patients with malignant melanoma. In principle, the hypothesis tested is considered reasonably founded: high intensity induction therapy, followed by prolonged therapy where the dose is adjusted according to tolerability.

The pivotal trial (Trial 18991) was designed, initiated and conducted by the EORTC as an open-label, multicenter, randomized study. Eligible subjects with Stage III melanoma within 70 days of undergoing dissection of the regional lymph node, to either adjuvant Peg-IFN alfa-2b treatment (Arm A) or observation only (Arm B) for a study period of up to 5 years. Dynamic allocation was used in order to handle a large number of stratification variables.

Subjects in Arm A received Peg-IFN alfa-2b at a dosage of 6 µg/kg subcutaneous (SC) once weekly during an 8-week induction period, and then received a maintenance dosage of 3 µg/kg SC once weekly for the remainder of the treatment period. Dose reductions were permitted and recommended to maintain an Eastern Cooperative Oncology Group Performance Status (ECOG PS) score of 0 or 1 (Karnofsky performance status score of 90% to 100%).

In response to regulatory guidance across regions received prior to database lock and data evaluation, disease-free survival (DFS) was designated as the regulatory primary endpoint. Distant metastasis-free survival (DMFS) the protocol-specified primary objective, was considered a secondary endpoint.

Enrolled patients are regarded as typical for high dose interferon studies and the treatment arms were well balanced.

Primary Endpoint

The EORTC designated primary endpoint was distant metastasis-free survival (DMS). After regulatory consultation, this was changed to disease-free survival (= recurrence-free survival). This, however, was not documented by amendment to the study protocol.

Table 21 Recurrence-Free Survival According to the Independent Review Committee (ITT Population): Estimated Median and Hazard Ratio With 95% Confidence Interval

Protocol No. EORTC Trial 18991

Treatment	Number of Subjects	Number Censored	Number of Events[a]	Estimated Median (Months)	Hazard Ratio[b]	95% CI for HR	P-value[c]
Peg-IFN alfa-2b	627	299	328	34.76	0.82	0.71-0.96	0.011
Observation	629	261	368	25.53			

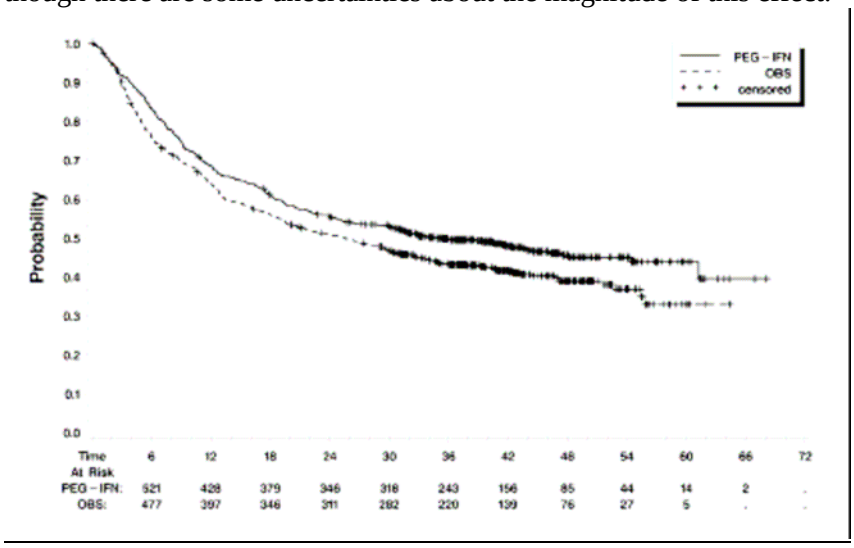
CI = confidence interval; HR = hazard ratio; ITT = intent-to-treat; Peg-IFN = pegylated interferon.

a: Events = relapses or deaths.

b: Hazard ratios presented as Peg-IFN alfa-2b/Observation; HR<1 indicates treatment effect in favor of test arm.

c: Unadjusted log-rank test.

The study was conducted open-label as the side effects of high dose intensity IFN therapy during the induction phase are too obvious and prevalent to be masked and due to the nature of recurrences, independent review of X-ray was not undertaken. In the response document a number of sensitivity analyses have been provided. These provide some insight. In addition, it should be noted that a simple comparison of proportion of recurrences indicate that a significant treatment effect is present, even though there are some uncertainties about the magnitude of this effect.

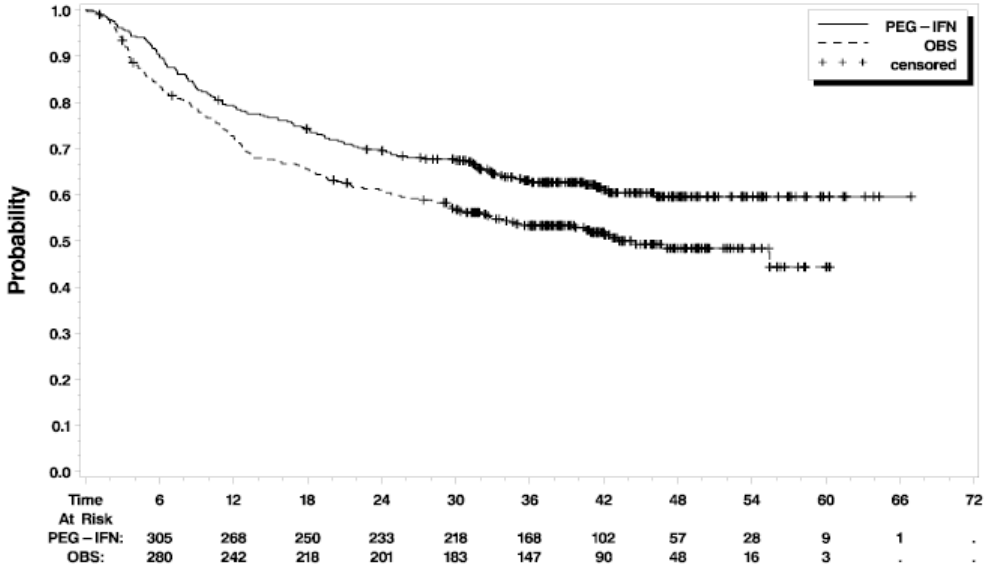


Due to the supportive value of other interferon studies, the p-value of about 0.01 as such is considered reasonably convincing for a single pivotal trial. The reported HR of 0.8 indicates a moderate treatment effect corresponding to a difference in event rate of about 6% and a median difference in time to recurrence about 9 months.

Subgroup analyses indicated that the treatment effect was more pronounced in patients with a better prognosis. Based on these data the sponsor has decided to request an indication restricted to patients with better prognosis and decided to use N1 (non-palpable, but microscopically involved lymph nodes) disease as defining variable.

Tumor Stage							
N1	Peg-IFN alfa-2b	271	163	108	NR	0.73	0.57-0.94
	Observation	272	135	137	42.55		
N2	Peg-IFN alfa-2b	356	136	220	18.23	0.86	0.72-1.04
	Observation	357	126	231	13.47		

Kaplan-Meier Curves for Recurrence-Free Survival (in Months) According to the Independent Review Committee (N1 Subgroup)



Some external support is given by another EORTC study (18952) conducted with interferon alfa-2b vs. observation in patients with stage III microscopic disease (N1) and stage IIb disease, were the outcome was clearly better in those with IIb disease at time of resection.

N1 and N2 status was used as stratification variables, but there was no associated a priori hypothesis to be tested. Neither was the testing strategy revised based on knowledge from study 18952 prior to unblinding of study data. While restricting an indication post hoc is considered rather uncontroversial as such in an overall positive study, the statistical and quantitative interpretation is not straight forward and the external support for the restriction is considered weak. In addition, the change of primary endpoint remains a concern. It is acknowledged, however, that microscopic involvement is a meaningful clinical entity due the widespread use of sentinel node biopsies in case of non-palpable lymph nodes.

While it is often considered acceptable to restrict an indication in a study where the results are overall positive with the caveats indicated above, the interpretation in relation to secondary outcome measures where the outcome is non-significant in the full study population is even more problematic. Distant metastasis free survival was the primary endpoint according to the plans of EORTC, but here no statistically significant treatment effect was demonstrated in the full study population (p=0.11). Otherwise, the results are similar e.g. according to subgroups. The difference in proportions of patients with event in stage III N1 patients, however, was “significant” (95% CI for difference -17%; -0.5%).

No treatment effect was shown on overall survival and there was only a weak trend (HR 0.88, 95% CI 0.64; 1.21) in Stage III N1 patients. This is somewhat surprising as DMFS would be expected to be a rather good predictor of survival. Data, however, are immature and thus dominated by events in N2 patients with rather poor prognosis. In the response document the MAH provided an updated survival analysis. In the full study population the HR was 0.96 at an event rate slightly below 50%. This corresponds to HR 1.01 in the N2 stratum and 0.84 in the N1 patients (95% CI 0.64; 1.11, event rate 94/271 vs. 108/272).

Results derived from a cure rate model were also reported. While the model as such has merits, the number of late observations is considered too small to conclude that that stable plateaus have been reach in the two treatment arms, not least as the planned duration of therapy was 5 years. Reasonably, "cure" should be analysed only when in practice almost all patients are off therapy so that a suppressive effect of IFN therapy can be disentangled from a treatment effect due to tumour cell kill and cure of the disease.

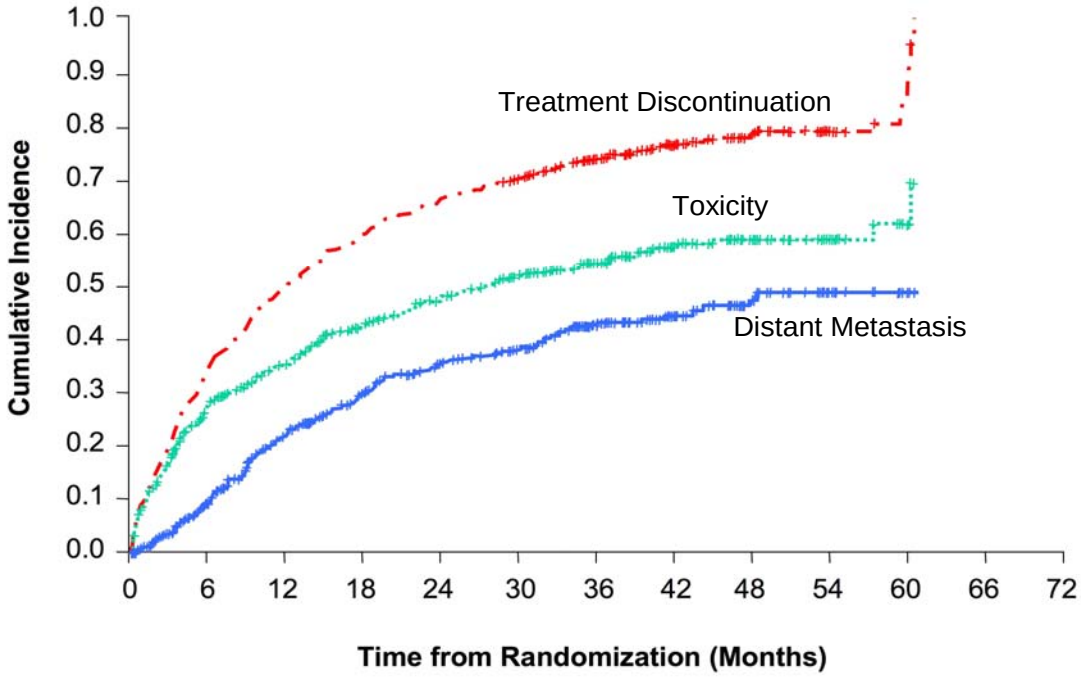
Clinical safety

A total of 936 subjects were treated in the melanoma/oncology program, including 871 subjects with 6.0 µg/kg/wk. Of these 936 subjects, 669 had resected Stage III melanoma, including 607 in the pivotal study, EORTC 18991. Deficiencies in the safety data base were detected. The source of these deficiencies has been identified and an update has been submitted. The numerical changes in the update are all considered insignificant from a clinical perspective and do not affect the conclusions drawn in the previous assessment report.

The safety/toxicity of Peg-IFN is considered qualitatively well known, also taking into account the experience with "high dose" conventional alpha interferon therapy.

Duration of therapy and intensity of the regimen proposed for licensing deviate from the schedules used in the treatment of CHC, but tolerability problems were foreseeable. Dose reduction was also recommended in the study protocol if found necessary to maintain a performance status score (ECOG) of 0 to 1. Performance status score of 0 to 1 is reported to have been maintained in ≥83% of subjects during the maintenance phase.

As an overall measure of tolerability, treatment discontinuation for toxicity and "refusal" is considered informative. After about 18 months altogether about 60% of the patients were off therapy, thereof 30% due to recurrence and 30% for toxicity and "refusal".



Reasons for discontinuing IFN therapy as delineated in the response document are summarised in the table below. The pattern is as would be expected and dominated by fatigue, anorexia, nausea, depression, but also abnormal liver function tests contributed. The table is also informative in the sense that data in relation to last dose level are reported.

Table 35 Adverse Events Associated With Study Discontinuation, by CTC Grade: Preferred Terms Regardless of Grade/Severity in Greater Than or Equal to 10% of Subjects in a Given Last Dose Level

Protocol No. EORTC Trial 18991

Preferred Term[a] n (%)	Grade 1	Grade 2	Grade 3	Grade 4	Total
Last dose = 1 μg/kg/week (n=77 subjects)[c]					
Any AEs[b]	5 (6)	18 (23)	20 (26)	2 (3)	45 (58)
Most frequent (≥10%)					
Nausea	6 (8)	4 (5)	1 (1)	0	11 (14)
Fatigue	10 (13)	20 (26)	4 (5)	1 (1)	35 (45)
Injection site reaction	8 (10)	0	0	0	8 (10)
Pyrexia	8 (10)	2 (3)	0	0	10 (13)
Liver function test	11 (14)	5 (6)	3 (4)	0	19 (25)
Anorexia	12 (16)	2 (3)	2(3)	0	16 (21)
Arthralgia	6 (8)	5 (6)	1 (1)	0	12 (16)
Myalgia	7 (9)	6 (8)	2 (3)	0	15 (19)
Headache	5 (6)	6(8)	2 (3)	0	13 (17)
Depression	10 (13)	9 (12)	6 (8)	0	25 (32)
Exfoliative rash	7 (9)	2 (3)	1 (1)	0	10 (13)
Last dose = 2 μg/kg/week (n=53 subjects)[c]					
Any AEs[b]	2 (4)	14 (26)	17 (32)	2 (4)	35 (66)
Diarrhoea	6 (11)	1 (2)	0	0	7 (13)
Nausea	8 (15)	4 (8)	0	0	12 (23)
Chills	3 (6)	3 (6)	1 (2)	0	7 (13)
Fatigue	4 (8)	19 (36)	6 (11)	1 (2)	30 (57)
Injection site reaction	4 (8)	5 (9)	2 (4)	0	11 (21)
Pyrexia	3 (6)	7 (13)	1 (2)	0	11 (21)
Liver function test	8 (15)	5(9)	2 (4)	0	15 (28)
Anorexia	3 (6)	5 (9)	3 (6)	0	11 (21)
Arthralgia	2 (4)	4 (8)	3 (6)	0	9 (17)
Myalgia	7 (13)	4 (8)	3 (6)	0	14 (26)
Dizziness	1 (2)	5 (9)	0	0	6 (11)
Dysgeusia	3 (6)	4 (8)	0	0	7 (13)
Headache	5 (9)	8 (15)	1 (2)	0	14 (26)
Depression	9 (17)	7 (13)	4 (8)	0	20 (38)
Exfoliative rash	4 (8)	3 (6)	1 (2)	0	8 (15)
Last dose = 3 μg/kg/week (n=99 subjects)[c]					
Any AEs[b]	5 (5)	18 (18)	29 (29)	6 (6)	58 (59)
Diarrhoea	8 (8)	2 (2)	0	0	10 (10)
Nausea	12 (12)	13 (13)	2 (2)	0	27 (27)
Vomiting	6 (6)	3 (3)	1 (1)	0	10 (10)
Chills	11 (11)	3 (3)	1 (1)	0	15 (15)
Fatigue	17 (17)	23 (23)	10 (10)	1 (1)	51 (52)
Injection site reaction	14 (14)	2 (2)	2 (2)	0	18 (18)
Pyrexia	9 (9)	7 (7)	1 (1)	0	17 (17)
Liver function test	20 (20)	5 (5)	1 (1)	0	26 (26)
Anorexia	18 (18)	18 (18)	3 (3)	0	39 (39)

Preferred Term[a] n (%)	Grade 1	Grade 2	Grade 3	Grade 4	Total
Arthralgia	10 (10)	6 (6)	1 (1)	0	17 (17)
Myalgia	10 (10)	8 (8)	2 (2)	0	20 (20)
Dizziness	8 (8)	2 (2)	3 (3)	0	13 (13)
Dysgeusia	8 (8)	6 (6)	0	0	14 (14)
Headache	12 (12)	7 (7)	3 (3)	0	22 (22)
Depression	18 (18)	10 (10)	4 (4)	1 (1)	33 (33)
Last dose = 4 µg/kg/week (n=1 subject, (%) not applicable)[c]					
Any AEs[b]	0	0	1	0	1
Chills	0	1	0	0	1
Fatigue	0	0	1	0	1
Pyrexia	1	0	0	0	1
Anorexia	0	1	0	0	1
Arthralgia	1	0	0	0	1
Myalgia	0	1	0	0	1
Dizziness	1	0	0	0	1
Headache	1	0	0	0	1
Depression	0	0	1	0	1
Last dose = 6 µg/kg/week (n=60 subjects)[c]					
Any AEs[b]	3 (5)	13 (22)	15 (25)	10 (17)	41 (68)
Diarrhea	4 (7)	3 (5)	3 (5)	1 (2)	11 (18)
Nausea	10 (17)	10 (17)	3 (5)	0	23 (38)
Vomiting	12 (20)	1 (2)	1 (2)	0	14 (23)
Chills	13 (22)	10 (17)	3 (5)	0	26 (43)
Fatigue	3 (5)	23 (38)	8 (13)	2 (3)	36 (60)
Injection site reaction	6 (10)	5 (8)	0	0	11 (18)
Pyrexia	4 (7)	17 (28)	4 (7)	0	25 (42)
Liver function test	13 (22)	2 (3)	1 (2)	1 (2)	17 (28)
Anorexia	8 (13)	10 (17)	4 (7)	0	22 (37)
Arthralgia	2 (3)	9 (15)	4 (7)	0	15 (25)
Myalgia	7 (12)	12 (20)	5 (8)	1 (2)	25 (42)
Dizziness	7 (12)	1 (2)	0	0	8 (13)
Dysgeusia	8 (13)	5 (8)	0	0	13 (22)
Headache	7 (12)	14 (23)	3 (5)	0	24 (40)
Depression	11 (18)	7 (12)	2 (3)	0	20 (33)
Exfoliative rash	4 (7)	1 (2)	1 (2)	0	6 (10)

AE = adverse event; CTC = Common Toxicity Criteria.

a: Ordered by System Organ Class (SOC).

b: Adverse events recorded prior to randomization are not included in this time period.

c: Last dose is rounded down to a whole number if it is ≤x.7 and up if it is ≥x.71 except ≥0.5 is rounded up to 1.0.

Source Data: **Appendix 9** .

As of 31 March 2007, 85 subjects were under active treatment in the 5th year of Peg-IFN alfa-2b. Year 1 median dose intensity for maintenance therapy was at 2.9 µg/kg/week, for a theoretical dose of 3.0 µg/kg/week. The median dose intensity was 2.2 µg/kg/week for Year 2 and stayed identical for Year 3+.

Also the overall pattern of reported adverse events is qualitatively as would be expected based on the large experience from treatment with IFN.

All Adverse Events That Occurred at an Incidence Greater Than or Equal to 5%, and Corresponding Grade

	Number (%) of Subjects		
	Peg-IFN alfa-2b (n=627)		
SOC/Preferred Term	All	Grade 3	Grade 4
Subjects Reporting Any AE	**608 (97)**	**239 (38)**	**58 (9)**
Gastrointestinal Disorders	**456 (73)**	**31 (5)**	**1 (<1)**
Diarrhea	217 (35)	8 (1)	1 (<1)
Nausea	392 (63)	18 (3)	0

	Number (%) of Subjects		
	Peg-IFN alfa-2b (n=627)		
SOC/Preferred Term	All	Grade 3	Grade 4
Vomiting	155 (25)	5 (1)	0
General Disorders and Administration Site Conditions	**603 (96)**	**110 (18)**	**11 (2)**
Chills	373 (59)	9 (1)	0
Fatigue	574 (92)	89 (14)	8 (1)
Injection Site Reaction	373 (59)	9 (1)	1 (<1)
Pyrexia	454 (72)	24 (4)	1 (<1)
Investigations	**500 (80)**	**83 (13)**	**8 (1)**
Blood Alkaline Phosphatase	134 (21)	0	0
Blood Bilirubin	82 (13)	4 (1)	0
Blood Creatinine	43 (7)	0	0
GGT	33 (5)	18 (3)	1 (<1)
Liver Function Test	467 (74)	61 (10)	2 (<1)
Weight Decreased	51 (8)	1 (<1)	0
Metabolism and Nutrition Disorders	**428 (68)**	**26 (4)**	**1 (<1)**
Anorexia	417 (67)	20 (3)	0
Musculoskeletal and Connective Tissue Disorders	**450 (72)**	**28 (4)**	**3 (<1)**
Arthralgia	306 (49)	18 (3)	0
Myalgia	408 (65)	22 (4)	1 (<1)
Nervous System Disorders	**514 (82)**	**43 (7)**	**5 (<1)**
Dizziness	215 (34)	12 (2)	1 (<1)
Dysgeusia	231 (37)	0	0
Headache	426 (68)	24 (4)	0
Paraesthesia	121 (19)	1 (<1)	0
Parosmia	139 (22)	0	0
Psychiatric Disorders	**372 (59)**	**42 (7)**	**1 (<1)**
Depression	360 (57)	38 (6)	1 (<1)
Renal and Urinary Disorders	**44 (7)**	**0**	**1 (<1)**
Proteinuria	39 (6)	0	0
Respiratory, Thoracic and Mediastinal Disorders	**63 (10)**	**7 (1)**	**5 (1)**
Dyspnoea	29 (5)	5 (1)	1 (<1)
Skin and Subcutaneous Tissue Disorders	**351 (56)**	**10 (2)**	**2 (<1)**
Alopecia	206 (33)	0	0
Exfoliative Rash	215 (34)	7 (1)	1 (<1)

The overall high incidence of adverse events is noticeable, not least as also grade 3 events likely to be related are very common.

Adverse Events That Occurred at an Incidence Greater Than or Equal to 5% by Time Period by System Organ Class and Preferred Term in the EORTC Trial 18991

MedDRA[a] SOC/PT	Peg-IFN alfa-2b ≤2 Months[b] (n=627)	Peg-IFN alfa-2b >2 Months to 1 Year (n=534)	Peg-IFN alfa-2b >1 Year to 2 Years (n=311)	Peg-IFN alfa-2b >2 Years (n=208)
Subjects Reporting Any AE	**604 (96)**	**448 (84)**	**253 (81)**	**164 (79)**
Gastrointestinal Disorders	**393 (63)**	**164 (31)**	**80 (26)**	**48 (23)**
Diarrhoea	155 (25)	69 (13)	39 (13)	21 (10)
Nausea	342 (55)	102 (19)	51 (16)	26 (13)
Vomiting	115 (18)	35 (7)	17 (5)	12 (6)
General Disorders and Administration Site Conditions	**591 (94)**	**366 (69)**	**206 (66)**	**113 (54)**
Chills	313 (50)	93 (17)	53 (17)	26 (13)
Fatigue	540 (86)	291 (54)	158 (51)	77 (37)
Injection Site Reaction	282 (45)	161 (30)	85 (27)	46 (22)
Pyrexia	402 (64)	125 (23)	65 (21)	38 (18)

MedDRA[a] SOC/PT	Peg-IFN alfa-2b ≤2 Months[b] (n=627)	Peg-IFN alfa-2b >2 Months to 1 Year (n=534)	Peg-IFN alfa-2b >1 Year to 2 Years (n=311)	Peg-IFN alfa-2b >2 Years (n=208)
Investigations	**449 (77)**	**260 (49)**	**126 (41)**	**79 (38)**
Blood Alkaline Phosphatase	91 (15)	47 (9)	13 (4)	15 (7)
Blood Bilirubin	56 (9)	29 (5)	19 (6)	10 (5)
Blood Creatinine	23 (4)	14 (3)	12 (4)	8 (4)
Liver Function Test	417 (67)	198 (37)	98 (32)	59 (28)
Metabolism and Nutrition Disorders	**360 (56)**	**156 (29)**	**55 (18)**	**26 (13)**
Anorexia	350 (56)	149 (28)	51 (16)	24 (12))
Musculoskeletal and Connective Tissue Disorders	**371 (59)**	**194 (36)**	**124 (40)**	**60 (29)**
Arthralgia	219 (35)	119 (22)	76 (24)	34 (16)
Myalgia	330 (53)	158 (30)	89 (29)	48 (23)
Nervous System Disorders	**437 (70)**	**251 (47)**	**127 (41)**	**72 (35)**
Dizziness	133 (21)	88 (16)	39 (13)	22 (11)
Dysgeusia	181 (29)	79 (15)	30 (10)	14 (7)
Headache	330 (53)	167 (31)	80 (26)	54 (26)
Paraesthesia	54 (9)	58 (11)	21 (7)	13 (6)
Parosmia	92 (15)	52 (10)	22 (7)	8 (4)
Psychiatric Disorders	**260 (41)**	**176 (33)**	**83 (27)**	**46 (22)**
Depression	252 (40)	170 (32)	79 (25)	44 (21)
Skin and Subcutaneous Tissue Disorders	**186 (30)**	**222 (42)**	**78 (25)**	**43 (21)**
Alopecia	76 (12)	146 (27)	39 (13)	20 (10)
Exfoliative Rash	114 (18)	98 (18)	43 (14)	27 (13)

The very high incidence of adverse events during the induction phase is expected, but the reported incidences also after more than 2 years are worth noticing taken into account the high attrition rates due to toxicity and refusal. Also serious events were frequently reported.

Serious Adverse Events That Occurred at an Incidence Greater Than or Equal to 2% in EORTC 18991

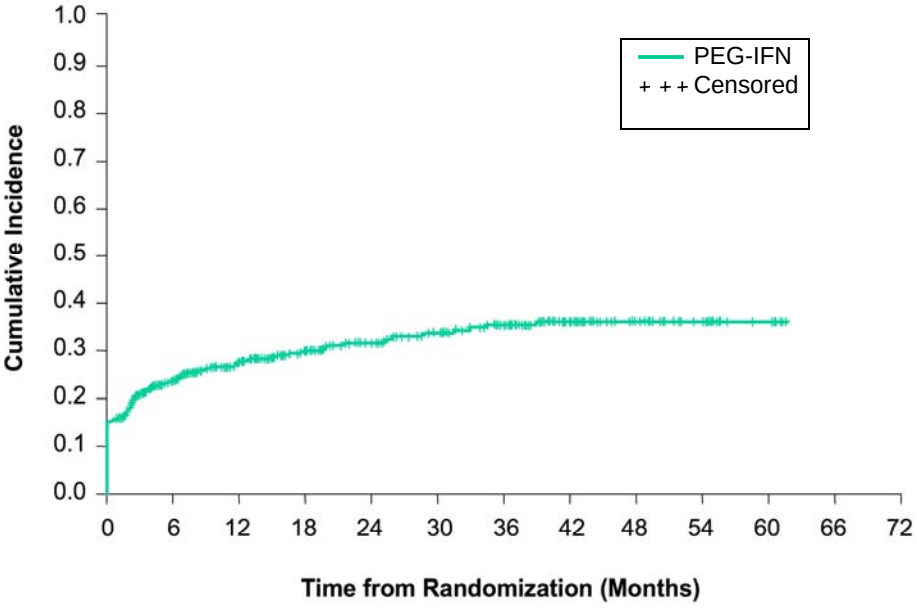
MedDRA[a] SOC/PT	Number (%) of Subjects Peg-IFN alfa-2b 6.0 µg/kg/wk for 8 wk then 3.0 µg/kg/wk for 5 yr (n=627)
Subjects Reporting Any Serious Adverse Event	**178 (28)**
Gastrointestinal Disorders	**26 (4)**
Nausea	13 (2)
General Disorders and Administration Site Conditions	**62 (10)**
Fatigue	39 (6)
Pyrexia	20 (3)
Investigations	**31 (5)**
Liver Function Test	20 (3)
Musculoskeletal and Connective Tissue Disorders	**20 (3)**
Myalgia	10 (2)
Nervous Systems Disorders	**42 (7)**
Headache	12 (2)

With respect events of importance for the tolerability of the regimen proposed for licensure, fatigue and depression are of special interest.

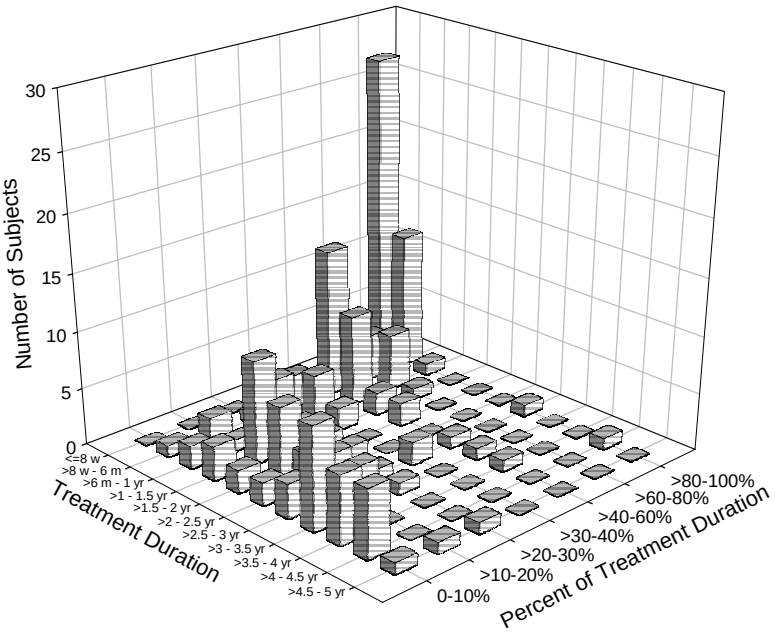
Psychiatric Adverse Events in the Melanoma Study EORTC Trial 18991

MedDRA[a] SOC/PT	Number (%) of Subjects		
	Peg-IFN alfa-2b 6.0 µg/kg/wk for 8 wk then 3.0 µg/kg/wk for 5 yr (n=627)		
	All Grades	Grade 3[b]	Grade 4[b]
Psychiatric Disorders	**372 (59)**	**42 (7)**	**1 (<1)**
Agitation	3 (<1)	1 (<1)	0
Anxiety	9 (1)	3 (<1)	0
Confusional State	3 (<1)	1 (<1)	0
Delusion	1 (<1)	1 (<1)	0
Depression	360 (57)	38 (6)	1 (<1)
Euphoric Mood	1 (<1)	1 (<1)	0
Hallucination	1 (<1)	1 (<1)	0
Insomnia	15 (2)	1 (<1)	0
Libido Disorder	10 (2)	0	0
Panic Attack	3 (<1)	2 (<1)	0
Stress	3 (<1)	0	0

Cumulative incidence over time from randomization of Grade 2 to 4 depression



Depression (Grade 2+) Duration vs Treatment Duration



Even though there is a clustering of early events and apparently brief episodes, a non-trival percentage of patients reported durable depressive symptoms. The pattern is very similar for « fatigue ».

As of 31 March 2006, an overall total of 262 subjects who had been treated with Peg-IFN alfa-2b died. The cause of death was malignant disease in 249 subjects. Four deaths were due to other causes (plane crash, euthanasia, malignant disease/acute cardiovascular failure, and intracerebral hemorrhage), 4 due to cardiovascular events, and 1 due to infection. The cause of death was missing in 4 cases; none of these latter deaths occurred while treated or within 30 days of the last dose.

Pharmacovigilance system

The Pharmacovigilance system as described by the Applicant fulfils the requirements and provides adequate evidence that the Applicant has the services of a qualified person responsible for Pharmacovigilance and has the necessary means for the collection and notification of any adverse reaction suspected of occurring in the Community or in a third country.

Risk Management Plan

Summary of the Risk Management Plan

Safety Concern	**Proposed Pharmacovigilance Activities (routine and additional)**	**Proposed Risk Minimization Activities (routine and additional)**
Important Identified Risks		
Acute hypersensitivity reactions	Routine pharmacovigilance	Warning in SPC
Severe psychiatric events,	Routine pharmacovigilance	Warning in SPC

Safety Concern	Proposed Pharmacovigilance Activities (routine and additional)	Proposed Risk Minimization Activities (routine and additional)
including depression, suicide, attempted suicide, and suicidal ideation	Update cumulative analysis at the time of the PSUR Include studies to be analysed	Additional risk minimization activities will be proposed as needed pending Interval update of the cumulative analysis and postmarketing close surveillance CME program
Cardiac events, including cardiomyopathy, cardiac ischemia, and myocardial infarction	Routine pharmacovigilance	Warning in SPC
Thyroid disorders, including hyperthyroidism and hypothyroidism	Routine pharmacovigilance	Warning in SPC Additional risk minimization activities will be proposed as needed pending interval update of the cumulative analysis and postmarketing close surveillance.
Autoimmune disorders, specifically Vogt-Koyanagi-Harada, pure red cell aplasia, and thrombotic thrombocytopenic purpura	Routine pharmacovigilance	Warning in SPC
Hematologic disorders, including anemia, leukopenia/neutropenia, and thrombocytopenia	Routine pharmacovigilance	Warning in SPC
Hearing loss	Routine pharmacovigilance	Warning in SPC
Ocular disorders, including decreased visual acuity, loss of vision, blindness, and retinal haemorrhage	Routine pharmacovigilance	Warning in SPC
Diabetes mellitus	Routine pharmacovigilance	Warning in SPC
Dental and periodontal disorders	Routine pharmacovigilance	Warning in SPC
Pulmonary disorders	Routine pharmacovigilance	Warning in SPC
Lactic acidosis in patients receiving HAART therapy	Routine pharmacovigilance	Warning in SPC
Skin: Stevens Johnson syndrome, toxic epidermal necrolysis, erythema multiforme	Routine pharmacovigilance	Labeled in Section 4.8 of the PegIntron SPC and the other going to Section 4.8 of the ViraferonPeg SPC
Important Potential Risks		
Neoplasms, benign and malignant	Routine pharmacovigilance Cumulative review of all cases of neoplasm every six months	If cumulative review demonstrates evidence of an association, SPC will be updated
Demyelinating disorders	Routine pharmacovigilance Cumulative analysis	If cumulative review demonstrates evidence of an association, SPC will be updated
Spontaneous abortion	Routine pharmacovigilance Cumulative review	Use in pregnant women is contraindicated.
Organ transplant rejection	Routine pharmacovigilance	If cumulative review demonstrates evidence of an association, SPC will be

Safety Concern	Proposed Pharmacovigilance Activities (routine and additional)	Proposed Risk Minimization Activities (routine and additional)
		updated
	Cumulative review	
Thrombotic microangiopathy	Routine pharmacovigilance	If cumulative review demonstrates evidence of an association, SPC will be updated. ITP and TPP are included in the SPC
	Cumulative review of issue	
Agranulocytosis	Routine pharmacovigilance	
	Cumulative review	
Pulmonary hypertension	Routine pharmacovigilance	
	Cumulative review	

The RMP is found adequate and all outstanding issues have been resolved.

IV. ORPHAN MEDICINAL PRODUCTS

N/A

V. BENEFIT RISK ASSESSMENT

V.1 Clinical context

Until now, no treatment administered in the adjuvant setting in patients with resected melanoma has shown increased cure rates or improved survival in any single trial, but metanalyses are compatible with a modest treatment effect (HR about 0.9) with respect to survival. Favourable results in terms of prolonged disease-free survival, however, have been repeatedly documented in patients treated with interferon alpha at different dosages and durations of therapy. In the adjuvant setting, disease-free survival is accepted as an outcome measure of relevance for the individual patient. However, to cite the current anti-cancer guideline “In some cases and due to toxicity concerns, favourable effects on OS have to be demonstrated”.

The primary endpoint for the pivotal EORTC study was changed prior to unblinding of study data from distant metastasis-free survival to disease-free survival (DFS). However, this change was not documented as an amendment to the protocol. Furthermore, the applicant has proposed that the indication should be restricted to patients with microscopic, non-palpable involvement of the lymph nodes.

V.2 Benefits

A statistically significant treatment effect compared with observation only was documented in the ITT population and in terms of disease-free survival (about p=0.01) at a Hazard Ratio of 0.8. This treatment effect corresponds to a difference in DFS of 9 months or a difference in event rate of about 6% at 3 years.

V.3 Uncertainties

The sponsor is requesting an indication restricted to patients with Stage III melanoma as evidenced by microscopic, non-palpable nodal involvement (N1). This restriction is based on study data indicating a modestly larger benefit in this group of patients (HR 0.73) compared with patients with resected N2 disease (HR 0.86). There is also some conceptual support for this notion from another EORTC study (18952). At three years the estimated difference in recurrence rates appears to be about 10% in patients with N1 disease.

A restriction of an indication, even if done post hoc, is not considered too controversial in an overall positive study, but the uncertainties with respect to the magnitude of the treatment effect constitute an issue. In patients with N1 disease at time of resection, but not in the full study population, there appears to be a "significant" treatment effect with respect to MFS (HR 0.75 95% CI0.57; 0.96). These data should be interpreted very cautiously due to the post hoc nature of the analysis and the weak external support as regards dichotomizing based on N1/N2 status.

In the response document the MAH provided an updated survival analysis. In the full study population the HR was 0.96 at an event rate slightly below 50%, corresponding to an HR of 1.01 in the N2 stratum and 0.84 in the N1 stratum (95% CI 0.64; 1.11, event rate 94/271 vs. 108/272).

It appears highly unlikely that a difference in survival will be possible to demonstrate in the full study population, but is not excluded in the N1 subgroup. Again, it will be very hard to interpret study data.

With respect to "cure", submitted data are considered immature as in practice almost all patients must be off therapy for a reasonable period of time in order to differentiate between tumour suppressive effects of ongoing therapy and "cure".

V.4 Risks

Prolonged IFN therapy at a rather high dose-intensity is associated with major tolerability and toxicity problems. As an overall measure, already at 18 months about 12% of the patients stopped therapy due to "toxicity" and about 18% stopped du to other reasons, mainly "refusal". Fatigue and depression were very prevalent, despite dose reductions undertaken to keep performance status better than 2. In addition, serious adverse events were reported by around 27% of the patients during the maintenance phase.

V.5 Balance

Assuming that the estimated benefit in the post hoc identified subgroup of patients actually is HR 0.75 and that the corresponding difference in DFS at three years is about 10% absolute, the treatment effect would be considered clinically meaningful. However, the poor tolerability and the toxicity of the selected interferon regimen make the benefit – risk relationship negative.

Given the tolerability/toxicity profile of the Peg-IFN alfa 2b regimen proposed for licensure, an increased cure-rate or a meaningful survival benefit would be needed for benefit – risk to be favourable. Based on currently available data, this might not be impossible to show in patients with Stage III, N1 disease. As survival and cure results are highly likely to remain negative for the full study population, much stronger external support would be needed, however, to support the validity of claims related to the subgroup of patients with N1 disease.

V.6 Conclusions

From a pharmaceutical and non-clinical perspective, the product is considered approvable, with two post-authorisation follow-up measures.

Form a clinical perspective, benefit – risk is unfavourable for the adjuvant treatment of patients with resected malignant melanoma Stage III with microscopic involvement only of lymph nodes.