SCIENTIFIC DISCUSSION

This module reflects the initial scientific discussion for the approval of Zevalin. For information on changes after approval please refer to module 8.

1. Introduction

Non-Hodgkin Lymphomas (NHL) as a group is the most common malignant haematologic disease.

NHL is the common name for a cluster of related but individual diseases, which have neoplastic transformation of a lymphoid cell as the common denominator. Eighty- five percent are B-cell derived, and 15% are of T-cell origin. Classification schemes have been based on histopathology and cytopathology, supplemented with immunopathology and molecular pathology. The use of the new DNA-arrays might lead to a further refinement in classification. The International Working Formulation (IWF) was standard in USA when the Zevalin studies were designed and therefore used for enrolment. Internationally it was followed by the REAL classification and later by its slightly modified version, the WHO classification. Translation of diagnoses within the systems is possible for most but not all classes.

The so-called indolent lymphomas or low-grade lymphomas (including small lymphocytic lymphoma, lympho-plasmacytoid lymphomas, follicular lymphomas, MALT lymphoma) comprise about 40% of the B-cell lymphomas with follicular lymphomas being the most frequent. In the present clinical studies of Zevalin 65-95% of the patients had follicular lymphoma.

The diagnosis of NHL is primarily based on lymph node biopsy and immuno-pathology and will today often be supplemented by molecular analyses. Cytogenetic changes are characteristic for some of the lymphomas, e.g. t(14:18) and the Bcl-2 gene rearrangement in follicular lymphoma.

The NHL's are disseminated diseases at diagnosis, either stage III (involvement of lymph node regions on both sides of the diaphragm) or IV (spread to extra lymphatic sites), while localized stages I and II are rare. In the present clinical studies around 90% of the patients had stage III/IV disease. Most patients with low-grade NHL are asymptomatic. Constitutional symptoms are seen in 10-15% of the cases.

Even within a single histologic NHL entity the clinical course can be very variable. The general pattern is a sequence of treatment responses and relapses, where response rates tend to diminish and response durations are becoming shorter following each new relapse and remission induction. For follicular lymphomas a final event is the biological tumour progression, where the lymphoma transforms to a more malignant subtype and/or involves unusual extra nodal sites. The survival is then usually only a few months. Prognostic factors have been identified in newly diagnosed patients. An international study of large cell lymphomas resulted in the International Prognostic Index (IPI), which led to a very useful and now widely accepted separation into prognostic groups. The index has also been useful in low-grade NHL. Negative factors comprise high age (>60), poor performance status, advanced stage (III/IV), several extra nodal sites (> 2), high levels of LDH.

The treatment of low-grade lymphomas has not been standardized. Initial therapy can vary from observation alone (in some asymptomatic patients only) to monotherapy with alkylating agents (probably the most used regimen) to 2-, 3- or 4-drug combinations of cyclophosphamide, vincristine, Adriamycin and prednisolone (with or without subsequent interferon-alfa), with overall response rates up to 80-90%, CR rates of 50-60% and response duration of 1-4 years. More intensive programs do not improve survival. Relapse treatment has also not been standardised and is depending on response to and response duration of initial therapy, growth pattern of the lymphoma, IPI score and symptoms. Repetition of the initial therapy is one option. Change to the purine analog fludarabine is another option. In selected patients myeloablative therapy with haemopoietic stem cell support is still investigative due to lack of documented durable remissions.

The anti-CD20 chimeric monoclonal antibody, rituximab, which has received Marketing Authorisation for treatment of relapsing patients, results in response rates of about 50% with a median time to progression of about 12 months in responding patients.

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Since all the treatment regimens used so far have only been palliative with decreasing success rate with each new relapse, more effective treatment regimens are needed.

Zevalin contains ibritumomab, an IgG1 kappa immunoglobulin produced in Chinese hamster ovary (CHO) cells which reacts specifically with the CD20 antigen found on the surface of normal and malignant B lymphocytes (inc. mature B cells, activated proliferating B cells and differentiating B cells), targets of its cytotoxicity. Ibritumomab is conjugated via a linker to the chelating agent MX-DTPA (tiuxetan), which securely chelates the radioisotope yttrium-90. Tiuxetan is stably bound to the antibody via a covalent, urea type bond.

Ibritumomab tiuxetan achieves selective targeting CD20+ cells, which are inherently sensitive to radiation. The radionucleide yttrium-90 (half-life of 64 hours) emits pure high-energy beta radiation with a local tissue penetration (5 to 10 mm) and effect.

The proposed Zevalin regimen combines the antibody-based tumour cell killing with rituximab with an antibody based radioimmuno-therapy and thus further tumor-cell killing, but with a different mechanism of action (radiation).

2. Part II: Chemical, pharmaceutical and biological aspects

Composition. Zevalin, supplied as kit for radiopharmaceutical preparation for intravenous use, contains four components, all the non-radioactive ingredients necessary to produce a single dose of [^{90}Y] ZEVALIN.

1 vial of ibritumomab tiuxetan 1.6 mg/ml

1 vial of 50 mM sodium acetate

1 vial of formulation buffer

1 empty reaction vial

Yttrium-90 [^{90}Y] is not part of the kit and should be provided by the end-user.

Composition of the components	Name of ingredient	Quantity pr. ml	Function	Reference to standards
1. Ibritumomab tiuxetan				
1	Ibritumomab tiuxetan	1.6 mg	Active substance	In house
2	Sodium chloride	8.8 mg	Isotonizing agent	Ph.Eur.
3	Water for injections	q.s.	Solvent	Ph.Eur.
2. 50 mM Sodium Acetate				
1	Sodium acetate (amount calculated as trihydrate)	6.8 mg	Buffering agent	Ph.Eur.
2	Water for injections	q.s.	Solvent	Ph.Eur.
3. Formulation buffer:				
1	Albumin Human	74.97 mg	Radioprotectant	Ph.Eur.
2	Sodium Chloride	7.56 mg	Isotonizing agent	Ph.Eur.
3	Sodium phosphate dibasic (dodecahydrate)	2.06 mg	Buffering agent	Ph.Eur.
4	Pentetic acid (DTPA)	0.40 mg	Chelating agent	USP
5	Potassium dihydrogen phosphate	0.19 mg	Buffering agent	Ph.Eur.
6	Potassium chloride	0.19 mg	Isotonizing agent	Ph.Eur.
7	Sodium Hydroxide 1N	q.s.	pH adjustment	Ph.Eur.
8	Hydrochloric Acid 1N	q.s.	pH adjustment	Ph.Eur.
9	Water for injections	q.s.	Solvent	Ph.Eur.

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Container

The container is the same for all components; a colourless Type I glass vial, teflon-faced gray bromobutyl rubber stopper, alu-cap, different coloured flip-off seal.

Clinical Trial Formula

There were no changes in composition of the intended commercial product from the phase III clinical trials for both ibritumomab tiuxetan and the 50mM Sodium Acetate components. For the Formulation Buffer component, there were two minor changes to provide conformity to pharmacopoeial monographs.

Data provided showed that the changes proposed do not affect the integrity and/or specificity of the antibody.

The manufacturing process for the ibritumomab tiuxetan solution has been changed to improve consistency. The original murine hybridoma was replaced by an ibritumomab producing CHO cell line during the initial preclinical and clinical trials. The ibritumomab producing CHO clone was manufactured by IDEC Pharmaceuticals Corp., San Diego, CA, USA (IDEC) and a master cell bank was established. The MCB was established and used for phase II and III clinical trials and is also used for the intended commercial product.

The commercial product will be manufactured by IDEC with the fill and finish conducted by Baxter Pharmaceutical Solutions LLC, Bloomington, IN, USA.

Ibritumomab tiuxetan has been shown to be comparable regardless of place of manufacture identified by equivalent molecular weight, amino acid composition, amino acid sequence, radioincorporation and binding. Post translational modifications were also comparable as identified by equivalent oligosaccharide profile, compositional monosaccharide content and N- and C-terminal processing.

The 50 mM sodium acetate bulk solution and the formulation buffer bulk solution are manufactured by IDEC Pharmaceuticals. The fill and finish as well as the manufacture of the reaction vial take place at Baxter Pharmaceutical Solutions LLC, Bloomington, IN, USA.

Production and Control of Starting Materials

Ibritumomab tiuxetan, IDEC-2B8-MX-DTPA is defined as the active substance in Zevalin. It is obtained by chemically linking the monoclonal antibody ibritumomab (IDEC-2B8) to the amino directed bifunctional chelate MX-DTPA.

Specifications and routine tests

A batch of antibody is defined as the product of a single inoculation step in the fermentation bioreactor followed by fermentation, harvest and purification steps. Specifications are established based on the batches produced during development and the qualification and consistency lots. They cover all the important quality aspects. The current limits for selected items will be assessed for relevance after gaining more manufacturing experience.

Development genetics

The monoclonal antibody ibritumomab is produced by genetically engineered Chinese Hamster Ovary cells.

The ibritumomab expression construct, containing a murine anti-CD20 light chain gene and a murine anti-CD20 heavy chain gene, has been thoroughly documented by the manufacturer and is described in the dossier.

The manufacture of ibritumomab at IDEC Pharmaceuticals begins with a genetically engineered Chinese Hamster Ovary master cell bank (MCB). The MCB has been thoroughly characterised according to current ICH guidelines (Q5D). The MCB was prepared without the use of animal- or human-derived components.

The manufacturer has demonstrated the integrity of the expression construct in the MCB following extended production culture according to current ICH guidelines (Q5B). No changes in integration sites, copy number, or immunoglobulin sequences were observed between MCB and EOP cell.

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Furthermore, tryptic map analysis of the immunogloblin gene protein product further confirmed genetic stability.

Genetic stability:

End of production cells (EOP) were characterised.

Cell Bank System

The cell bank system consists of a Master Cell Bank. No working cell bank has been established. The MCB inventory will ensure adequate supply.

A description of the characterisation of the MCB and the testing for adventitious contaminants of the MCB and End of Production (EOP) has been provided. The manufacturer has performed the necessary studies to confirm the integrity of the expression construct and the absence of endogenous viruses according to current ICH guidelines.

Production

The antibody ibritumomab is manufactured by IDEC Pharmaceutical Corporation, San Diego, CA.

Fermentation and Purification

In vitro viral and mycoplasma testing is performed by a qualified contract laboratory.

Flowchart of the fermentation and harvesting of ibritumomab has been provided in the dossier.

The purification process is based on a combination of chromatographic techniques, as well as viral inactivation and removal steps. An ultrafiltration/diafiltration step is performed to concentrate the antibody and perform buffer exchange. The solution is stored at 2-8 ^{o}C.

The presented holding times between the respective purification steps were validated and are found acceptable.

Sanitation of the chromatographic columns have been satisfactorily described as well as a maximum number of cycles have been proposed on the basis of studies performing repeated cycles for each chromatographic resins.

Conjugation of the Antibody

The manufacture of bulk ibritumomab tiuxetan at IDEC begins with the chemical reaction of ibritumomab with the heterobifunctional reagent MX-DTPA, a derivative of diethylenetriaminepentaacetic acid (DTPA).

An adequate description of the synthesis of MX-DTPA and specification are included in the dossier.

A flow chart of the conjugation of the antibody, and the critical parameters of the reaction are included in the dossier. Data demonstrate that the process limits specified in the manufacturing records will allow for optimal radioincorporation and CD20 binding activity.

The conjugated antibody, IDEC-2B8-MX-DTPA, is filled into sterile-vented, sterilized dedicated containers for storage, until is filled and finished at Baxter Pharmaceutical Solutions LLC, Bloomington, IN, USA. Storage time and conditions are adequately described.

Process Controls

A list of in-process controls performed during the manufacture of IDEC-2B8, conjugation, and final filling steps are included in the submitted documentation and are found acceptable.

Characterisation

The antibody, ibritumomab is a 1316 amino acid murine IgG1 antibody consisting of two light chains of 213 residues and two heavy chains of 445 residues. The antibody contains the entire murine light and heavy chain variable regions and the murine gamma 1 heavy chain and kappa light chain constant regions. The molecular weight calculated from the primary sequence of the reduced, non-glycosylated form is 144 248 Daltons.

A variety of methods were applied to confirm the primary, secondary, tertiary and quaternary structure of IDEC-2B8 as well as its biological activity.

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The glycosylation patterns were shown to have some minor variability caused by different glycoforms. The charge microheterogenicity was demonstrated to be as expected batch to batch consistent by appropriate chromatographic techniques. The applicant has sufficiently justified that the microheterogeneities that have been observed have no impact on the binding activity of IDEC-2B8.

A summary of all characterization studies including the obtained results has been provided by the applicant and data have shown comparability and consistency between lots.

Study reports of biological activity were performed with antibody obtained from both the initial murine hybridoma cell line and the CHO cell line. An overview on cross-reactivity with human tissues is provided in the Expert report on the toxico- pharmacological (non clinical) documentation.

The active substance ibritumomab tiuxetan is obtained by reaction of the antibody with the chelator, MX-DTPA. A schematic presentation of the reaction has been given. The consistency of the conjugation process is controlled by the relevant parameters. The applicant has committed to submit a report on the re-evaluation of the specification after a defined number of batches.

Data on characterisation, comparability and consistency confirmed that the overall structure was not negatively affected by the conjugation reaction.

Essentially the same methods used for characterisation of the antibody were used to characterise the conjugated antibody. The results showed no difference between IDEC-2B8 and IDEC-2B8-MX-DTPA. The changes observed were directly related to the conjugation ratio and the isoelectric focusing patterns were similarly affected.

Secondary and tertiary structure were shown not to be affected by the conjugation. The applicant has sufficiently shown that the conjugation reaction does not induce noticeable changes in the microheterogeneties that are present in the antibody. Binding activity studies with CD20 positive cells demonstrated that the conjugation reaction of IDEC-2B8 with MX-DTPA is associated with a small loss of immunoreactivity. The binding was however consistent with the reference material.

After radiolabelling the binding activity was not negatively impacted and the stability of the labelled complex in vitro was acceptable. Results of all studies are provided and found acceptable.

Analytical validation

Validation reports for all analytical methods applied to the antibody and the conjugated antibody are provided and found acceptable.

Test results demonstrate that the batch chosen to serve as reference standard is suitable with regard to structural and biochemical characteristics as well as potency and purity.

Process Validation

The process validation demonstrated that the process is able to reduce potential impurities such as host cell protein, host cell DNA, reagents. It is found acceptable that test for DNA and reagents used during manufacturing is not carried out routinely.

Data demonstrating the removal of residual MX-DTPA for three batches produced at full-scale have been submitted. The results are similar to the results of the small-scale validation. In addition, results of finished product release testing were all within specifications.

Even though batch results have shown that bacterial endotoxin is reduced below the detection limit during the manufacturing process a spiking experiment was performed to demonstrate the capability of a defined chromatographic step to reduce potential endotoxins. The study showed an acceptable reduction factor.

Excipients

All excipients used in the ZEVALIN kit except the pentetic acid (USP) comply with Ph. Eur. requirements.

None of the excipients used are animal or human-derived, with the exception of Human Albumin, which is a component of the Formulation Buffer vial.

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All routine test methods utilized for the evaluation of the excipients are described in the pharmacopoeia.

Human albumin is used as stabiliser in the formulation buffer to protect from radiolysis. A 20% human albumin solution complying with Ph.Eur. is used. A separate dossier including a plasma master file has been submitted in accordance with current recommendations. The expiry date of the Zevalin kit component "formulation buffer" will be for the time being limited by the expiry date of HSA batch used.

Finished Product

Development Pharmaceutics

The selected formulation of ibritumomab tiuxetan is ready to use and was chosen to retain potency, purity and protein integrity. A 0.2 µm filter is required for the administration of the finished product. This is stated in the SmPC text under the heading "Dosage".

Because of the protein present in the solution, it can not be terminally sterilised.

The 50 mM sodium acetate component is used to adjust pH of the yttrium-90 radioisotope solution in order to facilitate radioincorporation with ibritumomab tiuxetan. This component is terminally sterilised.

The formulation buffer component is added at the end of the radiolabelling reaction to stabilise the radiolabelled product and to provide buffering capacity around pH 6.5. Human Albumin serves as a radioprotectant from autoradiolysis of the labelled antibody. DTPA is present to chelate any trace amounts of free yttrium-90 remaining after reaction, to enhance rapid excretion. Because of the protein present in the solution it can not be terminally sterilised.

The empty reaction vial is included to allow preparation of the radiolabelled dose. It can not be terminally sterilised as there is no liquid present to perform moist heat sterilisation and the rubber stoppers and flip-off seals can not withstand irradiation or dry heat sterilisation.

Method of Preparation

The manufacture of ibritumomab, ibritumomab tiuxetan and of the other bulk components is performed by IDEC Pharmaceuticals. The bulk solutions are shipped to Baxter Pharmaceutical Solutions, LLC, Bloomington, IN, USA, this being under contract to IDEC to manufacture the four kit components (fill-finish). Both IDEC Pharmaceuticals and Baxter operate under CGMPs.

IDEC releases the kit components to Schering AG, Berlin, Germany, where they are labelled, packaged, re-tested and released as a kit for radiopharmaceutical preparation to distribution in the EU.

Schering AG, Berlin, Germany, performs packaging and EU release of the Zevalin kit.

Manufacturing Process

Flow charts of the manufacturing process and the filling have been submitted.

Manufacture of the antibody and conjugation with the chelator is adequately described. Adequate in-process controls are in place throughout the manufacturing process, including control of the filter integrity of all filters prior use. The filling process uses aseptic techniques and final sterile filtration prior to filling into sterile, depyrogenated vials.

The manufacture of 50 mM sodium acetate is performed using conventional techniques. The 50 mM sodium acetate is terminally sterilised.

The formulation buffer is manufactured using conventional aseptic techniques and final sterile filtration prior to filling into sterile, depyrogenated vials.

The empty reaction vial is manufactured using conventional aseptic techniques, using sterile, depyrogenated vials, and sterile stoppers.

In accordance with the Guideline, radiopharmaceuticals information on the final processing required to produce the radioactive medical product has been provided and it is included in the SPC.

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Transportation of the kit components to Schering AG and packaging of the kit has been adequately described.

Validation of the Process

The validation data support that the process will manufacture a product of consistent quality.

Specifications and Routine Tests

Release and shelf life specifications for ibritumomab tiuxetan, sodium acetate, reaction vial and formulation buffer have been provided.

The specifications have been found acceptable. The applicant has committed to evaluate the specification limits for certain items after more manufacturing experience has been gained.

Appropriate documentation has been submitted for finished product release testing, showing that methods in use have been successfully transferred.

Control methods

All testing methods are provided and found acceptable.

Analytical Validation

Validation reports for all tests performed on ibritumomab tiuxetan, sodium acetate, formulation buffer and reaction vial are provided and found satisfactory.

Reference material

A reference standard lot was established. The potency of the reference standard is set at 100% and assigned a specific activity of $1x10^3$ units/mg.

Stability and procedures for requalification/replacement of reference material have been sufficiently described.

Stability

Stability studies have been conducted in accordance with ICH guidelines.

Based on the available data provided, storage times for the formulation buffer and for the sodium acetate bulk solutions, until fill/finish at the contractor Baxter are acceptable.

Stability Tests on Active substance

Ibritumomab and ibritumomab tiuxetan

Based on the available data provided, the proposed storage time for ibritumomab and ibritumomab tiuxetan bulk substance at the conditions specified can be accepted.

Stability Tests on the Finished Product

On the basis of the available data, the shelf-life as provided in the SPC is acceptable

Conjugated antibody ibritumomab tiuxetan:

A stability protocol was conducted in accordance with ICH guidelines.

A shipping simulation study was conducted and results show that IDEC-2B8-MX-DTPA can be shipped to distribution sites under ambient temperatures.

Stability studies will continue, in accordance with the stability protocol. A commitment to submit real-time stability results of the ongoing stability studies has been provided.

Shelf life of the radiolabelled product: A shelf life of 8 hours for the radioactive labelled ibritumomab tiuxetan can be accepted.

In the SPC it is recommended to use the product immediately after radiolabelling.

Virological Documentation

The tests indicated comply with the NfG “Production and quality control of monoclonal antibodies”.

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HAP testing was originally performed on the MCB using a modified HAP/MAP testing protocol based on the recommendations found in the "Points to Consider in the Characterisation of Cell Lines to Produce Biologicals", 1993. IDEC has since performed additional antibody production testing to include RAP tests. The testing conducted is considered consistent with that recommended in the "Note for guidance on production and quality control of monoclonal antibodies" (Revised 1995).

The choice for cell cultures used for in vitro testing has been adequately justified. This includes MRC-5 and Vero cell lines routinely utilized for the detection of bovine viruses.

Viral validation studies have been performed for different steps of the manufacturing process. The model viruses were chosen for their range of physico-chemical characteristics and MuLV furthermore represents potential retrovirus contaminants in the bulk harvest.

Only steps, which potentially contribute, to clearance of that particular class of viruses were challenged. The studies were performed using suitable virus assays.

The scale down parameters and critical operation parameters were conserved to ensure that the down scaled virus validation studies were representative of the commercial process.

The manufacturing process has satisfactorily demonstrated to inactivate/remove a range of model viruses.

Study reports for the viral validation studies are provided and found satisfactory.

Viral clearance from chromatographic columns:

The ability of the chromatographic resins to clear viruses at the maximum number of cycles was confirmed with the viral validation studies performed with chromatographic resins used for a defined number of cycles.

The company's proposed maximum number of cycles for these columns is found acceptable.

Satisfactory log reduction factors were obtained from sanitation solutions used to inactivate viruses for the chromatographic resins.

Each lot of pre-harvest cell culture fluid is tested to ensure the freedom of adventitious virus (including Minute Virus of Mice) and mycoplasmas.

The analytical methods have been satisfactorily validated.

Extra PCR methods for the detection of Minute Virus of Mice and Mycoplasma are performed as rapid analysis for the mentioned viruses.

During the clinical trials the patients were observed for infections. There is no evidence that Zevalin administration can cause viral infections due to contamination of the product.

There are no specific plans with regard to viral pharmacovigilance, which is considered acceptable.

Conclusion

The Quality documentation is in general acceptable and EU guidelines are fulfilled. During the evaluation process, a number of questions were raised regarding specifications limits. Most of these have been adequately solved, while some remaining issues will be addressed on an ongoing basis.

3. Part III: Toxico-pharmacological aspects

Pharmacodynamics

Ibritumomab is conjugated via a linker to the chelating agent DTPA (tiuxetan), which securely chelates the radioisotope yttrium-90. Ibritumomab tiuxetan achieves selective targeting CD20+ cells, which are inherently sensitive to radiation. There is not evidence of antibody dependant cellular cytotoxicity. The radionuclide yttrium-90 (half-life of 64 hours) emits pure high-energy beta radiation with a local tissue penetration (5 to 10 mm) and exerts the cytotoxic effect.

- *In vitro* studies

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The *in vitro* immune reactivity and specificity studies both of the murine hybridoma derived antibody and of the CHO derived one – intended for the clinical use – showed that binding was only found to freshly isolated human B-cells, and revealed no species cross-reactivity. Studies where provided also indicating an equivalence of the hybridoma-produced and the CHO-produced ibritumomab with respect to specificity for the target antigen.

Studies of cytotoxic effect in two CD20 positive human cell lines could not demonstrate any antibody dependant cellular cytotoxicity (ADCC) and complement-mediated cytotoxicity.

Apoptosis could not be induced by ibritumomab in its monomeric form, but only after hyper-cross-linking via secondary antibodies.

Further characterisation studies were made both with the CHO-derived antibody alone and with the antibody-tiuxetan conjugate. The CHO derived antibody maintained the specificity for the CD20 antigen. The antibody and its conjugate showed a similar binding curve and a similar staining pattern in a number of different human tissues (lymphoid cells in bone marrow, lymph nodes, lymphoid nodules of the small and large intestine, thymus and tonsils and in the white/red pulp of the spleen). No reactivity was seen on other cells such as epithelia, neuro-ectodermal structures, mesenchymal tissues.

- *In vivo* studies

The only suitable animal model is the Cynomolgus monkey. Since there is no valid lymphoma model in monkeys a mice model was also used to investigate the effect of radio-labeled antibodies on tumours and also for bio-distribution studies and for estimation of the radiation doses to normal tissues.

Repeated administration in monkeys (7 doses over 13 days) of doses of 0.003, 0.03, and 0.3 mg/kg had only little effect on the circulating B-cells and no other significant abnormalities were found. Repeated administration of higher doses (0.6 up to 10 mg/kg) with different schedules led to a distinct depletion of circulating B-cells with up to >50% loss when compared to pre-treatment values with a recovery around day 50. When pre-treatment with rituximab was used in these experiments the depletion was almost complete, more prolonged and evident for all sites of B-lymphocytes. A saturation of the B-cells and antibody excess in plasma was seen from a dose of 0.6 mg/kg and upward. No effect was seen on T-cells and no adverse effects were noted. All monkeys developed monkey anti-mouse antibodies (MAMA) against the ibritumomab tiuxetan. The clinical preparation, the radioactive [^{90}Y]-conjugate, has not been examined in the monkey. Such a study, with or without pre-treatment with rituximab, would have given valuable information on the effect of the antibody delivered radiation on the decline and recovery times of the normal B-cells and would serve as a useful basis for examination of the effect in human lymphoma patients where also neoplastic B-cells are present.

In the mice model (Burkitt lymphoma cell line Ramos transplanted s.c. into athymic mice), in a saline controlled study with radio-labelled Zevalin, all animal groups – including the saline controls - showed reduced tumour growth, but no difference was seen between the three groups. As an antineoplastic effect was not demonstrated in the nude mouse model, these experiments should have been expanded.

Pharmacokinetics

The number of pharmacokinetic studies performed in animals was limited due to the lack of relevant animal models and due to the well documented pharmacokinetic profile of Zevalin in patients. Several batches of both murine and CHO-derived antibodies were used; two suppliers of yttrium-90 and two methods of purification of the final radioactive product were used. Differences were tested in comparative studies and were generally found to be without significant influence on the overall results.

Two groups of cynomolgus monkeys received on day 1 and 8 either an i.v. dose of non-radioactive [^{89}Y] ibritumomab tiuxetan 1.5 mg/kg alone (group 2 in Table below) or in combination with 30 mg/kg rituximab (group 3 in Table) and the pharmacokinetic profile was evaluated following the first dose. Co-treatment with rituximab increases the serum level and the half-life of the conjugate is prolonged from 17 to 73 hours:

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	Pharmacokinetic Parameters of [^{89}Y] ibritumomab tiuxetan				
Group	Cmax µg/mL	AUC µg.hr/mL	T½ hours	CI mL/hr	Vss mL
2	38.68	1030.17	17.19	5.02	126.41
3	49.95	2561.28	73.70	1.75	165.81

Bio-distribution studies with the radioactive compound were carried out in mice, in which the B-cells cannot bind the ibritumomab antibody. Estimation of human tissue radiation doses were made on the basis of this model, which has some limitations since the human situation implies radiation from both circulating and fixed antibody-complexed B-cell compartments of both neoplastic and normal nature. The treatment in humans requires two steps. The first is an attempt of clearing the blood of circulating normal and malignant B-cells using rituximab. The second step is after another dose of rituximab followed by the radiolabelled Zevalin. At the timepoint of the Zevalin injection, the circulating normal or malignant B-cells should be substantially reduced, allowing targeting of the B-cell lymphomas.

Toxicology

In an early acute toxicity study cynomolgus monkeys received a single i.v. dose of 10 mg/kg (480 times the suggested clinical dose in term of bodyweight) of murine hybridoma cell derived ibritumomab (non-conjugated). The only finding was a distinct depletion of the circulating B-cells without full recovery at day 52 in one of the animals.

Three products were examined in repeated dose studies: hybridoma-derived antibody, hybridoma-derived [^{89}Y]-labeled conjugate and CHO-derived [^{89}Y]-labeled conjugate. Moderate, but variable decrease in circulating B-cells was a consistent finding in all experiments. Pre-treatment with rituximab 30 mg/kg together with the 1.5 mg/kg of the conjugate led to a more pronounced and prolonged depletion of B-cells both in the circulation and in the tissues from day 2 with only a trend towards recovery at day 55.

Reproductive and developmental studies were not performed since no cross-reactivity of the antibody with human tissues other than the B-lymphocytes was seen. The antibody is therefore not suspected to have any specific effect on male or female fertility. However, a damaging potential is present from the ionizing radiation from yttrium-90. Zevalin is contraindicated during pregnancy and lactation. Due to the radiation it is recommended that male patients use contraceptive measures during treatment and for 12 months post treatment (20 times the half-life of yttrium-90 plus 3 spermatogenesis cycles). Likewise women of childbearing potential should use contraceptive methods for 12 months (SPC sections 4.4 & 4.6).

Mutagenicity studies have not been performed since it is generally accepted, that it is not applicable for biotechnological products as monoclonal antibodies. However, a mutagenic and a carcinogenic potential from the ionizing radiation from yttrium 90 cannot be ruled out. Again the estimated absorbed radiation dose to human tissues with the single use seems acceptable when the indication is considered.

No local tolerance adverse effects have been noted following i.v. administration. No other studies were performed.

Risks from the radiolabel: Due to the high rate of incorporation of the yttrium-90 (at least 95 % required for therapeutic use) little free yttrium-90 is expected to occur in the formulation and it will be complexed to the excess DTPA in the formulation buffer and therefore be excreted quickly after administration. Since the binding of the yttrium-90 in the ibritumomab-linker complex is very stable, the risk of incorporation of free yttrium-90 in any tissue is low. The radiation of non-target organs will therefore mainly occur by the circulating labelled antibody. Based on the mouse data described above the radiation dose to normal human tissue is expected to be not higher than 2000cGy for organs and 300cGy for bone marrow. The decay product of yttrium-90, zirconium-90, is a stable isotope with low toxic potential.

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In part of the clinical studies (imaging/ dosimetry) labelling of ibritumomab tiuxetan is done with 5-mCi indium-111. It has a short half-life, 2.8 days, emits gamma radiation and X-rays, and is considered a safe standard drug for diagnostic imaging. The risk is here restricted to the radiation derived from the circulating radiolabelled antibody and was by extrapolation from the mouse data found to be within acceptable limits.

Discussion on toxico-pharmacological aspects

The in vitro and in vivo pharmacodynamic studies have confirmed the specificity for the CD20 positive human cell antigen binding while no reactivity was seen on other cells such as epithelia, neuro-ectodermal structures, mesenchymal tissues. No effect was seen on T-cells and no adverse effects were noted.

There was not evidence of antibody dependent cellular cytotoxicity. The radionuclide 90Y (half-life of 64 hours) emits pure high-energy beta radiation with a local tissue penetration (5 to 10 mm) and exerts the cytotoxic effect. It should be noted that in the pre-clinical studies an antineoplastic effect was not demonstrated in the nude mouse model and that there were no studies conducted in other species with the radio-labelled ibritumomab tiuxetan, to further expand on the effect of the antibody delivered radiation on the decline and recovery times of the normal B-cells and would serve as a useful basis for examination of the effect in human lymphoma patients where also non neoplastic B-cells are present.

Some of the toxicity studies were conducted using hybridoma-derived antibody, hybridoma-derived [^{89}Y]-labeled conjugate and CHO-derived [^{89}Y]-labeled conjugate.

The consistent finding in toxicity studies was a variable depletion of the circulating B-cells. No other positive findings were observed. As the radioactive final product is solidly chelated to ibritumomab tiuxetan, the risk of incorporation of free yttrium-90 in any tissue is low: Toxicity risks appeared therefore to be mostly related to the radiation derived from the circulating radiolabelled antibody. Because of the radiation toxicity Zevalin is contraindicated during pregnancy and lactation and it is recommended that male likewise women of childbearing potential use contraceptive measures during treatment and for 12 months post treatment (SPC sections 4.4 & 4.6).

4. Part IV: Clinical aspects

Zevalin is a recombinant monoclonal murine IgG_1 kappa antibody, ibritumomab, directed against the B-lymphocyte membrane antigen CD20, covalently linked through a stable thiourea bond to a chelating agent tiuxetan to which a radioligand can be attached. Zevalin is supplied as a kit for radiolabelling with yttrium-90 ([^{90}Y]-labelled Zevalin). The radioisotope is not part of the kit.

The requested therapeutic indication is: 'Treatment of patients with rituximab relapsed or refractory, CD20+ follicular B-cell non-Hodgkin's lymphoma (NHL)'.

Treatment with [^{90}Y] Zevalin is preceded by infusion with rituximab (MabThera®) in order to optimise bio-distribution of radiolabelled antibody by blocking or depleting CD20 binding sites, i.e. those on circulating B-lymphocytes and in normal or involved tissues with large number of B-cells and with high blood flow (such as spleen and liver). Ibritumomab and rituximab contain identical Fab (Fragment antigen-binding) sequences and both antibodies bind strongly and specifically to the CD20 antigen. Rituximab, a chimeric human/murine IgG1 monoclonal antibody was licensed in the European Union for the treatment of relapsed or refractory follicular lymphoma in 1998.

In the present application of Zevalin preceded by rituximab, the recommended treatment schedule is as follows; day 1 an intravenous infusion of rituximab 250 mg/m^2, day 8 an intravenous infusion of rituximab 250 mg/m^2, immediately followed by a single [^{90}Y]- labelled Zevalin infusion. The recommended dose of [^{90}Y] Zevalin is either 0.4 mCi/kg body weight (up to a maximum of 32 mCi) for patients with a baseline platelet count $\geq$ 150,000/mm^3 or 0.3 mCi/kg for patients with a baseline platelet count between 100,000 and 150,000/mm^3 (up to a maximum of 32 mCi).

[^{90}Y] Zevalin achieves selective targeting of radiotherapy to lymphoma cells, which are inherently sensitive to radiolysis. As a pure, high energy, beta-emitting isotope, yttrium-90 can deliver energy to the tumour. The path length of radiation, 5 mm, allows to kill tumour cells in the vicinity of the antibody-bound cell without direct binding of the antibody (bystander effect). These characteristics may be especially advantageous in the treatment of bulky or poorly vascularised tumours. However,

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the increased beta range results in energy deposition throughout a larger volume, which may reduce the dose to some tumour regions. The bystander effect can also cause damage to healthy cells, e.g. bone marrow stem cells, in the vicinity of the antibody binding cells. The half-life of yttrium-90 (2.7 days versus 8 days for iodine-131) approximates the biological half-life of the radiolabelled antibody, which may minimise toxicity to non-target organs. As yttrium-90 is a pure beta emitter, it can be given on an outpatient basis with few radiation precautions.

The clinical trials were performed according to GCP standards.

Six clinical trials with a total of 306 patients with relapsed or refractory B-cell lymphoma have been submitted. The program comprised three dose finding, tolerability and pilot trials (106-01, 106-02 and 106-03), one multicentre, randomised active-controlled phase III trial (106-04, pivotal study) and two supportive phase II trials in special populations (106-05, 106-06). Study 106-05 was conducted to study the efficacy and safety of the reduced dose of 0.3 mCi/kg [^{90}Y]-Zevalin in patients with mild thrombocytopenia at baseline (100,000 to 149,000/mm^3). Study 106-06 was conducted in patients refractory to standard treatment with rituximab. Response rates and duration of response to [^{90}Y] Zevalin were compared to results obtained for each patient's last chemotherapy.

Summary table of Clinical Studies with [^{111}In] Zevalin and [^{90}Y] Zevalin

Study Protocol [ref]	**Title**	**Design and Enrolment**	**Treatment[1]**
106-01 [A00004]	Treatment of B-Cell Lymphoma with [^{90}Y]-labelled Pan B Monoclonal Antibody with Peripheral Stem Cell or Autologous Bone Marrow Transplantation.	Phase 1 Open-Label, ascending single dose escalation Trial; 17 patients enrolled, 14 treated with [^{90}Y] Zevalin.	Various treatments including pre-infusion with ibritumomab, [^{90}Y] Zevalin at 20-50 mCi.
106-02 [A00003]	A Phase I/II Clinical Trial of IDEC-Y2B8 Given Every Six to Eight Weeks to Patients with B-Cell Lymphoma.	Phase I Open-label, ascending multiple dose escalation trial; one patient enrolled and treated with [^{90}Y] Zevalin.	Pre-infusion with ibritumomab, [^{90}Y] Zevalin at 10-20 mCi every 6-8 weeks up to 4 doses.
106-03 [A00009, A00010]	A Phase I/II Clinical Trial to Evaluate the Safety and Clinical Activity of IDEC-Y2B8 Administered to Patients with B-Cell Lymphoma.	Phase I Open-label, ascending single-dose escalation trial. Phase II: Open-label fixed dose single-arm trial; 58 patients enrolled.[2]	Various treatments including pre-infusion with rituximab, [^{90}Y] Zevalin at 0.2-0.4 mCi/kg.
106-04 [A00007]	A randomised, Phase III Multicentre, Controlled Trial to Evaluate the Efficacy and Safety of IDEC-Y2B8 Radioimmuno-therapy Compared to Rituxan™ Immunotherapy of Relapsed or Refractory Low-Grade or Follicular B-Cell Non-Hodgkin's Lymphoma.	Phase III Randomised, active controlled, open-label, fixed-dose comparative trial; 143 patients enrolled (70 treated with rituximab, 73 with [^{90}Y] Zevalin).	Pre-infusion with rituximab, [^{90}Y] Zevalin at 0.4 mCi/kg, or 4 weekly infusions with rituximab at 375 mg/m^2.
106-05 [A00005]	A Phase II, Open-Label, Multicentre Trial to Evaluate the Safety and Efficacy of IDEC-Y2B8 Radioimmunotherapy of Relapsed or Refractory Low-Grade or Follicular	Phase II Open-Label, fixed dose single-arm trial; 30 patients enrolled.	Pre-infusion with rituximab, [^{90}Y] Zevalin at 0.3 mCi/kg.

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	B-Cell Non-Hodgkin's Lymphoma in Patients with Mild Thrombocytopenia.		
106-06 [A00006]	A Phase II, Open-Label Nonrandomised Controlled, Multicentre Trial to Evaluate the Efficacy and Safety of IDEC-Y2B8 Radioimmunotherapy in Patients with B-Cell Non-Hodgkin's Lymphoma Who Are Refractory to Prior Rituximab Therapy.	Phase II Nonrandomised within-patient controlled, open-label, fixed dose trial; 57 patients enrolled, 54 with follicular NHL.	Pre-infusion with rituximab, [^{90}Y] Zevalin at 0.4 mCi/kg.

[1] Imaging doses with [^{111}In] Zevalin were also administered to some or all patients in each study. Ibritumomab is a murine monoclonal antibody; rituximab is a chimeric monoclonal antibody.
[2] 50 patients received [^{90}Y] Zevalin; 6 received only [^{111}IN] Zevalin; 2 received no treatment.

70 of the 306 patients were randomly assigned to treatment with rituximab only (in study 106-04) and 10/306 patients were assigned to receive [^{111}In]-labeled Zevalin (one withdrew and 9 participated in early dosimetry studies). Of the remaining 226 patients 211 were assigned to the recommended treatment regimen sequence, pre-infusions with rituximab followed by a single dose of [^{90}Y]-Zevalin, and these 211 are the basis for the intent-to-treat safety analysis (one patient did not receive Zevalin).

Overall tumour response rate (ORR) was a primary efficacy parameter in the main studies using criteria that are generally accepted in evaluating response in NHL.

However, time-dependent and quality of life endpoints were also included as efficacy parameters. Duration of response (DR) was calculated as the time from the first report of either a PR or a CR to the first report of PD. Time to disease progression (TTP) was calculated as the time from treatment start to the time of first report of PD. TTP was reported for all patients as well as subsets of patients with objective tumour response. The pivotal trial 106-04 was not designed with a power to demonstrate differences in TTP between treatments.

Clinical pharmacology

Pharmacodynamics

Flow cytometry studies were available from 195 [^{90}Y]-Zevalin treated patients. CD19 was used as a B-cell marker instead of CD20, which was occupied by the antibody treatment. The surface antigens of CD45, CD14, and dual expression of CD3/CD4, CD3/CD8, CD5/CD19, CD10/CD19, CD56/CD16, kappa/CD19 and lambda/CD19 were all examined. The treatment only affected the B-cells and was without effect on NK cells, T-cells or other immune cells examined. The rituximab/[^{90}Y]-Zevalin treatment resulted in a marked and selective B-cell depletion with a time to full recovery ranging from 6 to 9 months.

Preliminary observations of the cytogenetic marker for follicular lymphomas, the bcl-2 rearrangement, indicated conversion to bcl-2 negative status in a high proportion of patients.

Levels of IgA and IgG remained within normal limits whereas IgM levels decreased to 40 mg/dl (normal lower limit 50 mg/dl) during the first 3 months after treatment and then recovered.

3/211 (1.4%) patients developed HAMA and one patient HACA during the studies, 4 other patients were positive prior to the treatment.

Pharmacokinetics

Two biodistribution studies (106-01 and 106-03) were conducted to optimise the biodistribution of [^{90}Y]-Zevalin by administering unlabelled anti-CD20 antibodies before [^{90}Y]-Zevalin.

In study 106-01 treatment with [^{111}In]-Zevalin alone led to a visualized labeling of only 10 – 20% of lymphomas (visible with CT scans). Pre-administration of one dose of unlabeled ibritumomab of either 1 mg/kg or 2.5 mg/kg increased the imaging to 50% and >90% of known disease, respectively. Blocking or depletion of CD20 binding sites on circulating lymphocytes and in normal and involved

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tissues with large numbers of B-cells and with high blood flow such as spleen and liver proved a necessary step prior to administration of ibritumomab tiuxetan .

In study 106-03, a phase I/II study, 58 patients with histologically confirmed relapsed or refractory B-cell lymphoma of any histologic subtype were enrolled. Biodistribution was studied by using rituximab rather than ibritumomab to deplete CD20+ cells. Advantages of using rituximab are the presumed therapeutic activity of rituximab and the reduced probability of HAMA reactions by avoiding multiple exposures to murine antibody.

Seven patients were included in the phase I, part 1 segment of this study, which was performed to determine the optimal dose of rituximab to be used before IDEC-In2B8 en IDEC-Y2B8 administration.

Blocking pretreatment on day 1 and 8 with rituximab 100mg/m^2 (3 patients) or 250 mg/m^2 (3 patients) followed by treatment with [^{111}In]-Zevalin led to a complete imaging of known disease for both groups with no qualitative or quantitative differences and no accumulation of [^{111}In]-Zevalin in normal organs. Since the higher dose of rituximab was supposed to have the best antineoplastic effect, this was selected for the infusion prior to [^{90}Y]-Zevalin in all subsequent patients in the Zevalin program.

Pharmacokinetic data were collected from all the clinical studies and only after the recommended rituximab pretreatment. Since the amount of ibritumomab antibody injected (about 2 mg) did not generate detectable serum levels by available assays, measurement of radioactivity from administered [^{111}In]-Zevalin was used. This was found to be an acceptable surrogate because of the stability of the conjugate. With this method the kinetics of Zevalin was shown to fit a linear and non-compartmental model.

Pharmacokinetic Results for yttrium-90 E Derived from indium-111 Activity in Blood

Dose Group (mCi/kg)		**N[1]**	**Median**	**Range**
0.2	AUC (hours)	4	15.49	8.54 - 24.28
	Biologic $T_{½}$ (hours)	4	34.27	18.03-60.20
	Effective $T_{½}$ (hours)	4	22.54	14.25-31.91
0.3	AUC (hours)	43	23.01	2.59 - 53.72
	Biologic $T_{½}$ (hours)	43	42.52	19.07-65.77
	Effective $T_{½}$ (hours)	43	25.55	14.69-33.27
0.4	AUC (hours)	98	27.07	3.33-102.35
	Biologic $T_{½}$ (hours)	98	47.09	22.03-140.33
	Effective $T_{½}$ (hours)	98	27.54	16.55-43.95
All	AUC (hours)	145	24.94	2.59-102.35
	Biologic $T_{½}$ (hours)	145	46.35	18.03-140.33
	Effective $T_{½}$ (hours)	145	27.06	14.25-43.95

[1] Data not available for all patients in the analysis population.

A median of 5.7% of the injected dose is eliminated in the urine over 7 days or about 1.9 mCi totals. Since the physical half-life of yttrium-90 is 2.7 days the environmental impact is small.

Dosimetry data following the injection on day one of 5 mCi [^{111}In]-Zevalin (plus rituximab pretreatment) were obtained from 179 patients in studies 106-03, -04, -05 and -06 and processed centrally. The optimum goal was to ensure that no patient received greater than 2000 cGy to normal organs and 300 cGy to the bone marrow.

The predicted tumor radiation absorbed dose from [^{90}Y]-Zevalin was calculated for 57 tumors in 38 of the 179 patients and estimated to be a median of 1480 cG (range 61-24,274) and the estimated median dose factor was 60 cG/mCi (3-778).

The central dosimetry data indicate that radiation dose delivered to normal organs and marrow by [^{90}Y] Zevalin even at the recommended dose of 0.4 mCi/kg are significantly below acceptable upper limits.

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Significant side effects of the [^{90}Y]-Zevalin treatment were severe granulocytopenia and thrombocytopenia, despite the fact that the bone marrow received a relatively small median dose of 60-70 cG. The correlation between myelotoxicity and bone marrow absorbed radiation dose was examined by comparing two groups of patients receiving 0.3 mCi/kg or 0.4 mCi/kg and by correlating the single patient absorbed dose (range 6.5 to 220 cG) to either nadirs of thrombocytes and granulocytes or to days to hematologic recovery. Surprisingly, no significant correlations could be demonstrated.

The conclusion of the biodistribution and dosimetry studies was that in the intended study population individual patient dosimetry would be unnecessary since the estimated absorbed radiation doses are substantially below recognized upper safety limits; variability in excretion is insignificant and individual dosimetry results are not predictive of treatment toxicity.

Clinical efficacy

Dose-response studies

Study 106-1

This phase I exploratory study had several objectives: to evaluate safety and tolerance of escalating doses of [^{90}Y]-Zevalin, to establish the MTD of [^{90}Y]-Zevalin (with stem cell rescue as back-up), to examine the effect of pre-treatment with murine ibritumomab, to examine PK/PD, dosimetry and tumour uptake of [^{111}In]-Zevalin and to compare delivered dose and measured effect.

17 patients, all refractory to standard treatment, were included (12 with SL or follicular lymphoma, 4 intermediate grade NHL and one NHL of undefined type).

The bio distribution and dosimetry aspects of these studies have been described in the previous section.

The MTD was 50 mCi [^{90}Y]-Zevalin with myelosuppression being the dose limiting toxicity.

For the 14 patients who received [^{90}Y]-Zevalin in cycle 1 the response rate was 64% (28% CR) and median time to progression was 9.3 months.

Study 106-2

A third dose finding study, 106-02 was terminated for administrative reasons after enrolment of one single patient. This study was designed to test a multiple low-dose treatment scheme for [^{90}Y] Zevalin instead of the single-dose administration recommended in this MAA. This study is only mentioned for completeness.

Study 106-03

A phase I –II study to examine the optimal pre-treatment with rituximab and the safety and toxicity of escalating doses of [^{90}Y]-Zevalin with rituximab pre-treatment. Overall 58 patients were enrolled. The 51 patients eligible for an intention-to-treat analysis had relapsed or refractory B-cell lymphoma (3 with SL, 33 with follicular lymphoma and 15 with other types of NHL). Seven patients were included for the study of rituximab doses only.

Doses of 0.2, 0.3, 0.4 and 0.5 mCi/kg were planned, but escalation was stopped at 0.4 mCi/kg, where 8/30 experienced grade 4 neutropenia or thrombocytopenia (9/30). 0.4 mCi/kg was therefore defined as the MTD with rituximab pretreatment and a total dose of 32 mCi for an 80 kg person was considered the upper limit.

Baseline platelet counts (considered a surrogate for the marrow damage of the previous therapy and for bone marrow involvement) appeared to predict for hematological toxicity and the findings led to the choice of a reduced dose, 0.3 mCi/kg, for patients with platelet counts 100.000 – 150.000/mm^3. Grading of bone marrow infiltration in 4 steps from 0 to 25% (patients with larger involvement were excluded) correlated to the thrombocytopenia.

The main efficacy end point was the response rate evaluated in relation to [^{90}Y]-Zevalin doses and response was seen at all doses:

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Tumour Response Rates for All Enrolled Patients in Study 106-03

Response[1]	0.2 mCi/kg (N=5) Pts (%)	0.3 md/kg (N=16) Pts (%)	0.4 mCi/kg (N=30) Pts (%)	Total (N=51) Pts (%)
ORR (CR+PR)	2 (40%)	12 (75%)	20 (67%)	34 (67%)
CR	1 (20%)	8 (50%)	4 (13%)	13 (25%)
PR	1 (20%)	4 (25%)	16 (53%)	21 (41%)

[1] Sponsor's assignment of tumor response

The overall response rate in patients resistant to any prior therapy was 50%. The response rate was higher in low-grade lymphomas (28/34, 82%) than in intermediate grade lymphomas (6/14, 43%).

As far as the time-related end point, median TTP for the 34 responders was 12.7 months, in the CR patients 23.6+ months. Duration of response varied across doses between 10.8 and 14.4 months.

Table 1.

Kaplan-Meier Median TTP and Duration of Response (DR) by Dose in Months

	TTP (Responders)	DR	TTP(CR)
0.2 mCi/kg	12.5	10.8	12.6
0.3 mCi/kg	13.3	11.7	14.4
0.4 mCi/kg	15.4	14.4	28.3 - 36.4+*

Source: Appendix A.I, A.2

•Indicates range; median not predicted by Kaplan-Meier because three patients still in remission

Efficacy studies

Selection criteria for the studies 106-04 and 106-05 mostly overlapped:

- Patients were required to have histologically confirmed, relapsed or refractory, low-grade or follicular B-cell NHL, or CD20+, B-cell NHL transformed from low-grade to intermediate grade.
- Patients were required to have bidimensionally measurable disease, with at least one lesion ≥ 2 cm in one dimension.
- Patients were required to have progressive or symptomatic disease requiring therapy.
- Patients were required to have WHO performance status of 0, 1, 2, and a life expectancy of at least 3 months.
- Patients were excluded if they had received prior myeloablative therapy with stem cell support, or external beam radiation to > 25% of active marrow, or if they had neutrophil counts < 1,500/mm^3, or > 25% marrow involvement of NHL, or abnormal liver function or abnormal renal function.
- Patients were excluded if they had CLL, or if total circulating lymphocyte counts were > 5,000/mm^3, or if they had CNS lymphoma, HIV or AIDS-related NHL, or if they had lymphoma-positive pleural or peritoneal invasion or effusion/ascites, or if they had received prior anti-CD20 therapy, including rituximab, or if they were positive in tests for HAMA.

An additional exclusion criteria for study 106-04 was a platelet count < 150,000/mm^3.

An additional requirement in study 106-05 was a mild thrombocytopenia, defined as a platelet count of 100,000 to 149,000/mm^3.

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In study 106-06, patients were required to have follicular lymphoma. Another requirement was that they had received treatment with rituximab at 375 mg/m^2 once weekly for 4 weeks, and either not responded to their most recent rituximab treatment with a CR or PR, or relapsed with disease progression within 6 months of first rituximab infusion. The other selection criteria were identical as in study 106-04.

In tables the demographic data and baseline disease status are presented respectively for patients enrolled in studies 106-04, 106-05 and 106-06.

In the protocol design of study 106-04 it is stated that follow-up evaluations were to be carried out at three month intervals for the first year following IDEC-Y2B8 or rituximab treatment, and at six months intervals thereafter, or until progression of the patient's disease necessitated intervention with another anti-cancer therapy. The follow-up period for a patient who demonstrated a clinical response to the study treatment was maximally four years. The overall duration of the study is therefore approximately five years from the time the first patient was enrolled in the study to the time the last patient completed follow-up. Similar follow-up and study duration designs are applied in study 106-05 and 106-06.

Demographic data for patients in studies 106-04, 106-05, and 106-06

	Study			
	106-04 (N = 143)		106-05 (N = 30)	106-06 (N = 57)
	[^{90}Y] Zevalin (N = 73)	Rituximab (N = 70)		
Age (Years)				
N	73	70	30	57
Median	60.0	57.0	61.0	54.0
Minimum	29.0	36.0	29.0	34.0
Maximum	80.0	78.0	85.0	73.0
Gender				
Female	38 (52.1%)	35 (50.0%)	12 (40.0%)	29 (50.9%)
Male	35 (47.9%)	35 (50.0%)	18 (60.0%)	28 (49,1%)
Weight Group				
< 80 kg	45 (61.6%)	41 (58.6%)	14 (46,7%)	35 (61,4%)
≥80 kg	28 (38.4%)	29 (41.4%)	16 (53.3%)	22 (38,6%)

Baseline disease status for patients in studies 106-04, 106-05, and 106-06

	Study			
	106-04 (N = 143)		106-05 (N = 30)	106-06 (N = 57)
	[^{90}Y] Zevalin (N = 73)	Rituximab (N = 70)		
Disease Stage at Study Entry				
I/II	8 (11.0%)	6 (8.6%)	3 (10.0%)	4 (7.0%)
III/IV	65 (89.0%)	64 (91.4%)	27 (90.0%)	51 (89.5%)

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Unknown	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (3.5%)
Pathology Report Histology Type				
A	9 (12.3%)	8 (11.4%)	2 (6.7%)	2 (3.5%)
Follicular	55 (75.3%)	58 (82.9%)	25 (83.3%)	54 (94.7%)
Transformed	9 (12.3%)	4 (5.7%)	3 (10.0%)	0 (0.0%)
Other	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.8%)
Bone Marrow Involvement				
0%	42 (57.5%)	46 (65.7%)	10 (33.3%)	39 (68.4%)
0.1 - 5%	3 (4.1%)	5 (7.1%)	0	3 (5.3%)
5 - 20%	20 (27.4%)	15 (21.4%)	12 (40.0%)	12 (21.1%)
≥ 20%	8 (11.0%)	4 (5.7%)	8 (26.7%)	3 (5.3%)
Splenomegaly				
Yes	7 (9.6%)	3 (4.3%)	7 (23.3%)	7 (12.3%)
Extranodal Disease				
0, 1	60 (82.2%)	61 (87.1%)	24 (80.0%)	47 (82.5%)
≥ 2	13 (17.8%)	9 (12.9%)	6 (20.0%)	10 (17.5%)
Bulky Disease				
< 5 cm	40 (54.8%)	39 (55.7%)	16 (53.3%)	15 (26.3%)
5 - < 7 cm	18 (24.7%)	13 (18.6%)	9 (30.0%)	17 (29.8%)
7 - < 10 cm	9 (12.3%)	13 (18.6%)	3 (10.0%)	14 (24.6%)
≥ 10 cm	6 (8.2%)	5 (7.1%)	2 (6.7%)	11 (19.3%)
WHO Performance Status				
0, 1	72 (98.6%)	68 (97.1%)	29 (96.7%)	54 (94,7%)
≥ 2	1 (1.4%)	2 (2.9%)	1 (3.3%)	3 (5.3%)
Unknown	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Number of Prior Regimes				
Median	2.0	2.0	2.0	4.0
Range	(1.0 - 6.0)	(1.0 - 5.0)	(1.0 - 9.0)	(1.0 - 9.0)
IPI Risk Group				
Low (=0-1)	25 (34.2%)	32 (45.7%)	10 (33.3%)	25 (43.9%)
Low / Intermediate (=2)	38 (52.1%)	23 (32.9%)	10 (33.3%)	12 (21.1%)
Intermediate / High (=3)	5 (6.8%)	7 (10.0%)	6 (20.0%)	7 (12.3%)
High (=4-5)	3 (4.1%)	2 (2.9%)	2 (6.7%)	4 (7.0%)
Unknown	2 (2.7%)	6 (8.6%)	2 (6.7%)	9 (15.8%)

Efficacy endpoints

ORR (CR plus CCR plus PR) was the primary efficacy parameter in all-clinical studies. CR rates include CCR rates in this report. Response was defined by the reduction in the overall size of measured lesions. All responses assigned by the investigator were subsequently verified by IDEC,

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based upon the reported lesion dimensions. In the phase III study 106-04 and the phase II study 106-06 response was re-evaluated by an independent panel of radiologists and oncologists. These clinicians conducted a third party, blinded evaluation of CT scans for all patients who were classified as responders and for patients with stable disease exhibiting at least a 40% reduction in total tumour size. This LEXCOR evaluation, when performed, was conclusive.

Secondary efficacy parameters comprised:

- time to response, defined as the time from treatment start to the time of the first reported confirmation of response.
- DR, calculated as the time from the first report of either a PR or a CR to the first report of PD.
- TTP, calculated as the time from treatment start to the time of first report of PD.
- Time to next anti-cancer treatment, calculated as the time from treatment start to the time of the first administration of any subsequent treatment for NHL.
- quality of life determined by a FACT-G quality of life analysis performed at baseline and at 13 weeks after the start of treatment, and evaluation of B-symptoms and disease-related signs and symptoms, most importantly tumour pain.

Overall survival was not included as a study objective due to the expected long survival in indolent lymphomas.

Study 106-04

This was a prospective, randomised controlled phase III clinical study comparing the efficacy and safety of [^{90}Y]-Zevalin/rituximab with rituximab alone.

The study was designed with 80% power to detect a 25% difference between treatment groups in the overall response rate, with a two-sided alpha level of 0.05; it was deliberately not powered to detect a statistical difference in TTP between [^{90}Y] Zevalin and rituximab. The protocol stated, “The target median TTP and response duration time for the Zevalin group will be either equivalent to or better than that of the rituximab group”. Equivalence in TTP was to be declared if the difference in the median TTP between the two treatments was less than 1.5 months.

The treatment in the Zevalin arm consisted of a pre-infusion of rituximab at 250 mg/m^2 followed by an injection of 5 mCi of [^{111}In]-Zevalin for dosimetry/imaging. 6-8 days later, after the completion of the dosimetry analyses, the patients received a second infusion of rituximab 250 mg/m^2 immediately followed by iv injection of [^{90}Y]-Zevalin at 0.4 mCi/kg. Patients randomised to treatment with rituximab received four weekly infusions of rituximab at 375 mg/kg. The follow-up period of the study was 4 years.

Patients with relapsed or refractory low-grade or follicular (IWF A-D) or transformed from low grade to intermediate grade histology (IWF E-G) CD20-positive B-cell NHL requiring treatment as by defined criteria were included. Bone marrow involvement should be less than 25% and no prior ABMT should have been administered.

Tumor response was assessed by conventional methods. Responses were also analyzed according to the more recently published International Workshop Criteria (IWRC), which only vary slightly except that there is no minimum duration in the CR/PR definition and CCR (clinical complete remission) is named CRu (u for unconfirmed). An independent panel of radiologists and oncologists (termed LEXCOR for Lymphoma Expert Confirmation Of Response) also evaluated tumor response. This panel was ”blinded” to treatment assignment and investigators evaluation of response.

Seventy-three patients were allocated to the Zevalin treatment and 70 to the rituximab treatment. There were no significant differences in the demographic data for the two groups.

The treatment results were updated as of October 1, 2002. The response rates for the ITT population are shown in the table below, they were calculated by LEXCOR both according to the protocol definitions and according to IWRC.

Overall Response Rates in the Phase III 106-04 Study

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	Protocol-Defined Response Criteria			International Workshop Response Criteria		
	Zevalin	**Rituximab**	**p-value***	**Zevalin**	**Rituximab**	**p-value***
ORR (%)	73	47	0.002	80	56	0.002
CR (%)	18	11	0.326	30	16	0.040
CCR/CRu (%)	3	4	-	4	4	-

Source: Integrated Summary of Safety and Efficacy

*Adjusted p-values generated by Cochran-Mantel-Haenszel test by pathology report histology type

The median time to progression (TTP) for all patients was 10.6 months for the Zevalin group (0.8 – 49.0+) and 10.1 months (0.7 – 51.3) for rituximab (NS, p= 0.540).

In the subgroup of patients with follicular lymphomas the corresponding figures were 15.0 months versus 10.2 months for rituximab (p=0.203).

For the Zevalin patients achieving a CR or CCR the median TTP is 24.7 months in the Zevalin group versus 13.2 months in the rituximab group (p=o.764).

The TTP was defined a secondary endpoint of efficacy in the protocol and the objective was to demonstrate equivalence. The study was not powered to demonstrate superiority.

The estimated duration of response (DR) was 13.9 months for the Zevalin group (01.0- 47.6+) and for the rituximab group 11.8 (1.2- 49.7+) months (p= 0.555). The DR in patients with follicular lymphomas was 16.7 months versus 11.2 for the rituximab group (p=0.925).

The proportion of patients with ongoing responses in relation to observed patients was calculated at 6, 9 and 12 months and the percentages were 62, 46 and 34 for Zevalin-treated patients and 46, 34 and 23 for rituximab-treated patients. The differences were statistically significant at 6, 9 and 12 months but not at the later time points.

Time to next lymphoma therapy (TTNT) was 17.6 months versus 12.4 months in the rituximab group (p=0.221)

Overall survival was not included as a study objective due to the expected long survival in indolent lymphomas. In the October 2002 update more than 67% of the patients in both groups were still censored. The median cannot yet be determined for the Zevalin group and is estimated to be 48.8 months in the rituximab group. The same figures are true for follicular lymphoma patients.

Quality of life: FACT-G analysis

Eighty-one patients completed the FACT-G survey at baseline and at week 12 post-treatment. In the [^{90}Y] Zevalin group (n=45) a statistically significant increase in FACT-G score between baseline and week 12 was observed. The mean scores in the rituximab group (n=36) improved but were not significantly different.

B-symptoms and tumour related pain

So-called B-symptoms (tumour-related fever, night sweats, weight loss) occurred infrequently in both groups (n=11 in the Zevalin arm, n=12 in the rituximab arm). These symptoms resolved or improved in most patients. No difference in alleviation of B-symptoms was found between the treatment groups. Pain was present in 20/73 patients in the Zevalin arm, which resolved or improved in 17 patients. In the rituximab arm 19/70 patients experienced pain, which resolved or improved in 12 patients. No significant difference between the two treatment groups was found.

Response rate and TTP was examined in relation to baseline characteristics and prognostic factors. Some of the subgroups have too small numbers, but with this reservation it seems that the Zevalin results with respect to response rates are largely independent of age, gender, stage, splenomegaly, extranodal disease, bulky disease (except $\geq$ 10 cm), years elapsed since diagnosis, number of prior regimens (except $\geq$ 4) and prior radiotherapy. In the histology classes follicular lymphomas seemed to respond better than the IWF group A and the transformed lymphomas.

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63/143 patients had positive bcl-2 status in peripheral blood at baseline. In patients with bcl-2 follow-up data, 17/21 (81%) converted to negative status in the Zevalin-group versus 11/15 (73%) in the rituximab-group.

Dosimetry data in 73 patients revealed radiation doses within the planned ranges. There was no correlation between dosimetric figures and response or hematologic toxicity.

The conclusions of the final analyses (except for survival) of the study thus confirm the superiority of the Zevalin regimen with respect to response rate, but although the numerical values are improved in all time related parameters (TTP, DR, TTNT) none of the differences are statistically significant. The survival analysis still has more than 67% of the patients censored, in the other time-related analyses the censored figures are below 20%.

Study 106-05

A single arm multicenter phase II study examining the safety and efficacy of the [^{90}Y]-Zevalin regimen in a reduced dose (0.3 mCi /kg of [^{90}Y]-Zevalin) in 30 patients with relapsed or refractory follicular lymphoma and with mild thrombocytopenia (platelets 100.000 – 149.000/mm$^{3)}$.

The overall response rate as evaluated by the sponsor was 66.7%, by the investigator 76.7% and according to IWC 83.3%.

The CR rates were 33.3 – 36.7%.

The estimated duration of remission was 11.8+ months (3.6 – 17.4 months) and the TTP for responding patients was 12.6+ months (4.9-18.6). The TTP for all patients was 9.3+ months.

It is noteworthy that the response rate remains the same as in study 106-04, despite the reduction in Zevalin dose.

Study 106-06

A single arm multicentre phase II study using the patients own previous treatment results as control in evaluating the efficacy of [^{90}Y]-Zevalin in rituximab refractory patients. The study population consisted of 54 heavily pre-treated (median 4 prior regimens) patients with follicular lymphoma. 3 additional non-follicular patients were included for safety data collection.

The population was defined by lack of response (CR or PR) to the conventional rituximab regimen (375 mg/m^2 weekly times 4) and now with progressive disease or initial response and relapse within 6 months. Treatment regimen and endpoints were identical to studies 106-04 & 05.

The response rate in 54 ITT patients with follicular NHL ranged from 59.3% (LEXCOR evaluation) to 74.1 % (IWRC), and the CR% ranged from 3.7% (LEXCOR) to 14.8 % (IWRC).

The ORR was compared to the response seen following the patients' previous rituximab treatment and was found statistically improved (59.3% vs. 31.5%, p=0.002).

19/37 patients (51.4%) who did not respond at all to their previous rituximab now responded to [^{90}Y]-Zevalin/rituximab, while 13/17 (76.5%) patients, who were short-term responders (<6 months) to rituximab now achieved CR or PR following Zevalin.

Likewise, 8/17 (47.1%) of the patients who did not respond to their last chemotherapy, now responded to [^{90}Y]-Zevalin.

With data from the October 2002 follow-up, the median TTP for all patients is 6.8 months (1.1-50.9) and for responders 8.7 months (1.7-50.9 months). Less than 20% are now censored. Median duration of remission (DR) was 6.4 months (0.5-49.9+) with 17.5% censored.

The DR is statistically longer than that resulting from the patients' most recent prior rituximab therapy (6.4 vs. 4.0 months, p<0.001) and is similar to that from the patients' most recent chemotherapy.

Disease-related symptoms resolved or improved in 17/22 patients, worsened in one and were unchanged in 4.

Clinical safety

Since the Zevalin regimen consists of a combination of 2 doses of rituximab and one dose of [^{90}Y]-Zevalin it seems necessary to evaluate the safety of each of the components. Administration of 0.4

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mCi/kg of [^{90}Y]-Zevalin does lead to a significant yttrium-90 radiation dose which can be expected to lead to the standard radiation effects particularly on dividing cells. Since the radiation source is bound to the B-cell antibodies, and therefore to B-cells, the main radiation effect can be expected to occur in lymphomas, bone marrow, lymphoid tissues and organs containing lymphoid cells.

The ”cold” Zevalin antibody +chelator in animal experiments only led to a dose-dependant and moderate B-cell depletion and no general pharmacologic effects were observed. The chimeric mouse/human CD20 antibody rituximab has a more significant B-cell depleting effect due to its more pronounced lytic action (ADCC, CDC and apoptosis) and in clinical trials it has produced many infusion related side effects.

The randomised phase III trial 106-04 does offer an opportunity to compare the side effects of the rituximab/[^{90}Y]-Zevalin regimen to those seen after rituximab.

The overall incidence of AE (except for hematologic toxicity) was similar between the Zevalin/rituximab-pretreatment group and the rituximab group both during treatment (98.6 vs. 95.7 %) and during follow-up (34.2% vs. 27.1%). No patient had treatment discontinued due to an AE.

The most frequently reported events in the study are characteristic of rituximab and occur with comparable frequency in each group. Only grade 1 and 2 respiratory symptoms are significantly more frequent in the Zevalin group and grade 1 and 2 nausea, vomiting and anorexia also seem marginally more frequent. The most frequently reported AE in the follow-up period was in both groups asthenia. Grade 3 or 4 AE were seen infrequently with no significant differences between the 2 groups of treatment. 9 deaths in the Zevalin group were all due to progressive disease, none related to treatment. 7 of the 9 had received additional treatment for their disease. In the rituximab group 5/7 deaths were due to disease progression, one was due to pancreatic cancer and one was due to sepsis following administration of additional chemotherapy for progressive disease. 5 other patients had received additional lymphoma therapy prior to death.

Adverse Events Related to Treatment or of Unknown Relationship in ≥ 5% of Patients: Study 106-04 (Treatment Period)

	[^{90}Y] Zevalin N=73	Rituximab N=70	
	N (%)	N (%)	p-value[1]
Any Adverse Event[2]	63 (86.3)	62 (88.6)	0.803
Body as a Whole	50 (68.5)	50(71.4)	0.719
Asthenia	29 (39.7)	23 (32.9)	
Chills	13(17.8)	20 (28,6)	
Throat Irritation	13(17.8)	10(14.3)	
Fever	10(13.7)	11 (15.7)	
Headache	9(12.3)	11 (15.7)	
Pain	7 (9.6)	5(7.1)	
Flushing	6 (8.2)	4(5.7)	
Abdominal Pain	6 (8.2)	3(4.3)	
Chest Pain	4 (5.5)	2 (2.9)	
Back Pain	1 (1.4)	4 (5.7)	
Cardiovascular System	11 (15.1)	11 (15.7)	1.000
Hypotension	6(8.2)	7(10.0)	
Digestive System	28 (38.4)	17 (24.3)	0.075
Nausea	24 (32.9)	10(14.3)	
Vomiting	10(13.7)	4 (5.7)	
Anorexia	6(8.2)	1 (1.4)	
Diarrhea	2 (2.7)	4(5.7)	
Hemic and Lymphatic System[3]	10(13.7)	3 (4.3)	0.079
Ecchymosis	5 (6.8)	0(0.0)	
Metabolic And Nutritional Disorders	12(16.4)	12(17.1)	1.000
Angioedema	6 (8.2)	11 (15.7)	
Peripheral Edema	5 (6.8)	0 (0.0)	
Musculoskeletal System	12(16.4)	6 (8.6)	0.209

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Arthralgia Myalgia	8(11.0) 4 (5.5)	3 (4.3) 4 (5,7)	
Nervous System Dizziness	14(19.2) 8(11.0)	10(14.3) 3(4.3)	0.505
Respiratory System Increased Cough Infection Bronchospasm Rhinitis	21 (28.8) 8(11.0) 5 (6.8) 4 (5.5) 3(4.1)	10(14.3) 1(1.4) 1 (1.4) 1 (1.4) 5(7.1)	0.043
Skin and Appendages Rash Pruritus	19(26.0) 8(11.0) 6 (8.2)	19(27.1) 7(10.0) 10(14.3)	1.000

Note: Treatment period is the time interval from first infusion (rituximab) to 12 weeks after [^{90}Y] Zevalin

[1]p-value generated by Fisher's exact two-tailed test.

[2]The category "Any Adverse Events" includes all patients with ≥ 5% Adverse Events, but excludes neutropenia, leukopenia, thrombocytopenia, and anemia.

[3]For hematological toxicity see chapter 2.5.5 "Hematological Toxicity".

Thus, the major difference between the 2 regimens related to the more significant but transient haematologic toxicity.

In the Zevalin group there was a 32% incidence of Grade 4 neutropenia (vs. 0 in the rituximab group), a 5.5 % incidence of thrombocytopenia (vs. 0 in the rituximab group) and a 2.7% incidence of Grade 4 anaemia (vs. 0 in the rituximab group). Median nadir counts for Zevalin patients versus rituximab patients were for neutrophils 0.9 vs. 2.9 x 103/mm^3 , for platelets 41.0 vs. 188.5 x 103/mm^3 and for hemoglobin 10.8 vs. 12.9 g/dL showing the more intense myelosuppressive effects of the Zevalin regimen.

The nadirs occurred much later for the Zevalin group than with rituximab: 63 vs. 27 days for neutrophils, 54 vs. 28 days for platelets and 70 vs. 25 days for hemoglobin.

The recovery from nadir to pre-defined values took 2 weeks for Zevalin patients and longer, 3-4 weeks, for rituximab patients. Eight patients received one or more hemopoietic growth factors.

B-lymphocyte depletion in peripheral blood was an expected pharmacodynamic result. The recovery was somewhat slower in the rituximab group than in the Zevalin treated patients (12 months to reach the lower normal limit versus 7 months)

Based on limited experience, Zevalin treatment did not seem to compromise patients' ability to receive subsequent aggressive therapy.

Infections were significantly more frequent in the Zevalin group: 30/73 vs. 13/70 during the treatment period, but not different in the follow-up period (8 vs.8).

The infections were mainly of Grade 1-2 as shown in Table below:

Incidence of Infection in by Grade During Treatment for Zevalin Patients (N=73)

	Grade				Total
Adverse Event	1	2	3	4	
All Any Infection	12	13	5	0	30(41.1)
Bacterial Infection Urinary Tract Infection Lymphangitis Sepsis	2 0 1 0	0 1 0 0	0 1 0 1	0 0 0 0	2(2.7) 2 (2.7) 1(1.4) 1(1.4)
Fungal Infection Moniliasis	2 1	0 0	0 0	0 0	2 (2.7) 1 (1.4)

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Oral Moniliasis	1	0	0	0	1(1.4)
Not Otherwise Specified					
Bronchitis	1	0	0	0	1(1.4)
Cold Syndrome	1	1	0	0	2(2.7)
Coniunctivitis	0	1	0	0	1(1.4)
Flu Syndrome	0	1	0	0	1(1.4)
Infection	6	4	1	0	11(151)
Urinary Tract Infection	1	1	2	0	4(5.5)
Neutropenia	0	0	1	0	1(1.4)
Sinusitis	0	3	0	0	3(4.1)
Stomatitis	1	0	0	0	1 (1.4)
Viral					
Gastroenteritis	0	1	0	0	1(1.4)
Herpes Zoster	0	1	0	0	1(1.4)

Source: Appendix D.95

Note: Patient is counted under the worst grade. This breakdown is not additive because some patients experienced more than one type of infection.

Pooled analysis of safety data from the 4 clinical studies 106-03, 106-04, 106-05 and 106-06, a total of 211 Zevalin treated patients, were presented in a number of tables in the application. The results from the 3 studies did not deviate from the Zevalin results from the 106-04 study. Only a few notes will be given here.

Overall incidence of infections in the treatment period was 37%. The majority was grade 1 or 2, 3.8% were grade 3 and 1.4% were grade 4. Infection led to hospitalisation in 16 (7.6%). Sepsis was reported for 3 patients. 17 patients (8.1%) experienced infection during the follow-up period, 1.9% were grade 3 and 0.5 % were grade 4.

The company presents safety data from study 106-98, which in USA was open for patients not eligible for other Zevalin studies. Relapsed/refractory patients with follicular or transformed B-cell NHL were treated with one course of Zevalin. Among 449 patients 25% had grade 4 neutropenia and 10% grade 4 thrombocytopenia. A total of 12.2% were recorded as having SAE.

A summary of safety events (March 1 2001- April 9, 2002) in 660 patients treated with Zevalin radio immunotherapy was submitted. Events during the reporting period were predominantly grade 1 and 2 asthenia, chills and fever. The grade 3-4 AE's in study 106-98, 8%, were predominantly infectious and hematologic. For studies 03, 04, 05 and 06 no cases were reported in the period.

For studies 03, 04, 05, 06 the Company committed to closely monitor the long-term safety aspects of immunogenicity and secondary neoplasias:

280 patients have so far been tested for HAMA. 6 patients or 2.1% had positive tests, two at baseline. At present only two patients continue to have positive tests.

4 patients (1.4%) had positive tests for HACA, 3 of these at baseline. Two patients continue to test positive.

The incidence of MDS and AML is monitored in all Zevalin radio immunotherapy studies. Cumulatively 9 patients of 655 have been diagnosed: two in study 106-03, one in each of 106-04 and 106-05, two in 106-06 and three in study 106-98. All have been heavily pretreated and whether the secondary neoplasias are related to the previous alkylating agent therapy or the Zevalin regimen can not be decided. Two patients had pre-existing morphologic or cytogenetic abnormalities of the bone marrow. The annualised rate based on calculation of the number of events per person-year from the first infusion of rituximab is 0.79% (1144.7 person-years) and from the date of diagnosis is 0.23% (3906.3 person-years). This rate is similar to that described in published reports of MDS/AML in NHL.

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5. Overall conclusions, benefit/risk assessment and recommendation

Quality

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

During the evaluation process, a number of questions were raised regarding specifications limits. Most of these have been adequately solved, while some remaining issues will be addressed on an ongoing basis.

Overall, viral safety and batch to batch consistency of the product is satisfactorily documented and the relevant test will be performed according to the specifications.

Preclinical pharmacology and toxicology

Overall, the primary pharmacodynamic studies have confirmed the specificity for the CD20 positive human cell antigen binding of ibritumomab while no reactivity was seen on other cells as epithelia, neuro-ectodermal structures, mesenchymal tissues. No effect was seen on T-cells and no adverse effects were noted.

There was no evidence of antibody dependent cellular cytotoxicity. The radionuclide yttrium-90 (half-life of 64 hours) emits pure high-energy beta radiation with a local tissue penetration (5 to 10 mm) and exerts the cytotoxic effect.

It should be noted that in the pre-clinical studies an antineoplastic effect was not demonstrated in the nude mouse model and that there were no studies conducted in other species with the radio-labelled ibritumomab tiuxetan, to further expand on the effect of the antibody delivered radiation on the decline and recovery times of the normal B-cells and would serve as a useful basis for examination of the effect in human lymphoma patients where also non neoplastic B-cells are present.

Nevertheless, in light of the pre-clinical PD and PK studies considered jointly with clinical data it is considered that the mechanism of action and concept of therapeutic plausibility is established and there is no need to submit additional preclinical studies.

The consistent finding in toxicity studies was a variable depletion of the circulating B-cells. No other positive toxicity findings were observed. Toxicity risks appeared to be mostly related to the radiation derived from the circulating radiolabelled antibody. Because of the radiation toxicity Zevalin is contraindicated during pregnancy and lactation and it is recommended that male likewise women of childbearing potential use contraceptive measures during treatment and for 12 months post treatment (SPC sections 4.4 & 4.6).

Efficacy

[^{90}Y]-Zevalin represents an innovative and potentially valuable radioimmuno- treatment approach for follicular B-cell lymphomas. The applicant has carried out a series of clinical phase I-II trials and one phase III trial, which together demonstrate that the [^{90}Y]-Zevalin regimen as described

- is tolerable
- does deliver a predicted radiation dose
- has pronounced antineoplastic activity in follicular B-cell lymphomas with a 50 – 70% response rate, which seems independent of previous treatment and of a number of prognostic factors
- demonstrates superiority over rituximab in a randomised comparative trial with respect to response rate (76% vs. 47 % response), but not with respect to TTP or DR. Fraction of patients in remission at 6, 9 and 12 months was statistically higher, but TTP and DR showed only a numerically but not statistically significant improvement and there was thus no proof of a translation into a clinical benefit (study106-04)

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- at a 25% reduced dose demonstrates a high response rate (66 -83%) in a population of heavily pre-treated follicular lymphoma patients with moderate thrombocytopenia (106-05)
- demonstrates a high response rate (59-74%) in an end stage patient population refractory to rituximab and chemotherapy with a duration of remission significantly longer than that following the previous rituximab treatment (study 106-06)

With respect to the pivotal randomised study 106-04 the statistical power of the study with only 55 and 58 patients in each of the two arms is limiting for the analysis of differences in time dependent parameters and one is left with the open question whether the definite proof of efficacy only is lacking because of insufficient powering of the trial (the consistency of the trends would speak in favour of this hypothesis) or whether the two regimens are of about the same efficacy with respect to the decisive time dependent parameters (the almost identical but preliminary survival curves seem to speak in favour of this hypothesis).

In light of the weaknesses of the phase III pivotal trial, and taking into account the results of this study the CPMP concluded that the indication needed to be restricted to patients with rituximab relapsed or refractory CD20+ follicular B-cell non-Hodgkin's lymphoma (NHL).

In study 106-06 in rituximab refractory patients

- the overall response rate was 59.3% (LEXCOR) to 74.1 % (IWRC)
- 19/37 (51.4%) patients who did not respond to their last rituximab treatment now responded to the [^{90}Y]-Zevalin-rituximab combination.
- 47.1% of the patients who did not respond to their last chemotherapy now responded to the Zevalin combination.
- median duration of response was 6.4 months (0.5 – 49.9+ months)

Safety

Compared to rituximab alone the typical additional toxicities associated with Zevalin are of 3 types: gastrointestinal, respiratory and haematologic.

The gastrointestinal side effects nausea, vomiting and anorexia were mild and connected to the administration of the radiation dose.

The respiratory symptoms, mainly cough, infection and bronchospasm were also mild and did not form a treatment obstacle.

The main problem is the haematologic toxicity, which with the late occurring nadirs seems to be caused by a radiation effect on the stem cells. The stem cell effects seem to be transient as judged from the recovery and as judged from the ability of the patients to receive subsequent therapy.

A prolonged neutropenia and lymphocytopenia would normally be associated with a marked increase in the infection rate. This was also the case during the treatment period, but not in the follow-up period.

The Company has committed to a long term follow-up of late complications as secondary neoplasias, and it is comforting that with the October 2002 update in hand no increase has so far been observed as compared to other published NHL series.

Benefit/risk assessment

[^{90}Y]-Zevalin represents an innovative and valuable radioimmuno- treatment approach for follicular B-cell lymphomas. The applicant has carried out a series of clinical phase I-II trials and one phase III trial, which together demonstrate that the [^{90}Y]-Zevalin regimen as described

- is tolerable
- does deliver a predicted radiation dose
- has pronounced antineoplastic activity in follicular B-cell lymphomas with a 50 – 70% response rate, which seems independent of previous treatment and of a number of prognostic factors

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- demonstrates superiority over rituximab in a randomised comparative trial with respect to response rate (76% vs. 47 % response), but not with respect to TTP or DR. Fraction of patients in remission at 6, 9 and 12 months was statistically higher, but TTP and DR showed only a numerically but not statistically significant improvement and there was thus no proof of a translation into a clinical benefit (study106-04)
- at a 25% reduced dose demonstrates a high response rate (66 -83%) in a population of heavily pre-treated follicular lymphoma patients with moderate thrombocytopenia (study 106-05)
- demonstrates a high response rate (59-74%) in an end stage patient population refractory to rituximab and chemotherapy with a duration of remission significantly longer than that following the previous rituximab treatment (study 106-06)

In a heavily pre-treated patient population with end-stage follicular lymphoma refractory also to rituximab the 59-74% chance of achieving a complete or partial response is of potential benefit. Since Zevalin as compared to the patients last rituximab treatment also significantly prolongs the duration of remission (with the limitations of the comparative methods used in a phase II trial) and since the toxicity for these patients seems to having been acceptable, the benefit/risk is favourable.

In light of the weaknesses of the phase III pivotal trial, and taking into account the results of this study the CPMP concluded that the indication needed to be restricted to patients with follicular lymphomas who did not respond satisfactorily to their last rituximab treatment (population included in study 106-06).

Recommendation

”Based on the CPMP review of data on quality, safety and efficacy, the CPMP considered by consensus that the benefit/risk profile of Zevalin in the treatment of patients with rituximab-relapsed or refractory CD20+ follicular B-cell non-Hodgkin's lymphoma (NHL) was favorable and therefore recommended the granting of the marketing authorization under exceptional circumstances.”

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