European Medicines Agency

ASSESSMENT REPORT
FOR
ZEVALIN

International non-proprietary name/Common name:
ibritumomab tiuxetan

Procedure No.EMEA/H/C/000547/II/0018

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

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1. Introduction

Ibritumomab tiuxetan is a recombinant murine IgG1 kappa monoclonal antibody specific for the B-cell antigen CD20. Ibritumomab tiuxetan targets the antigen CD20 which is located on the surface of malignant and normal B-lymphocytes . During B-cell maturation, CD20 is first expressed in the midstage of B-lymphoblast (pre-B-cell), and is lost during the final stage of B cell maturation to plasma cells. It is not shed from the cell surface and does not internalise on antibody binding. The conjugated antibody has an apparent affinity constant for the CD20 antigen of approximately 17 nM. The binding pattern is very restricted, with no cross-reactivity to other leukocytes or to other types of human tissue.

[90Y]-radiolabeled Zevalin binds specifically to B-cells, including CD20-expressing malignant cells. The isotope yttrium-90 is a pure β-emitter and has a mean path length of about 5 mm. This results in the ability to kill both targeted and neighbouring cells.
Rituximab pre-treatment is necessary to clear circulating B-cells, enabling Zevalin to deliver radiation more specifically to the lymphomas. Rituximab is administered in a reduced dose when compared with the approved monotherapy.

Zevalin has been granted approval under exceptional circumstances by the EU Commission on January 16, 2004. The [90Y]-radiolabeled Zevalin is indicated for the treatment of adult patients with rituximab relapsed or refractory CD20+ follicular B-cell non-Hodgkin's lymphoma (NHL).

The safety and efficacy of the Zevalin therapeutic regimen were evaluated in two multi-center trials enrolling a total of 197 subjects. The Zevalin therapeutic regimen was administered in two steps. The efficacy and toxicity of a variation of the Zevalin therapeutic regimen employing a reduced activity of [90Y]-Zevalin was further defined in a third study enrolling a total of 30 patients who had mild thrombocytopenia (platelet count 100 to 149 x 10^9/L).

The scope of this variation is extension of the indication. It is proposed to add the following to the currently approved indication: *"The [90Y]-radiolabeled Zevalin is indicated as consolidation therapy after remission induction in previously untreated patients with follicular lymphoma.*

1.2 Clinical aspects

The basis of the application is the clinical study 304820 which was performed as EU post-approval obligation in 1st line consolidation of indolent NHL This study was performed in patients with Stage III or IV follicular NHL who received Zevalin versus no further treatment after having achieved partial or complete remission after remission-induction chemotherapy. Primary objective was a difference in progression-free survival (PFS). Prior to study start, the study design was approved by the CHMP via EU Scientific Advice. The MAH has provided a copy of this advice together with the minutes of the presubmission meetings with the Danish and the Dutch authority.

The submission of study 304820 within this application fulfills the obligation yhe remaining specific obligation SOB020 linked to the initial authorisation of Zevalin.

Information on the safety of Zevalin is provided with regard to the clinical study 304820, but also as related to Zevalin as marketed product. The safety information from the clinical study 304820 is put into perspective to the information as obtained from earlier Zevalin trials that led to approval and to postmarketing information. These earlier trials are not submitted again, but would be available on request.
Main study

The clinical efficacy is based on the results of one multicenter randomized prospective phase III trial (304820) investigating the efficacy and safety of a single course of [90Y]-ibritumomab tiuxetan given at a dose of 15 MBq/kg (0.4 mCi/kg, maximum 1200 MBq or 32 mCi) to 414 patients with stage III or IV follicular non-Hodgkin's lymphoma who had achieved a PR or CR after first line chemotherapy with either single agent or combination chemotherapies. Overall 208 patients were randomized to Zevalin and 206 patients were randomized to no further treatment.

Methods

The following criteria were used to evaluate patients for inclusion in the study:
1. Histologically confirmed (according to the REAL/WHO classification) CD20 positive follicular (grade 1 or 2) non-Hodgkin's lymphoma, stage III or IV at timepoint of diagnosis
2. Patients with a CR or PR (according to the "International workshop to standardize response criteria for non-Hodgkin´s lymphomas") after first line chemotherapy, which should have been given as the immediate prior front line therapy before beginning study drug treatment
3. No less than 6 weeks and no more than 12 weeks since last doses of chemotherapy or chemotherapy and interferon (in case of combination therapy)
4. Age 18 years or older
5. World Health Organization (WHO) performance status of 0 to 2
6. Absolute neutrophil count (ANC) of 1.5 x 10 9/L or higher
7. Hemoglobin (Hb) of 9 g/dl (90 g/l) or higher
8. Platelet count of 150 x 10 9/L or higher
9. Less than 25% bone marrow involvement (measurement of bone marrow biopsy)
10. Life expectancy of at least 3 months
11. Written informed consent obtained

The following criteria were used for the exclusion of patients from the study:
1. Any other anticancer treatment for NHL except the preceding first-line chemotherapy
2. Prior radiation therapy
3. Prior myeloablative therapy
4. Patients who did not recover from the toxic effects of the first-line therapy
5. Any other malignancy or history of prior malignancy except non-melanoma skin tumors or stage 0 (in situ) cervical carcinoma within the past ten years [see also below "protocol amendment 6"]
6. Presence of symptomatic CNS lymphoma
7. Patients with known HIV positivity
8. Patients with known seropositivity for HCV, HbsAG or other active infection uncontrolled by treatment
9. Patients with pleural effusion or ascites
10. Patients with abnormal liver function: total bilirubin > 1.5 x ULN or ALAT > 2.5 x ULN
11. Patients with abnormal renal function: serum creatinine > 2.5 x ULN
12. IgG < 3 g/l
13. Presence of anti-murine antibody (HAMA) reactivity
14. Known hypersensitivity to murine antibodies or proteins
15. Immunotherapy during the preceding 6 months (including antibodies, interleukins, interferon maintenance - combination of first-line chemotherapy with interferon or
rituximab was allowed) [see also below "protocol amendment 6"]
16. Female patients who were pregnant or breast feeding, or adults of reproductive potential not employing an effective method of birth control during study treatment and for at least
12 months thereafter. (Women of childbearing potential must have had a negative serum pregnancy test at study entry)
17. Concurrent severe and/or uncontrolled medical disease (e.g. uncontrolled diabetes, congestive heart failure, myocardial infarction within 6 months prior to the study, unstable and uncontrolled hypertension, chronic renal disease, or active uncontrolled infection) which could have compromised participation in the study
18. Patients who received any investigational drugs less than 4 weeks before entry in this study or who had not yet recovered from the toxic effects of such therapy
19. Patients who underwent surgery within 4 weeks of entering the study or patients who had not yet recovered from the side-effects of such treatment
20. Patients with a history of psychiatric illness or condition which could have interfered with their ability to understand the requirements of the study (this included alcoholism/drug addiction)
21. Patients who were unwilling or unable to comply with the protocol

In Protocol Amendment 6 (21 Jan 2004) Exclusion criterion 15 was modified allowing patients who had received immunotherapy with rituximab to be included in the study. This modification was added after new results in the literature showed that CVP in combination with rituximab prolonged time to progression in patients with follicular non-Hodgkin's lymphoma. Since this was the same indication as in the present trial, it was considered appropriate to include patients with rituximab pretreatment.

Primary and secondary efficacy variables of study 304820

The primary efficacy variable for study 304820 was progression free survival (PFS). Secondary efficacy variables included overall survival, improvement in complete response rate, improvement in molecular response rate, and health related quality of life (HRQL).

The overall PFS was analyzed for all patients in the Zevalin and control group. The main subgroups for the primary efficacy variable included analysis of PFS according to:

- First-line treatment strategy ("Immediate treatment" and with "Wait and See" treatment strategies)
- Response to first-line treatment
- Specific type of first-line treatment.

Results

Dataset and patient disposition

An overview of the analysis sets in study 304820 is presented in the Table below

Table 15: Number of subjects for the different analysis sets by treatment as randomized - All screened subjects

	Screening failures	Control	Zevalin	Total
Number of subjects	88 (100.0%)	206 (100.0%)	208 (100.0%)	502 (100.0%)
Full Analysis Set				
no	88 (100.0%)	0 (0.0%)	0 (0.0%)	88 (17.5%)
yes	0 (0.0%)	206 (100.0%)	208 (100.0%)	414 (82.5%)
Per Protocol Set				
no	88 (100.0%)	110 (52.6%)	97 (47.3%)	295 (58.8%)
yes	0 (0.0%)	99 (47.4%)	108 (52.7%)	207 (41.2%)
Safety Analysis Set				
no	88 (100.0%)	4 (1.9%)	1 (0.5%)	93 (18.5%)
yes	0 (0.0%)	205 (98.1%)	204 (99.5%)	409 (81.5%)

Of the 208 patients who were randomized to Zevalin treatment 3 patients never received [90Y]-ibritumomab tiuxetan treatment and therefore were allocated to the control group for the safety analysis. Of these three patients, 2 patients discontinued study treatment due to adverse events (1 patient due to CTC grade 3 neutropenia, and 1 patient due to throat swelling and chills during the Week 1 rituximab infusion, also considered as being a protocol deviation), and 1 patient discontinued due to other reasons (this patient received only one dose of rituximab and no further treatment due to dosimetry results). These three patients were added to the 206 patients that were randomized to the control group.

Table 26: Disposition of patients by treatment group including the number of subjects who prematurely discontinued the study according to the main reason SAF

	Control	Zevalin	Total
Number of subjects	205 (100.0%)	204 (100.0%)	409 (100.0%)
Study course			
completed	199 (97.1%)	200 (98.0%)	399 (97.6%)
prematurely discontinued	6 (2.9%)	4 (2.0%)	10 (2.4%)
withdrawal of consent	4 (2.0%)	1 (0.5%)	5 (1.2%)
protocol deviation	2 (1.0%)	1 (0.5%)	3 (0.7%)
adverse event	0 (0.0%)	2 (1.0%)	2 (0.5%)

Baseline characteristics of the study population

Overall the patients were well matched with respect to Ann Arbor stage at baseline. Over two thirds of the patients in both groups were Ann Arbor stage IV; 66.3% in the control group and 63.7% in the Zevalin group. Approximately one-third of the patients in both groups were Ann Arbor stage III; 30.7% in the control group and 35.3% in the Zevalin group. The Zevalin and Control patients were comparable with regard to: age (mean of 53.2 and 52.1 years respectively). There were slightly more female patients compared with male patients in the study (209 female compared with 200 male patients); 52.5% of the Zevalin patients (107 patients) were female and 47.5% (97 patients) were male. The control group was more equally distributed between male and female patients with 49.8% female (102 patients) and 50.2% male patients (103 patients).

A treatment group comparison with regard to first-line treatment is presented in the table below:

Table 18: Frequency table of actual first-line treatments by treatment - SAF

	Control	Zevalin	Total
Number of subjects	205 (100.0%)	204 (100.0%)	409 (100.0%)
Category of malignancy treatment			
CHOP	58 (28.3%)	64 (31.4%)	122 (29.8%)
CVP / COP	54 (26.3%)	52 (25.5%)	106 (25.9%)
CHOP- like	31 (15.1%)	30 (14.7%)	61 (14.9%)
Fludarabine	11 (5.4%)	11 (5.4%)	22 (5.4%)
Chlorambucil	19 (9.3%)	20 (9.8%)	39 (9.5%)
Rituximab combination	32 (15.6%)	27 (13.2%)	59 (14.4%)

Response to first-line treatment

Patients' actual responses to first-line treatment were different from the response used for randomization because corrections were made after central assessment.

According to the central evaluation of response, 89 patients who were originally randomized as having a PR were later categorized as having a CR/CRu (CR unconfirmed), and 31 patients originally randomized as having CR were later categorized as having a PR. In addition, 4 patients originally randomized as PR were later categorized as being in stable disease. One further patient originally randomized as PR later seen as not assessable during central assessment. This resulted in an overall discrepancy between response as randomized and actual response in the SAF population of approximately 30%.

The frequency of actual responses to first-line treatment stratified by treatment group for the FAS is shown in table below.

Table 21: Actual response to first-line treatment stratified by treatment group FAS

	CR/CRu	PR or worse
Zevalin (N=208)	107 (51.4%)	101 (48.6%)
Control (N=206)	109 (52.9%)	97 (47.1%)

The frequency of CR/CRu after first-line treatment were higher after CHOP, CHOP-like treatment, and fludarabine treatment in patients randomized to the control group; 47.5% for the control versus 37.9% for Zevalin after CHOP; 74.2% for the control group versus 56.6% in the Zevalin group after CHOP-like treatment; 72.7% for the control group versus 54.6% for the Zevalin patients after Fludarabine.

The CR/CRu rate was higher after treatment with CVP/COP, chlorambucil, and rituximab combination therapy for patients randomized to Zevalin: 58.5% for Zevalin versus 45.2% for the control group after CVP/COP treatment; 35% for Zevalin versus 31.6% for the control group after chlorambucil; 75% for Zevalin and 61.3% for the control group after rituximab combination treatment.

Efficacy Results

PFS

With a median follow-up of two years and a maximum follow-up of 5.3 years after study treatment, the median progression free survival (PFS) increased from 13.5 months (control) to 37 months (Zevalin; $p<0.0001$; HR 0.465 according to the primary analysis). For patient subgroups in PR or CR after induction, the median PFS was 6.3 versus 29.7 months ($p<0.0001$; HR 0.304) and 29.9 versus 54.6 months ($p=0.015$; HR 0.613), for the control and Zevalin groups respectively. Figure 1 depicts the Kaplan-Maier plot for the analysis of the primary objective, and a short summary of the main analyses is provided in Table 1.

Fig. 1: Kaplan-Meier plot of progression free survival by treatment

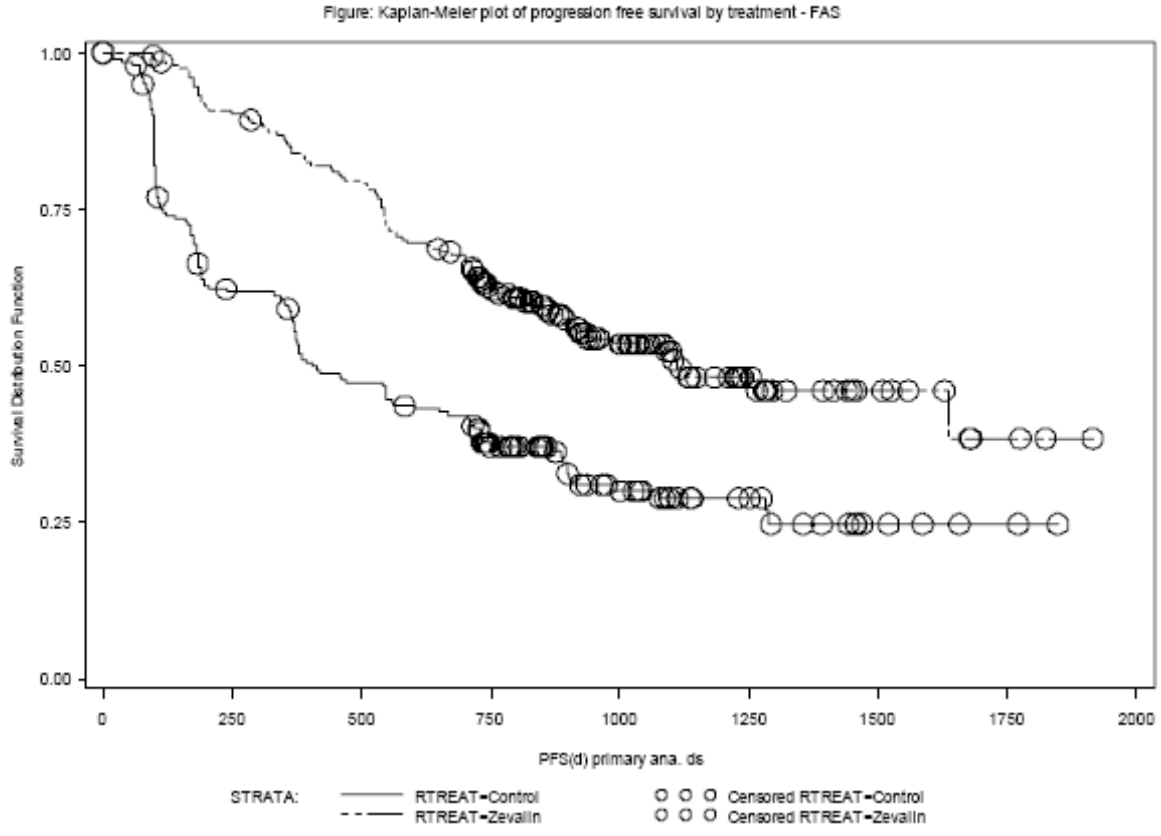

Table 1: Progression free survival (PFS) for the Full Analysis Set (FAS) of patients

Stratum	Zevalin Events/ Patients	Zevalin Median in days (95% CI)	Control Events/ Patients	Control Median in days (95% CI)	Hazard ratio (95% CI)	p-value log rank test	p-value LR test
Overall (unstratified)	95/208	**1111** (901;n.d.)	134/206	**406** (369; 602)	0.445 (0.340; 0.582)	< 0.0001	< 0.0001
First-line treatment strategy							
Immediate treatment	83/183	**1126** (868:n.d.)	118/187	**471** (371;708)	0.491 (0.371; 0.651)	< 0.0001	< 0.0001
Wait and See*	12/25	**1091** (631;n.d.)	16/19	**240** (110;414)	0.247 (0.112; 0.546)	0.0002	0.0005
Response to first-line treatment							
PR	53/ 101	**890** (720; 1126)	78/ 97	**190** (161; 373)	0.304 (0.213; 0.434)	< 0.0001	< 0.0001
CR	42/ 107	**1638** (1104; n.d.)	56/ 109	**897** (708; n.d.)	0.613 (0.410; 0.914)	0.0154	0.0158
Specific first-line treatment							
CHOP	32/ 66	**1091** (845; n.d.)	43/ 61	**379** (188; 649)	0.391/ (0.246; 0.622)	< 0.0001	0.0001
CVP/COP	29/ 53	**868** (712; 1638)	40/ 53	**240** (169;406)	0.383 (0.235; 0.625)	0.0001	0.0001
CHOP-like	10/30	n.d. (786;n.d.)	18/ 31	**887** (353;n.d.)	0.474 (0.219; 1.029)	0.0533	0.0529
Fludarabine	6/ 11	**1260** (392; n.d.)	6/ 11	**739** (106; n.d.)	0.884 (0.283; 2.769)	0.8332	0.8334
Chlorambucil	9/ 20	**n.d.** (532; n.d.)	15/ 19	**362** (96; 750)	0.344 (0.150; 0.793)	0.0088	0.0105
Rituximab combination	9/ 28	**n.d.** (n.d.; n.d.)	12/ 31	**n.d.** (668; n.d.)	0.722 (0.304; 1.714)	0.4583	0.4578

* Wait and See treatment strategy is defined as treatment that was started after more than 183 days after diagnosis

The study was not powered to detect significant differences between subgroups with regard to PFS. Nevertheless, the effect of Zevalin consolidation was so marked, that statistically significant differences could be calculated across almost all subgroups when comparing treatment arms for first-line treatment strategy ("Immediate" treatment and "Wait and See" strategy) or response to first-line treatment (PR and CR). When comparing the differences in PFS according to specific first-line induction chemotherapy, significant effects were seen in patients who received CHOP, CVP/CVP, or Chlorambucil. With CHOP-like treatment borderline significance was seen. Favorable trends were observed in patients who received fludarabine and rituximab containing therapies.

It is noteworthy that Zevalin consolidation therapy significantly prolonged PFS even in the subgroup of patients who achieved a CR after first-line induction treatment suggesting that Zevalin consolidation has a role in eliminating residual disease and thereby enhances PFS outcomes also for patients with very low tumor burden.

Zevalin patients who were PCR negative or positive for the BCL-2 gene rearrangement at the start of treatment had a notably longer median PFS than the corresponding control group patients; 1091 days versus 546 days for BCL-2 negative patients (p-value for log-rank test 0.0008) and 1260 days versus 370 days for BCL-2 positive patients (p-value for log-rank test less than 0.0001) for Zevalin and control patients respectively. The hazard ratios were in favor of Zevalin treatment with 0.561 (2-sided 95%-CI: 0.398; 0.792) for BCL-2 negative patients, and 0.336 (2-sided 95% CI: 0.219; 0.515) for BCl-2 positive patients.

Response to treatment

87.4% of the Zevalin patients achieved a CR/CRu as best response at any time during the study compared with 53.3% of the patients in the control group. The control group had a higher frequency of PR compared with the Zevalin group with 18.9% versus 10.1% respectively.

A treatment group comparison for best response to treatment at any time during the study for the FAS is presented in table below.

Table 5: Best response to treatment by treatment - FAS

	Control	Zevalin	Total
Number of subjects	201 (100.0%)	207 (100.0%)	408 (100.0%)
Best response			
complete response	88 (43.8%)	157 (75.8%)	245 (60.0%)
complete response unconfirmed	19 (9.5%)	24 (11.6%)	43 (10.5%)
partial response	38 (18.9%)	21 (10.1%)	59 (14.5%)
stable disease	1 (0.5%)	0 (0.0%)	1 (0.2%)
progressive disease	37 (18.4%)	1 (0.5%)	38 (9.3%)
relapse	18 (9.0%)	4 (1.9%)	22 (5.4%)

The Zevalin patients consistently showed a notably higher frequency of CR/CRu reported as best response during the study than the control group regardless of the type of first-line therapy received with CRs ranging from 84.6% to 100% for the Zevalin group and 31.6% to 71.0% for the control group.
77.2% of the Zevalin patients (95% CI: 67.80%; 85.00%) and 17.5% of the control patients (95% CI: 10.60%; 26.60%) achieved a CR or CRu after having entered the study with a response different from a CR or CRu. The Zevalin group had proportionately more patients than the control group who improved to CR or CRu after randomization regardless of the type of firstline treatment administered.

Molecular response rate was defined as the percentage of patients who became PCR negative for the Bcl-2 rearrangement after [90Y]-ibritumomab tiuxetan treatment. This was determined from samples of peripheral blood and bone marrow biopsies. Patients were defined as Bcl2-PCR positive, in case of at least one positive assessment after randomization: Patients who had assessments post randomization, but were not defined as positive were defined as negative. The Zevalin group had a higher proportion of patients who became Bcl2-PCR negative in blood and bone marrow samples after randomization compared with the control group; in blood 96.8% Bcl2-PCR negative for Zevalin versus 44.7% for the control group; in bone marrow 75.9% Bcl2- PCR negative for Zevalin versus 38.9% for the control.

The Zevalin group patients had a significantly longer time to subsequent treatment than the control group with 1854 days compared with 993 days for the control group (p-value for the logrank test was <0.0001).

No conclusions can be drawn with regard to improvement in overall survival after Zevalin treatment since the median had not yet been reached in either group due to the low number of deaths; 6 out of 208 in the Zevalin group and 5 out of 206 in the control group.

Patients randomized to Zevalin treatment had a median follow-up time of 822 days compared with 536 days for the control group.

There were no notable treatment group differences with respect to changes in the Euro-QOL overall scores or the Visual analogue scale (VAS) by timepoint or in terms of changes from baseline. This was also true for the analysis of subgroups by gender, age, and firstline treatment. There were no notable treatment group differences with respect to changes in the absolute EORTC QLQ-C30C scores either by timepoint or in terms of changes from baseline for the following scores: Global health status, Physical functioning, Role functioning, Emotional functioning, Cognitive functioning, Social functioning, Nausea and vomiting, Pain, Dyspnea, Insomnia, Appetite loss, Constipation, Diarrhea,

and Financial difficulties. This was also true for the analysis by subgroups for gender, age, and first-line treatment.

Clinical studies in special populations

None performed.

Analysis performed across trials (pooled analyses and meta-analysis)

Not applicable

Conclusion on Efficacy

Zevalin has been shown to be effective in significantly prolonging remission-free survival in patients with follicular lymphomas who achieved a response (CR or PR) after first-line chemotherapy. With a median follow-up of two years and a maximum follow-up of 5.3 years after study treatment, the median progression free survival (PFS) increased from 13.5 months (control) to 37 months (Zevalin; $p<0.0001$; HR 0.465 according to the primary analysis). After consolidation treatment with Zevalin the overall complete response increased from 51.4% to 87.4% (75.8% CR and 11.6% CRu). The PR to CR conversion rates with Zevalin consolidation were of the same magnitude regardless of the first-line treatment administered, which included less potent regimens such as chlorambucil single agent treatment. The conversion rates to CR as well as the final CR rates were similar in the CHOP and CVP/COP pretreated patients; these were the largest pre-treatment groups.

After Zevalin treatment a high proportion of patients changed from Bcl-2 positive to Bcl-2 negative in blood and bone marrow samples (96.8% in blood and 75.9% in bone marrow became Bcl-2 PCR negative).
These results are clearly positive and clinically relevant adding further information to the efficacy database for Zevalin as requested by the CHMP.

Standard of care for patients with follicular lymphoma now includes combination chemotherapy *plus* rituximab, and therefore the protocol amendment is understandable. However, the amendment makes it difficult to assess the benefit of Zevalin consolidation in responding patients where some have received B-cell depleting therapy prior to consolidation and others not. The background chemotherapy is heterogenous and includes CHOP or CHOP-like, CVP/COP and monotherapy with chlorambucil or fludarabine. Relatively few patients received rituximab as add-on the chemotherapy.

Unfortunately, Zevalin consolidation has not been used in combination with the now accepted standard of care, chemotherapy + rituximab, and therefore the SPC information must reflect the insufficient knowledge of the efficacy of Zevalin in rituximab pretreated patients.

1.3 Clinical safety

The Summary of Clinical Safety is based on the results of one multicenter randomized prospective phase III trial (304820) that included 414 patients (208 patients randomized to Zevalin and 206 randomized to no further treatment). The study was designed to determine the efficacy and safety of a single course of [90Y]-ibritumomab tiuxetan given at a dose of 15 MBq/kg (0.4 mCi/kg, maximum 1200 MBq or 32 mCi) in patients with stage III or IV follicular non-Hodgkin's lymphoma who had achieved a PR or CR after first line chemotherapy with either single agent or combination chemotherapies.

Patient exposure

Table 1: Exposure to [^{90}Y]-ibritumomab tiuxetan by dose category - SAF

	Control	Zevalin	Total
Number of subjects	0	204 (100.0%)	204 (100.0%)
Dose exposure of [90Y]-ibritumomab tiuxetan			
> 9.25-12.95 MBq/kg	0	29 (14.2%)	29 (14.2%)
> 12.95-16.65 MBq/kg	0	173 (84.0%)	173 (84.0%)
> 16.65 MBq/kg	0	2 (1.0%)	2 (1.0%)

Adverse events

In study 304820 adverse events (AEs) were reported as either non-hematological orhematological. Table 6 summarizes the overall frequencies of these AEs in each treatment group.

Table 6:Number of patients with AEs (hematological and non-hematological AEs) by treatment - SAF

	Control	Zevalin
Number of patients	205 (100.0%)	204 (100.0%)
Any adverse event	165 (80.5%)	201 (98.5%)
Non-hematolgical AEs	164 (80.0%)	194 (95.1%)
Hematological AE*	30 (14.6%)	148 (72.5%)

Any AE includes both hematological and non-hematological AEs
*Hematological AEs were defined as those AEs involving CTC grade 4 thrombocytopenia, anemia, and leukopenia and all other hematological values that were considered to be clinically relevant. All other abnormal laboratory findings were reported as AEs when considered to be clinically relevant.

Overall 98.5% of the Zevalin patients (201 out of 204 patients) were reported to have had an AEof any kind during the study compared with 80.5% (165 out of 205 patients) of the control group; 95.1% of the Zevalin patients had non-hematological (non-hemotoxic) AEs compared with 80% of the control group; 72.5% of the Zevalin patients had hematological (hemotoxic)AEs compared with 14.6% of the control group.

A treatment group comparison of the frequency of non-hematological AEs during the study is presented in Table 7. Most of the AEs reported occurred more frequently in the Zevalin group than in the untreated control group. The most frequently reported AEs by SOC (those AEs that occurred in at least 20% of either treatment group) were: Infections and Infestations reported in 60.8% of the Zevalin group and 38% of the control group; General Disorders and Administration Site Reactions reported in 58.3% of the Zevalin group and 30.2% of the control group; Gastrointestinal Disorders in 46.6% of the Zevalin group and 24.9% of the control; Musculoskeletal and Connective Tissue Disorders in 46.6% of the Zevalin group and 33.2% of the control group; Skin and Subcutaneous Disorders in 36.8% of the Zevalin group and 16.1% of the control group; Respiratory, Thoracic, and Mediastinal Disorders in 32.4% of the Zevalin group and 16.6% of the control group; Nervous System Disorders in 28.9% of the Zevalin group and 22.4% of the control group.

Table 7: Number of subjects with non- hematological AEs by treatment group and system organ class according to MedDRA - SAF

Events (MedDRA)	Control N=205 (100%)	Zevalin N=204 (100%)	Total N=409 (100%)
ANY EVENT	164 (80.0%)	194 (95.1%)	358 (87.5%)
Blood and lymphatic system disorders	8 (3.9%)	8 (3.9%)	16 (3.9%)
Cardiac disorders	8 (3.9%)	10 (4.9%)	18 (4.4%)
Congenital, familial and genetic Disorders	3 (1.5%)	1 (0.5%)	4 (1.0%)
Ear and labyrinth disorders	3 (1.5%)	10 (4.9%)	13 (3.2%)
Endocrine disorders	2 (1.0%)	6 (2.9%)	8 (2.0%)
Eye disorders	8 (3.9%)	15 (7.4%)	23 (5.6%)
Gastrointestinal disorders	51 (24.9%)	95 (46.6%)	146 (35.7%)
General disorders and administration site conditions	62 (30.2%)	119 (58.3%)	181 (44.3%)
Hepatobiliary disorders	3 (1.5%)	3 (1.5%)	6 (1.5%)
Immune system disorders	2 (1.0%)	7 (3.4%)	9 (2.2%)
Infections and infestations	78 (38.0%)	124 (60.8%)	202 (49.4%)
Injury, poisoning and procedural Complications	14 (6.8%)	39 (19.1%)	53 (13.0%)
Investigations	16 (7.8%)	23 (11.3%)	39 (9.5%)
Metabolism and nutrition disorders	13 (6.3%)	30 (14.7%)	43 (10.5%)
Musculoskeletal and connective tissue Disorders	68 (33.2%)	95 (46.6%)	163 (39.9%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	4 (2.0%)	13 (6.4%)	17 (4.2%)
Nervous system disorders	46 (22.4%)	59 (28.9%)	105 (25.7%)
Psychiatric disorders	30 (14.6%)	39 (19.1%)	69 (16.9%)
Renal and urinary disorders	6 (2.9%)	8 (3.9%)	14 (3.4%)
Reproductive system and breast disorders	18 (8.8%)	25 (12.3%)	43 (10.5%)
Respiratory, thoracic and mediastinal Disorders	34 (16.6%)	66 (32.4%)	100 (24.4%)
Skin and subcutaneous tissue disorders	33 (16.1%)	75 (36.8%)	108 (26.4%)
Surgical and medical procedures	16 (7.8%)	11 (5.4%)	27 (6.6%)
Vascular disorders	16 (7.8%)	34 (16.7%)	50 (12.2%)

Note: events are given as System Organ Class=SOC name. Note: MedDRA = Medical Dictionary for Regulatory Affairs

119 patients in the Zevalin group (58.3%) had AEs that were related to the study treatment compared with 1 patient (0.5%) in the control group. Some of the more frequently reported treatment related AEs reported for the Zevalin group involved General disorders and administration site reactions (36.3%), gastrointestinal disorders (19.1%), Infections and infestations (15.7%), and Skin and subcutaneous tissue disorders (12.7%). None of the control patients were reported to have treatment related AEs for these system organ classes.

The majority of non-hematological AEs reported during the study were of CTC grade 1 or 2 intensity with approximately 65% of the AEs in the Zevalin group and 60% in the control group. CTC grade 3 or 4 non-hematological AEs occurred at a frequency of 28.9% in the Zevalin group and 19.1% in the control group.

CTC grade 3 non-hematological AEs were reported for 48 Zevalin patients and 27 control patients while CTC grade 4 AEs were documented for 12 patients in each treatment group. Notable treatment group differences with respect to CTC grade 3 AEs were seen with respect to Gastrointestinal disorders (8 patients in the Zevalin group compared with 2 in the control group),General disorders and administration site conditions (10 patients in the Zevalin group compared with 1 in the control group), Infections and infestations (14 patients in the Zevalin group versus 5 in the control group; 2 CTC grade 4 infections with Zevalin versus none in the control group), Respiratory and mediastinal disorders (6 patients in the Zevalin group versus 1 in the control group), and Vascular disorders (10 patients in the Zevalin group versus 3 in the control group).

Five patients had CTC grade 3 pyrexia which was considered to be treatment related (3 of these cases were SAEs); all of the patients were reported to have recovered. One patient had CTC grade 4 pyrexia that was considered unrelated to study treatment (not a SAE). CTC grade 3 or 4 pyrexia was also more common in the Zevalin group with 6 patients versus none in the controlgroup.
16 patients in the Zevalin group had CTC grade 3 infections compared with 5 patients in the control group. CTC grade 4 infections were reported for 2 Zevalin patients (both patients had CTC grade 4 neutropenic sepsis, one of these patients also had CTC grade 3 oral candidiasis). Nine of these patients had infections that were considered treatment related. All of these patients were reported to have recovered from these incidents of infection. The rate of infections requiring hospitalization was 7.4%.

A treatment group comparison of the worst hematological toxicity reported during the study for platelets, neutrophils and hemoglobin is presented in Table 13.

Table 13: Worst CTC grade of hematological toxicity based on routine laboratory evaluations of platelets, neutrophils, and hemoglobin

	Control N=205	Zevalin N=204
Platelets		
Grade 1	18 (8.9%)	47 (23.0%)
Grade 2	0	31 (15.2%)
Grade 3	0	120 (58.8%)
Grade 4	0	4 (2.0%)
Neutrophils		
Grade 1	33 (16.3%)	15 (7.4%)
Grade 2	18 (8.9%)	43 (21.1%)
Grade 3	4 (2.0%)	82 (40.2%)
Grade 4	1 (0.5%)	54 (26.5%)
Hemoglobin		
Grade 1	75 (36.9%)	110 (53.9%)
Grade 2	2 (1.0%)	59 (28.9%)
Grade 3	0	6 (2.9%)
Grade 4	0	1 (0.5%)

Numbers indicate the number and percentage of patients in each treatment group

For all patients in the Zevalin group, lymphocyte counts were the earliest to reach nadir at a median of 33 days after starting treatment followed by platelet counts at a median of 49 days, leukocytes at a median of 56 days, hemoglobin values at a median of 69 days, and total neutrophils at a median of 61 days.
In this study a patient was considered to have recovered from hematological values of CTCgrade 2 toxicity or higher when these values returned to CTC grade 1 or CTC grade 0.
For the patients who recovered in the Zevalin group, platelet counts were the quickest to recover at a median of 14 days, followed by neutrophil counts at a median of 15 days, leukocytes at a median of at 21 days, and lymphocytes at a median of 42 days. The median time to nadir for hemoglobin was 0 days indicating that there was no notable change in these values for Zevalin patients who recovered.

Almost one-third (31.7%) of the patients with CTC grade 3 and all 4 patients with CTC grade 4 thrombocytopenia received platelet infusion. Altogether 11% of the patients with CTC grade 3 and 50% of the patients with CTC grade 4 neutropenia received growth factors. Three patients with CTC grade 3 and 1 patient with CTC grade 4 anemia received red blood cell transfusions.

Of the 82 patients with CTC grade 3 neutropenia, 44 patients (54%) were reported to have developed infections at any time during the study; 23 of these 82 patients (28 %) developed infections within the 14 week safety period; only 3 of the 82 patients had CTC grade 3 infections (no grade 4 infections were reported).
Of the 54 patients with CTC grade 4 neutropenia, 41 patients (76%) were reported to have developed infections at any time during the study; 21 of these 54 patients (39%) developed infections during the 14 week safety period; 10 of the 54 patients developed infections of CTC grade 3 or 4 intensity (9 patients with CTC grade 3 and one patient with grade 4). All of these patients were reported to have recovered.

Serious adverse events and deaths

During study 304820 there was one death reported in the control group. This patient developed metastases of the meninges and was reported to have died about one month after entering the study.
During the observation period, 4 deaths were reported in the control group and 6 deaths in the Zevalin group. Three of the deaths in the control group were due to disease progression and one was due to AEs (sepsis). Three deaths in the Zevalin group were due to disease progression and 3 deaths were due to other reasons; one death due to acute sepsis after neutropenia following subsequent chemotherapy, one death due to pancreatic carcinoma, and one death due to acutemyeloblastic leukemia.
Of the 76 Zevalin patients with SAEs, 53 patients had at least one SAE that was considered to be study treatment related; none of the control patients' SAEs were treatment related. All except one of the 53 patients had at least one report involving hematologic toxicities such as neutropenia, leukopenia, lymphopenia, thrombocytopenia, or anemia. Hematologic toxicity is a known side-effect of Zevalin treatment.

Laboratory findings

There were no notable or consistent treatment group differences with regard to high, low, or normal values at any timepoint during the study with regard to levels of alkaline phosphatase, ASAT/GOT, ALAT/GPT, total bilirubin, LDH, c-reactive protein, total protein, albumin, glucose, urea, creatinine, uric acid, potassium, sodium, calcium, and chloride with the majority of the patients (75% to over 90%) in both groups showing normal values.

Safety in special populations

No specific studies performed.

In a clinical trial in which Zevalin was administered as consolidation after prior first line chemotherapy, a higher frequency of severe and prolonged neutropenia and thrombocytopenia was observed in patients who had received Zevalin within 4 months after a combination chemotherapy of fludarabine with mitoxantrone and/or cyclophosphamide compared to those patients who had received any other chemotherapy. Hence, the risk of hematological toxicity may be increased when Zevalin is administered shortly (< 4 months) after fludarabine containing regimens.

Conclusion on safety

From the safety data base for the approved indication, it is known that the primary toxicity is reversible myelosuppression, which typically developed by weeks 4 to 6, reached a nadir at weeks 7 to 9, with recovery within 1 to 4 weeks.

Myelotoxicity is also the most prominent toxicity when Zevalin is used as consolidation after standard chemotherapy regimens for follicular lymphomas. The overall frequency of CTC grade 3 or 4 neutropenia was comparable to previous results; in the present study, CTC grade 3 and grade 4 neutropenia was reported in 40.2% and 26.5% of the patients. 58.8 % of the patients in the Zevalin group developed CTC grade 3 thrombocytopenia; only 2 % developed CTC grade 4 thrombocytopenia. However, the time to marrow recovery may be slightly prolonged in the consolidation setting as compared to monotherapy for refractory patients.

This toxicity is serious but manageable.

Risk Management Plan

The risk management plan (RMP) is summarized in the following table:

Safety concern	**Proposed pharmacovigilance activities**	**Proposed risk minimization activities**
Severe neutropenia and subsequent infection	Routine pharmacovigilance	SPC ("Special Warnings"): SPC ("Undesirable effects"):
Severe thrombocytopenia and subsequent bleeding	Routine pharmacovigilance	SPC ("Dosage and method of administration"): SPC ("Special warnings"): SPC ("Undesirable effects"):
Carninogenicity (secondary malignancies, including AML/MDS)	Routine pharmacovigilance *Enhanced pharmacovigilance*	SPC ("Undesirable effects"):
Congenital anormaly	Routine pharmacovigilance *Enhanced pharmacovigilance*	SPC ("Contraindication"): SPC ("Pregnancy and lactation"): SPC ("Undesirable effects"):

Benefit – Risk assessment

The results from the submitted randomized prospective phase III trial (304820) are clearly positive and clinically relevant adding further information to the efficacy database for the product as requested by the CHMP in the context of the specific obligations for the Marketing Authorisation for Zevalin..

Zevalin has been shown to be effective in significantly prolonging remission-free survival in patients with follicular lymphomas who achieved a response (CR or PR) after first-line chemotherapy. With a median follow-up of two years and a maximum follow-up of 5.3 years after study treatment, the median progression free survival (PFS) increased from 13.5 months (control) to 37 months (Zevalin; $p<0.0001$; HR 0.465 according to the primary analysis). After consolidation treatment with Zevalin the overall complete response increased from 51.4% to 87.4% (75.8% CR and 11.6% CRu). The PR to CR conversion rates with Zevalin consolidation were of the same magnitude regardless of the first-line treatment administered, which included less potent regimens such as chlorambucil single agent treatment. The conversion rates to CR as well as the final CR rates were similar in the CHOP and CVP/COP pretreated patients; these were the largest pre-treatment groups.
After Zevalin treatment a high proportion of patients changed from Bcl-2 positive to Bcl-2 negative in blood and bone marrow samples (96.8% in blood and 75.9% in bone marrow became Bcl-2 PCR negative).

The benefit of adding Zevalin to a rituximab containing regimen is currently unknown. The rituximab naïve and rituximab pre-treated patients in the submitted randomized prospective phase III trial (304820) should have been considered as separate groups, and the results in terms assessment of primary endpoint should be analyzed separately (and power calculations should be (have been) amended accordingly). Only a small proportion of patients (N=59) in the submitted trial had received rituximab-chemotherapy combinations. The submitted trial was not designed to address that question.

It may be that adding Zevalin to rituximab pretreated patients will not add further to clinical benefit or that safety profile is different for these more immunocompromised patients.

Although it is agreed that achievement of CR is associated with longer duration of response, the benefit/risk ratio of adding Zevalin to the now-standard rituximab-chemotherapy regimens cannot be addressed with the currently submitted data.
The submitted additional abstract data (Jankowitz; J Clin Oncol 2007, 25: 18S; 8005) (Shipley and et al; JCO 2005; 23: 16S: 6577) suggest that the complete remission rate (the primary endpoint) was increased was increased when 90Y ibritumomab was added to the schedule, however, the data do not allow assessment of benefit- and (longer term) risk in these patients. Both studies were non randomized phase II studies (thus lacking a control arm) and results were only reported in abstract form. Furthermore, in both studies no standard chemotherapy regimens for the target population with follicular NHL was used (only 3 courses of R-CHOP and 4 weekly courses of rituximab followed by 3 courses of R-CHOP respectively). Moreover, no effects on PFS and overall survival were addressed requiring longer term follow up.

Therefore, the therapeutic indication is worded as follows: *The [90Y]-radiolabelled Zevalin is indicated as consolidation therapy after remission induction in previously untreated patients with follicular lymphoma. The benefit of Zevalin following rituximab in combination with chemotherapy has not been established.*

Myelotoxicity is the most prominent toxicity when Zevalin is used as consolidation after standard chemotherapy regimens for follicular lymphomas. The overall frequency of CTC grade 3 or 4 neutropenia was comparable to previous results; in the present study, CTC grade 3 and grade 4 neutropenia was reported in 40.2% and 26.5% of the patients. 58.8 % of the patients in the Zevalin group developed CTC grade 3 thrombocytopenia; only 2 % developed CTC grade 4 thrombocytopenia. However, the time to marrow recovery may be slightly prolonged in the consolidation setting as compared to monotherapy for refractory patients. This toxicity is serious but manageable and reversible.

The prolongation in PFS as compared to an acceptable safety profile for an anticancer medicinal product indicates a positive risk-benefit balance.

However, Zevalin consolidation has not been used in combination with the now accepted standard of care, chemotherapy + rituximab, and therefore the SPC information must reflect the insufficient knowledge of the efficacy of Zevalin consolidation in rituximab pretreated patients.

The MAH will monitor late occurring events such (opportunistic) infections including progressive multifocal leukoencephalopathy (PML) and malignancies (haematologic and non-haematologic) in subsequent PSURs.

II. CONCLUSION

On 19 March 2008 the CHMP considered this Type II variation to be acceptable and agreed on the amendments to be introduced in the Summary of Product Characteristics, Annex II and Package Leaflet.