SCIENTIFIC DISCUSSION

This module reflects the initial scientific discussion for the approval of Simulect. This scientific discussion has been updated until 1 October 2004. For information on changes after this date please refer to module 8B.

1. Introduction

Simulect contains the active substance basiliximab, which is a chimeric murine/human monoclonal antibody (MAb). Basiliximab reacts with the CD25 antigen on T-cells, inhibiting the binding of interleukin-2 (IL-2) to its receptor (IL-2R), and functions as an immunosuppressive agent. *In vitro* tests with human tissues indicate that basiliximab binds only to activated T-lymphocytes and to monocytes/macrophages.

Simulect is a sterile freeze-dried powder for intravenous infusion or injection after reconstitution with the solvent, water for injection. Simulect is marketed in the 20 mg strength. Post-Authorisation, a second strength of 10 mg is authorised.

In adult patients, peak basiliximab serum concentration following a 20-30 minute infusion of 20 mg Simulect is 7.1 ± 5.1 mg/ml. The elimination half-life is 7.2 ± 3.2 days, and total body clearance is 41 ± 19 ml/hr. In infants and children (age 1–11 years, n=25), distribution volume and clearance are reduced by about 50 % compared to adult renal transplantation patients whereas disposition in adolescents was similar to that in adult patients.

The applied indication of Simulect was first for the prophylaxis of acute organ rejection in *de novo* allogeneic renal transplantation and to be used concomitantly with cyclosporin for microemulsion- and corticosteroid-based immunosuppression in patients with panel reactive antibodies less than 80%. In the meantime the indication has been extended for paediatric patients and for the prophylaxis in the triple maintenance immunosuppressive regimen containing ciclosporin for microemulsion - and corticosteroids, and either azathioprine or mycophenolate mofetil.

The proposed standard total dose in adults is 40 mg, given in two doses of 20 mg each. The first dose should be given within 2 hours prior to transplantation surgery. The second dose should be given 4 days after transplantation. Elderly patients do not require a different dosage from younger adult patients.
In paediatric patients weighing less than 35 kg, the recommended total dose is 20 mg, given in two doses of 10 mg each. In paediatric patients weighing 35 kg or more, the recommended dose is the adult dose, i.e. a total dose of 40 mg, given in two doses of 20 mg each. The first dose should be given within 2 hours prior to transplantation surgery. The second dose should be given 4 days after transplantation. The second dose should be withheld if post-operative complications such as graft loss occur.
Reconstituted Simulect can be administered as an intravenous bolus injection or as an intravenous infusion over 20–30 minutes.

2. Part II: Chemical, pharmaceutical and biological aspects

Basiliximab, the active substance of Simulect, is a chimeric murine/human monoclonal antibody (MAb) of the IgG class. The variable regions of the heavy and light chains are of murine origin, and the constant regions are of human origin.

Composition

Simulect is a white lyophilisate to be dissolved in the solvent, water for injection, before administration. Each vial contains 10 mg or 20 mg basiliximab. Buffering agents, sodium chloride, sucrose and mannitol are also present and comply with Ph. Eur. Specifications. The qualitative composition for both strengths is identical. The filling weight indicated corresponds to a 4.0 ml theoretical filling volume for the 20 mg strength and to 2.0 ml theoretical filling volume for the 10 mg strength, respectively. The 7.5% overfilling which permits the withdrawal of the nominal dose from the single-dose container is not included.

Formulations of 5, 10 and 20 mg lyophilisates were used in clinical studies.

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The container is a 6 ml colourless glass vial (borosilicate glass, type I, Ph. Eur.) closed with a rubber stopper and sealed with an aluminum cap with a blue polypropylene flip-off cover.

Development pharmaceutics

The size of the galenical form, of the composition, manufacturing procedure and packaging material has been described sufficiently and in very detail.

Method of preparation

The required amounts of excipients are dissolved in water for injections. The frozen solution of the drug substance is thawed in a laminar flow environment and the calculated amount is added to the excipient solution. Samples of the resulting solution are retained for in-process controls (IPC). The bulk solution is prefiltered in a sterilised vessel and transported to the filling area. It is then sterile filtered and aliquots are dispensed into depyrogenised glass vials. After stoppering, the vials are lyophilised using a procedure which is validated by the quality of the batches produced. Drug product vials are stored at 2-8°C pending analytical release. Particular manufacturing precautions like thawing and equilibration time, maximum standing time of ingredients, requirements for tubings and membrane filters, stirring requirements, are specified.

Production and control of starting materials

The active ingredient in the drug product is a chimeric monoclonal antibody, which recognises the CD25 antigen on the surface of T-cells and inhibits the binding of interleukin-2. The antibody has a molecular weight of ca. 150`000 daltons and comprises light and heavy chains with variable regions of murine origin and constant human regions. The antibody has been developed under the laboratory code, SDZ CHI 621. The proposed International Nonproprietary Name (INN) is basiliximab.

Development genetics

Simulect originates from a murine hybridoma cell line (RFT5, IgG 2a) producing a monoclonal antibody against the alpha chain of the human IL-2-receptor. In order to retain high avidity to CD25 and reduce immunogenicity in humans, the variable regions of the heavy and light chains are of murine origin, and the constant regions are of human origin. In order to construct and express a monoclonal antibody binding to the CD25 epitope, the genetic information for the heavy and light chain variable regions from an existing murine antibody (RFT5) as well as for the constant parts from other sources had to be isolated. The heavy and light chain variable regions of Simulect were isolated after the construction of genomic libraries from the hybridoma cell line RFT5. Positive clones isolated from the libraries were characterised for the existence of the complete promoter/enhancer/leader/exon sequences and the deduced amino acid sequences from the heavy and light chain variable region exons were compared to the AA-sequence resulting from direct protein sequencing. The heavy and light chain variable region exons including regulatory sequences were cloned in front of human heavy and light chain constant regions. The resulting expression constructs were either the murine variable light chain and human light chain constant region or the murine variable heavy chain and human heavy chain constant region in the background of the pSV2neo plasmid. A mutated DHFR gene was introduced in the light chain construct to allow the amplification of the introduced constructs in transfected cells after selection with methotrexate.

Both constructs were transfected by electroporation into a cell line, which was negative for the background expression of immunoglobulins. Transfected cells were selected by the addition of G418, cloned by limiting dilution and screened for their ability to inhibit the binding of iodine labelled hIL-2 to either human PBL or MT4 cells. The clone producing the highest amounts of antibodies were used to construct the MCB. An estimation of the number of integrated copies of the two constructs in the MCB and the MWCB revealed 2 copies for the heavy chain and 4 for the light chain construct. Genetic stability of the cell lines was adequately demonstrated. Stability of the expression of the constructs was determined by Northern blot analysis of the heavy and light chain mRNA and indicated stable expression in the MCB, MWCB and 2 post production lots.

Cell bank system

The antibody is expressed in murine myeloma cells in cell culture. The cell bank system was tested appropriately according to the CPMP/III/5271/94 and CPMP/ICH/295/95 guidelines.

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The MCB was established in 1990. Vial 4 of the primary seed lot was used to prepare a Master Cell Bank (MCB). The cells were cultivated in serum-free medium, but for long term storage were resuspended in a freezing medium which contains foetal calf serum. Thus, FCS was used only during the establishment of the MCB. The supplier for the foetal calf serum (US origin) guarantees that the serum is free of mycoplasmas and viruses. The MCB was shown to be free of viral contamination of bovine origin. Today, after a storage period of 7 years, no significant decrease in the viability after thawing is observed. Vial 14 of the MCB was used to prepare a Working Cell Bank (WCB). In the medium (2057.24.02) bovine-derived insulin was replaced by recombinant human insulin from Escherichia coli. Cells were grown in a T-flask and then expanded to roller bottles. Cells were harvested by centrifugation and resuspended in a new freezing medium (without calf serum) prior to dispensing into vials. The vials were frozen and stored in the vapour phase of liquid nitrogen. Vials were labelled with a laboratory code (CHI 621), the code identifying the primary seed lot, MCB vial number and the vial number of the WCB 1-95.

All test results indicate that the cells are well characterised and stable. The absence of detectable adventitious viruses, bovine viruses and murine viruses has been demonstrated with the only exception of a xenotropic retrovirus which is not unexpected for a murine cell line. It could be shown that this retrovirus is an infectious retrovirus derived from the persistently infected SP2/0 murine myeloma cell line. It was demonstrated that the retrovirus was not able to infect cell lines of human origin. Therefore, the cell line can be classified as case B according to section 5 of the CPMP/ICH/295/95 guideline and can be accepted as a basis for the production of a medicinal product. According to the CPMP/ICH/295/95 guideline, three batches of the unprocessed bulk were tested for retroviruses and for adventitious viruses with negative result. Only in one of three batches tested about 10^6 retroviral particles per ml were determined in the bulk harvest.

The drug substance is manufactured at Novartis Pharma AG in Basel and the finished medicinal product at Novartis Pharma AG in Stein (both Switzerland). The solvent, water for injection, is manufactured at Novartis Pharma AG, Stein, Switzerland, and Nycomed Austria GmbH, Linz, Austria.
For production, the cells are cultured in serum-free medium with recombinant human insulin as the only component of biological origin resulting in a high safety level of the source material for the manufacture of Simulect. The antibody is produced using cell culture technology.

Purification

The purification process comprises eight steps, two of which are robust procedures for viral inactivation and removal. The sequences of operations was changed during the development program to improve the logistics of viral clearance. Steps following viral clearance are carried out in separate rooms from preceeding steps to avoid cross contamination. Validation studies show that process-related impurities, such as column leachables, host cell proteins and DNA are efficiently and reproducibly eliminated. Structural variants of the chimeric antibody such as dimers and degradation products remain at low concentrations. The most common impurities identified were trace amounts of antibody-related by- and degradation products. The production of the finished product is well described. After lyophilisation, the vials are closed, sealed and examined. The quality of the lyophilised cake was improved during development by adding mannitol to the excipients. The market formulation is identical to that used in Phase III clinical trials.

Facility, equipment, cleaning procedures, in-process controls, re-use of columns, medium preparation has been described sufficiently.

Definition of a batch

A harvest lot is defined as the amount of culture filtrate which has been in the harvest tank and has been transferred to the storage tank. Each harvest lot which meets the IPC specifications is purified individually up to product fraction step 3. When all harvest lots from one cell cultivation run have been purified to this stage, the resulting lots of product fraction step 3 must be released before pooling. Part harvests are processed individually to Step 3 of the process. The resulting product fractions from three part harvests are pooled and processed as a single batch through the remaining steps of the process. Thus a single cultivation, which yields six part harvests results in two batches of purified drug substance.

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Process validation

The following topics were addressed by the process validation:

Medium preparation and medium stability, consistency of inoculum preparation, seed culture preparation and production culture, stability of cellular productivity, microbial contamination control during harvest, adventitious agent testing of bulk harvest, consistency of yield of individual purification steps, microbiological monitoring of purification and buffer preparation, removal of process related contaminants, stability of intermediates, consistency of isoform distribution, column performance and life-time of columns and virus removal and inactivation (validated with small scale process), homogenisation of drug substance solution after thawing, homogenisation of bulk formulated solution, pre-filtration to transport vessel, washing and sterilisation of stoppers, washing and depyrogenisation of vials, filtration to filling line, vial filling process, lyophilisation process. Studies to demonstrate material compatibility with tubings, sterile filteres and stoppers were performed.

Characterisation

The chimeric antibody including the batch No. 94904, which is used as reference substance, is extensively characterised using a battery of modern analytical techniques. Data on the following parameters are provided:

- Structural formula (sequence of the light and heavy chains)
- Molecular formula based on the amino acid sequence
- Relative molecular mass of 144 354.19 Daltons
- Amino acid composition
- Isoelectric points of the three isoforms
- Structural evidence for the active substance
    - Post translational modifications (amino acid sequence, carbohydrate linkage)
    - Molecular mass determination by MALDI-TOF MS
    - Amino acid sequence determination (N-terminal sequencing, peptide mapping, microheterogeneity of the C-terminal part)
- Physico-chemical characteristics
    - SDS-PAGE (reduced)
    - IEF
    - Cation exchange chromatography
    - Size exclusion chromatography
- Biological characterisation
    - Inhibition of the mixed lymphocyte reaction
    - Inhibition of IL-2 receptor binding
    - Cross-inhibition of IL-2 receptor binding by CHI 621 and RFT5
    - Immunoglobulin subclass determination
    - Staining of various tissues with biotinylated CHI 621 and RFT5

Analytical development

In addition to the validation of the routine tests, the dossier contains description on the validation of methods used during development. The validation studies have been performed very well. The choice of routine tests is described comprehensively.

Clearly defined and scientifically justified specifications have been set. This includes suitable packaging for the drug substance, shelf life and storage conditions, release and shelf life specifications

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for each quality characteristic. Most of the specifications are obtained from the results of the long-term stability testing programme.

In addition to the routine release tests, the following tests are performed to characterise the reference material: amino acid composition, subclass determination, molecular mass determination of the heavy and light chains, peptide mapping, determination of free SH-groups, quantification of isoforms, oligosaccharide characterisation.

Data are submitted on all listed parameters which show that the process is considered as consistent.

Impurities

The most common impurities identified were trace amounts of antibody-related by- and degradation products. The removal of various process-related impurities was also investigated. The results demonstrate the removal of these substances during the purification process. Testing for these compounds will no longer be included in the release criteria for SDZ CHI 621 drug substance solution.

Control tests on the finished product

The control tests and specifications for the drug product include controls on purity, by-products and sterility. Batch analysis shows that for all parameters a constant quality is achieved for pilot and the four production scale batches.

Stability

Active substance

Stability data show that a temperature of less than -60^0C is the preferred storage temperature for the drug substance. Stability data up to 12 months are available for material produced at pilot scale. Three batches from the full scale production plant have been put on stability and 6 month data are available at the time of filing. The data have been approved to support a re-test date of 36 months for the active ingredient stored at < -60°C.

Finished product

Stability data for pilot batches stored for up to 24 months are available and show that at -20^0C and 5^0C the drug product remains stable and within specifications. Three further batches of drug product produced at production scale have been put on stability. Data of 12 months are available at the time of filing.

Post-authorisation, the applicant submitted additional stability data obtained from three production batches, which sufficiently justify the extension of the shelf life as declared in the SPC.

Virus validation

The overall viral safety of Simulect has been demonstrated. Four steps have been identified to ensure the viral safety of the product. Enveloped and non-enveloped viruses are effectively removed by a 15nm filtration step. Two chromatographic steps further contribute to virus removal. The re-use of chromatography columns has been validated and the lifetime of the columns has been established. Retroviruses and other pH-sensitive viruses are inactivated during incubation at low pH.

TSE compliance

Compliance with Directive 1999/82/EEC has been sufficiently demonstrated.

3. Part III: Toxico-pharmacological aspects

Part III of the dossier was considered as of very good quality. Documents were filed according to the Notice to Applicants. The studies were performed according to the principles of GLP. The results of pre-clinical screening do not reveal adverse effects against the use of Simulect in the clinical setting.

Pharmacodynamics

Pharmacodynamic studies with Simulect or its murine progenitor were either performed with mononuclear cell fractions prepared from peripheral blood from 4 different species (human, rhesus,

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cynomolgus and dog), standard tissues of human origin or IL-2-receptor expressing cell lines. Simulect bound specifically to the α-chain of the primate IL-2-receptor, but not to the dog IL-2 receptor. Simulect inhibited the binding of human IL-2 to its receptor at concentrations of 1µg/mL. Receptor blocking profiles of Simulect and its murine progenitor RFT5 were comparable; they demonstrate equal potency in their ability to inhibit the binding of radiolabelled IL-2 on the IL-2 receptor expressed on T-lymphocytes. The binding of IL-2 and consequentially lymphocyte proliferation are completely inhibited at concentrations achieved in the clinical setting, thus indicating the successful grafting and expression of the variable regions of the heavy and light chain. Binding studies of Simulect with standard tissues of human origin indicate specificity for cells expressing CD25 which mostly exist within lymphoid organs.

Pharmacokinetics

Two different assay systems (ELISA and RIA) were used to determine Simulect concentrations in rhesus monkeys or human blood samples.

Pharmacokinetics of SDZ CIH 621 following single or multiple administration were studied in rhesus and cynomolgous monkeys in a 4-weeks intravenous toxicity studies.

Toxicology

Single dose and repeated dose toxicity

While classical single dose toxicity studies have not been performed, the results of several repeated dose toxicity studies in Rhesus monkeys indicated no toxic effects up to the maximum dose of 5mg/kg. Repeated dose toxicity study has been performed in monkeys (4 weeks intravenous in the rhesus monkey with an 8 week treatment, doses at 0.5 to 4.5 mg/kg every 4th day). No mortality and apparent signs of toxicity were revealed. No drug-related effects on body weight, no clinical or hematological findings, ophalmoscopic or electrocardiographic findings. No effects on organ weight, macroscopic and microscopic necroscopy.

Apart from the studies performed in primates, no toxicity studies in rodents or non-rodent animals except primates could have been carried out because of the species specificity of the antibody. Increased clearance occurred in the low dose group corresponding to the occurrence of anti-idiotypic antibodies in 75% of the animals of this group after four weeks of administration. The mean elimination half-time was approximately 5.5 days.

Reproduction studies

Three groups of 12 pregnant cynomolgous monkeys were treated intravenously with 0 (placebo), 1 and 5 mg/kg b.w. / day twice weekly on days 20, 24, 27, 31, 34, 38, 41, 45 and 48 of gestation. At 5 mg/kg no maternal toxicity was observed. Two abortions out of 12 pregnancies could be dose - related. Mean fetal weight was lower than in control group.

A linear relationship between dose and exposure was observed after single administration. Elimination was slow in both groups, with an apparently biphasic pattern.

Maternal pharmacokinetics showed that at low dose (1 mg/kg) there were marked interindividual differences, which might be due to differences in antibody levels. Differences were not important at the high dose, thus their role in Simulect embryofetotoxicity is possibly a minor one. In the absence of maternal toxicity both dose levels induced dose-related intrauterine growth retardation. At the high dose there were cases of abortion (2/12, 17%) and a single instance of malformation.

Studies on the embryo-fetal development in Cynomolgus monkeys did not indicate an impact of the intravenous administration of Simulect on the foetus.

Mutagenic potential

Negative results have been obtained in the Ames test and in chromosomal aberration tests with V79 Chinese Hamster Cells as expected for a proteinous substances like Simulect. The compound was unable to induce mutations in *S. typhimurum.*

The mutagenic/oncogenic potential has not been investigated which is acceptable for a monoclonal antibody.

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Local tolerance

Effects of local tolerance/toxicity were studied in rabbits, an animal system which does not express the epitope Simulect is binding with. The results of the studies did not indicate significant local irritations due to the test substance.

Immunotoxicity

There was evidence of anti-idiotype antibody formation in toxicokinetic studies.

Cross reactivity studies on many human tissues indicate that no immunological reactions are to be expected in man.

4. Part IV: Clinical aspects

Simulect is a monoclonal antibody directed against the α-chain of the IL-2 receptor. Binding leads to an inhibition of activated T-lymphocytes. The indication for Simulect is the prophylaxis of acute organ rejection in *de novo* allogenic renal transplantation and is to be used concomitantly with ciclosporin for microemulsion- and corticosteroid-based immunosuppression, in patients with panel reactive antibodies less than 80%, or in a triple maintenance immunosuppressive regimen containing ciclosporin for microemulsion, corticosteroids and either azathioprine or mycophenolate mofetil.

Renal transplantation is an efficient therapy of end-stage renal failure. One of the major problems to be managed for successful organ transplantation is the reaction of the immune system of the recipient against the donor organ. This could lead to acute or chronic rejection, and in case of unsuccessful treatment to the loss of the transplant.
In renal transplantation, the majority of centres report the incidence of acute rejection to be between 10 - 40%, and approximately 80-90% of first rejections occur within the first 6 weeks of transplantation. Acute and chronic rejection are the most common causes of graft failure. The acute rejection episode is a risk factor for chronic rejection and graft loss. Further studies have shown that especially late acute rejection episodes (> 60 days) are combined with the risk of chronic rejection. Nevertheless, the benefit of therapy of acute rejection and the frequency of acute rejection episodes are also important for the risk of chronic rejection. Graft function is usually measured by glomerular filtration rate, and serum creatinine levels.

The most common regimens for immunosuppression used are the “double”“ (cyclosporin and steroids) and the„“triple”“ (cyclosporin, azathioprine and steroids) therapy regimes. Biological anti-lymphocyte preparations, such as polyclonal anti-T cell immunoglobulins are additionally used for prevention or treatment of rejection episodes. The decision to use one of these medication combinations mainly depends on the immunological risk profile of the patient. Currently, only one monoclonal antibody is approved for treatment of rejection episodes, i.e., the anti-CD3 antibody Orthoclone OKT3. Because these agents interact with all T lymphocytes, significant side-effects occur. The binding of these preparations is rather unspecific with all T lymphocytes. In the last years, non-specific immunosuppressive agents have been developed, e.g. mycophenolate mofetil, tacrolimus and sirolimus. During the immune reaction of the host against the transplant, IL-2 induces the rapid proliferation of T lymphocytes by binding to its high-affinity receptor on the surface of antigen-activated T lymphocytes. IL-2R comprises three trans-membrane protein chains: α (CD25), β (CD122) and γ (CD132). The expression of CD25 is low on resting T lymphocytes but is induced due to allogenic stimulation after grafting, thus leading to a high level of expression on the surface of activated T lymphocytes. The predominant role of the IL-2/IL-2R pathway in T-lymphocyte proliferation and the selective expression of CD25 on activated T lymphocytes led to the identification of CD25 as a potential target for monoclonal antibody therapy. Simulect is a monoclonal chimeric mouse-human antibody directed against the α -chain of the IL-2 receptor. The mechanism is the inhibition of immunocompetent cells which are involved in the acute rejection. At the time of the assessment of the marketing authorisation for Simulect, the use of monoclonal anti-IL-2 receptor antibodies was not approved for any kind of diseases. In other clinical studies, murine anti-IL-2 receptor antibodies were tested, but without clinical benefit.

Clinical studies

457 adult renal recipients received Simulect in three phase I-II studies and two phase III studies. Ninety-four patients received Simulect in three phase I-II and 363 adult kidney transplant recipients

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received Simulect in two phase III studies. In addition paediatric renal and liver transplant patients were treated with Simulect. Moreover, adult liver transplant recipients were included in two clinical studies but the applicant did not pursue the claim for the liver transplantation indication.

The studies had the following aims:

- Dose finding studies: The results of phase I-II/dose-finding studies did not show any dose-dependence from body weight, gender, age or race. The analysis of the phase I-II studies (B101, B105, B106) shows that 40 mg Simulect are efficient in suppressing CD25-positive T-lymphocytes over 4-6 weeks.
- Developing of a dose regime which prevents over-immunosuppression: The dose regime of 2 x 20 mg Simulect on the days 0 and 4 does not lead to over-immunosuppression. The rate and kind of infections were similar in both arms of Phase III trials.
- Determination of immunogenicity: Screening was performed both during and following Simulect treatment for a variety of potential antibody responses, e.g. human anti-chimeric antibodies (HACA), human anti-mouse antibodies (HAMA) and other. HAMA responses to Simulect treated patients were rare (3-5%).
- Reduction of the rate of acute rejection: The reduction of the rate of acute rejection was the primary endpoint of two phase III studies. Simulect treated patients had a lower risk of developing an acute rejection episode. However, the patient and graft survival rate was similar in the Simulect- and placebo-group.
- Safety profile: 94 patients in phase I-II and 363 in phase III patients received cumulative doses of Simulect. All patients were followed up for 12 months and up to 5 years (study extension). There were no additional adverse events reported in the Simulect-group compared with the placebo-group. Furthermore, the incidence and the kind of adverse events were similar.

Summary of the clinical studies submitted for the Marketing authorisation assessment:

Table 1: summary of studies included in the clinical development program

Study No.	Country	Design and number of patients (n)	Dosage regimen (total Simulect dose)
Phase I-II studies			
B101	UK	Open (n=24)	15 - 150 mg between days 0 - 24
B105	UK, NL	Open (n=39)	15 mg or 20 mg between days 0 - 10
B106	FR	Open (n=32)	40 mg, 60 mg on day 0
Phase III-studies			
B201	BE, Can, CH, FR, DE, NL, UK	randomised, double-blind, placebo-controlled (n=380)	40 mg divided between days 0, 4
B352	USA	randomised, double-blind, placebo-controlled (n=346)	40 mg divided between days 0, 4

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Clinical studies submitted subsequently, after the Marketing authorisation:

Table 2: summary of studies included in the clinical development program

Study Code	Study Objective (assessments)	Patient Population, no. randomized	Study duration	Simulect doses and control groups
I	**Studies in renal transplantation in adults using triple immunosuppressive therapy**			
INT-10	Efficacy, Safety, tolerability, at 6m post transplantation, limited follow-up at 12m	345 adult, renal 1st or 2nd transplantation, aged 18-70, male/female	6 months Doses on day 0 (<2h pre-Transplantation) and day 4.	2 x 20mg (n=172) placebo (n=173) [All pts also had Cyclosporine, steroids, azathioprine]
INT-11	Safety, tolerability, efficacy at 6m post transplantation, follow-up at 12m	123 adult, renal transplantation, aged 18-70, male/female, first or second transplantation	6 months Doses on days 0 (<2h pre-transplantation) and 4.	2 x 20mg (n=59) placebo (n=64) [All pts also had Cyclosporine, steroids and mycophenolate mofetil]
US-01	Safety, tolerability, efficacy (+health economics) at 6 and 12m post transplantation.	138 adult, primary renal transplantation aged 18-75, male/female	12 months Doses on days 0 (<2h pre-transplantation) and 4.	2 x 20mg Simulect plus: early Cyclosporine (n=70) delayed Cyclosporine + ATGAM (n=68)
II	**Studies on transplantation in paediatric patients**			
B152	PK evaluation, safety, efficacy at 6m and 12m post transplantation.	41 paediatric, renal, transplanted patients either sex aged <16 yrs	12 months Doses at days 0 and 4.	2 x 12mg/m^2 to a max 2 x 20mg (n=13) 2 x 10 or 20mg (n=28) [All pts also had Cyclosporine and steroids]
C102	PK evaluation, safety, efficacy, at 6m and 12m post transplantation	20 paediatric male/female liver transplanted patients aged <16 yrs	12 months Doses on days 0 and 4.	2 x 12mg/m^2 to a max 2 x 20mg (n=20) [in addition both groups had Cyclosporine and steroids]
III	**Supportive Studies in liver transplantation in adults : Unclaimed indication**			
C304	Efficacy safety, tolerability at 6m and 12m. Also PK characteristics.	381 adult, de novo liver transplanted patients aged 18-75, male/female	12 months Doses on days 0 (<6h after reperfusion of graft) and 4.	2 x 20mg (n=188) placebo (n=193)
INT-13	Efficacy, safety, tolerability, at 6m post transplantation, follow-up at 12m	101 adult, de novo liver transplanted patients aged 18-75, male/female	6 months Doses on days 0 (<6h after reperfusion of graft) and 4.	2 x 20mg (n=101) [in addition, patients received Cyclosporine, steroids, azathioprine)

(Studies B152, C102, C304, INT-10 and CHI-US-01 also provide PK or PD data to the program)

Pharmacodynamics

Pharmacodynamic data were obtained from all 7 studies performed. Assays performed were mainly flow cytometry of $CD25^+$-T-cells, measurement of soluble IL-2R serum levels and antibody response - immunogenicity screening.

A concentration of 0,2 µg/ml Simulect is sufficient to decrease the percentage of CD25α-positive T-lymphocytes to less than 3% (receptor-saturating threshold).

Simulect does not influence other cells, and in particular T-cell subsets like CD3, CD4 etc. Soluble IL-2 receptor shedding from the surface of activated T-cells shows an inverse pattern to CD25α-positive T-lymphocytes. Furthermore, data are available regarding body compartments. Pelvic lymph nodes of 11 patients were analysed and IL-2R was blocked in 7/11 (64%) patients, 1-6 hours after application of Simulect. Comparable results were obtained from renal biopsies.

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The immunogenicity of Simulect is low, only 1 of 270 tested patients developed anti-chimeric antibodies. Six of 172 patients developed anti-mouse antibodies, whereas 4 of them also received OKT3 in addition to Simulect.

Pharmacokinetics

The analysis regarding pharmacokinetic included data from all seven clinical trials (two studies ongoing). An idiotypic-specific ELISA method was used to measure the Simulect serum levels. This ELISA was shown to be specific and sensitive and to have minimal interferences from soluble IL-2R α.

In adults, after administration of a single dose of 40 mg of Simulect, the steady-state distribution volume is 8.8 ± 3.2 l, the elimination half life is 5.8 ± 2.0 days, and the total body clearance is 46.2 ± 16.1 ml/h. Mean peak serum concentration following a single dose of 20 mg of Simulect is 7.1 ± 5.1 μg/ml. No clinically relevant influence of body weight on pharmacokinetic data was noted.

In infants and children (age 1–11 years, n=25), the steady-state distribution volume was 4.8±2.1 l, half-life was 9.5±4.5 days and clearance was 17±6 ml/h. In adolescents (age 12–16 years, n=14), the steady-state distribution volume was 7.8±5.1 l, half-life was 9.1±3.9 days and clearance was 31±19 ml/h. Drug clearance and volumes in children were on average half of those in adults; whereas disposition in adolescents was similar of that of adults.

When administered as 20 mg on days 0 and 4 in the context of triple therapies including azathioprine or mycophenolate mofetil (studies INT-10 and US-01), Simulect did not appear to alter the pharmacokinetic-dynamic relationship compared with dual therapy. It showed similar ranges of CD25 saturation compared with dual therapy, and the efficacy-safety profile did not raise any concerns in multicenter controlled trials.

Efficacy

Use of dual Immunosuppressive regimen

Two phase III studies were performed to determine the efficacy and safety of Simulect in adult patients. Most of the patients received cyclosporin and steroids (dual therapy). Some patients were additionally treated with azathioprine or mycophenolate mofetil (MMF). The Simulect and placebo-group were well matched in terms of age, gender, race, weight, height, cause of end stage renal disease, cold ischemic time of the transplant, mismatches etc.

The primary endpoint was the percentage of patients free of rejection during the first 6 months post-transplant. Treatment with Simulect leads to a significant reduction of first acute rejection episodes. But there were no significant differences between the two arms in patient or graft survival after 6 and 12 months (combined data from the two studies are presented in table 3). With regard to secondary end-point, Simulect reduced the number of rejection episodes requiring antibody or alternative immunosuppressive agents. Fewer graft losses attributed to rejection were observed in the Simulect group as compared to placebo. In the Simulect group, a lack of late rejections was observed. At the time of the initial assessment, the CPMP did not agree with the estimate of the applicant that Simulect could replace polyclonal or monoclonal anti-T-cell antibody preparations because OKT3 was not approved in Europe for prophylactic use and since Simulect had not been investigated against these two agents.

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Table 3: Primary and secondary efficacy endpoints (Intent to treat population - Month 0-6 and 0-12):

Endpoint	Month: 0 - 6					Month: 0 - 12				
	Simulect (N=363)		Placebo (N=359)		P-value	Simulect (N=363)		Placebo (N=359)		P-value
Primary endpoint										
Death, graft loss or first rejection episode	145	40%	201	56%	0.001	159	44%	213	59%	0.001
Secondary endpoints										
Death	12	3%	8	2%	0.378	14	4%	12	3%	0.711
Death or graft loss	32	9%	36	10%	0.577	42	12%	46	13%	0.610
Graft loss	24	7%	29	8%	0.450	32	9%	37	10%	0.496
First rejection episode	126	35%	187	52%	0.001	137	38%	197	55%	0.001
Second rejection episode	37	10%	57	16%	0.023	43	12%	65	18%	0.018
First biopsy confirmed rejection episode	108	31%	152	45%	0.001	115	33%	162	48%	0.001
Death, graft loss or first biopsy confirmed rejection episode	129	36%	167	47%	0.003	140	39%	181	50%	0.001
Graft loss preceded by a rejection episode	11	3%	18	5%	0.175	17	5%	24	7%	0.245
Graft loss preceded by a rejection episode treated with antibody therapy	4	1%	16	4%	0.006	9	2%	18	5%	0.073
First rejection episode treated with antibody therapy	51	14%	91	25%	0.001	54	15%	94	26%	0.001
First rejection episode treated with antibody therapy, tacrolimus, MMF, or azathioprine	64	18%	112	31%	0.001	71	20%	121	34%	0.001

The results of 5-years follow-up of the Phase III trials (B201 and B352) have been submitted after the marketing authorisation, as follow-up commitment. With regard to efficacy, particular reference was made to the clinically relevant parameters (such as chronic rejections, graft and patient survival), needed for rejection treatments.
In a pooled analysis of these two five-year open-label extension studies (586 patients total), the combined graft and patient survival rates were not statistically different for the Simulect and placebo groups. These extension studies also showed that patients who experienced an acute rejection episode during the first year after transplantation experienced more graft losses and deaths over the five-year follow-up period than patients who had no rejection. Simulect did not influence these events.

Use of triple Immunosuppressive regimen

Simulect is effective in reducing the incidence of acute rejection episodes in *de novo* organ transplant recipients. This benefit was clearly demonstrated in the triple therapy renal studies.

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Of the three adult studies reported, both placebo controlled studies INT-10 and INT-11 demonstrated significantly superior efficacy to placebo, and compared against an active comparator in the third study US-01 the treatment effect was equivalent.

- During the 6-month pivotal double-blind multicenter study INT-10, Simulect proved highly significant in reducing the incidence of an acute renal rejection (20.8% in Simulect *versus* 34.9% in placebo, p=0.005); this difference of 14% corresponded to a relative reduction of 40% in crude incidence. The difference in the proportion of patients experiencing an acute rejection episode at 4 weeks post-transplant is approximately 16%. Approximately 30% of the placebo treated group experienced acute rejection by 4 weeks, indicating that Simulect almost halved the incidence of acute rejections. Treatment failure (acute rejection, graft loss or death) was also lower in the Simulect group (25.6% in Simulect *versus* 39.5% in placebo, p=0.008).

- The second placebo-controlled study INT-11 showed similarly favourable results though this study was not powered to demonstrate statistical significance. The crude rate for first acute rejection episode was lower in the Simulect group (15.3%) that in the placebo group (26.6%), a relative reduction of 42.5% within the first 6 months post-transplantation. Although this difference was not statistically significant, the magnitude of relative reduction was in accordance with the findings of the CHI INT-10 study. Between-group differences in all efficacy variables assessed favoured Simulect. Both rejection episodes treated with antibody therapy (p=0.079) and treatment failure (p=0.061) were borderline statistically in favour of Simulect (despite the study not being powered to show a difference) and the incidence of graft loss was less with Simulect (5.1% vs. 7.8% in the placebo group).

Using Kaplan-Meier analysis, the difference in survival estimates was statistically significant in favour of Simulect at month 6 for both first acute rejection episode and treatment failure (p=0.002 for difference in Kaplan-Meier estimates in both cases).

- The third study compared Simulect to an active comparator ATGAM, and demonstrated efficacy at a near identical level. ATGAM is not to consider as a relevant comparator since it is not licensed in all European countries. Polyclonal anti-T-cell sera can differ markedly with respect to clinical efficacy and safety parameter. Therefore, the ATGAM arm should only be considered carefully as model for ATGs. The data on comparison with an ATG were limited.

Simulect in combination with early Neoral was as efficacious as ATGAM and delayed Neoral in the prophylaxis of acute rejection in this study. The rate of biopsy proven acute rejection was similar between the treatment groups at 6 and 12 months post-transplant (approximately 20% in each treatment group at both timepoints). The incidence of treatment failure was also similar, at 21.4% in the Simulect group at both 6 and 12 months compared to 20.0% and 23.1% respectively in the placebo group. The time to first biopsy proven acute rejection was longer in the Simulect group than in the ATGAM group; an estimate of the time until one quarter of the patients had experienced their first treated rejection episode was longer in patients treated with Simulect than with the active comparator. Death-censored graft survival was similar between the treatment groups and was 97% and 97% in the Simulect and ATGAM groups respectively.

Overall conclusions with regard to the use of Simulect in triple immunosuppressive regimens:

- The pivotal double-blind multicenter study INT-10 demonstrated a favourable and statistically significant benefit for Simulect in rejection prophylaxis, when used with triple background maintenance immunosuppressive therapy regimen (with azathioprine).
- In the smaller placebo-controlled study INT-11, between-group differences in all efficacy variables assessed favoured Simulect. Relative reduction in the rate of first acute rejection episode seen at 6 months, at 42.5%, was similar to that seen in the pivotal study. Treatment failure, compared using Kaplan-Meier survival estimates, was statistically significantly lower in the Simulect group.
- Compared to an active comparator ATGAM, in study US-01 Simulect demonstrated efficacy at a near identical level.
- Incidence of graft loss was low and comparable between treatments in all studies.

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Safety

Simulect did not appear to add to the background of adverse events seen in organ transplantation patients as a consequence of their underlying disease and the concurrent administration of immunosuppressants and other medications. In the four placebo-controlled trials, the pattern of adverse events in 590 patients treated with the recommended dose of Simulect was indistinguishable from that in 595 patients treated with placebo. Simulect did not increase the incidence of serious adverse events observed when compared to placebo. The overall incidence of treatment-related adverse events among all patients in the individual studies was not significantly different between the Simulect (7.1 % - 40 %) and the placebo (7.6 % - 39 %) treatment groups.

In adult patients:
The most commonly reported (> 20 %) events following dual or triple therapy in both treatment groups (Simulect vs. placebo) were constipation, urinary tract infections, pain, nausea, peripheral oedema, hypertension, anaemia, headache, hyperkalaemia, hypercholesterolaemia, surgical wound complication, weight increase, increased serum creatinine, hypophosphataemia, diarrhoea and upper respiratory tract infection.

In paediatric patients: The most commonly reported (> 20 %) events following dual therapy in both (< 35 kg vs. ≥ 35 kg weight) cohorts were urinary tract infections, hypertrichosis, rhinitis, fever, hypertension, upper respiratory tract infection, viral infection, sepsis and constipation.

Incidence of Malignancies: The overall incidence of malignancies among all patients in the individual studies was similar between the Simulect and the comparator treatment groups. Overall, lymphoma/lymphoproliferative disease occurred in 0.1 % (1/701) of patients in the Simulect group compared with 0.3 % (2/595) of placebo patients. Other malignancies were reported among 1.0 % (7/701) of patients in the Simulect group compared with 1.2 % (7/595) of placebo patients.

Incidence of Infectious Episodes: The overall incidence and profile of infectious episodes among dual and triple therapy patients was similar between the Simulect and the placebo treatment groups (Simulect = 75.9 %, placebo = 75.6 %); the incidence of serious infections was 25.2 % in the Simulect group and 24.8 % in the comparator group. The incidence of CMV infections was similar in both groups (14.6 % vs. 17.3 %), following either dual or triple therapy regimen.

The incidence and causes of deaths following dual or triple therapy were similar in Simulect (2.8 %) and placebo groups (2.6 %), with the most common cause of deaths in both treatment groups being infections (Simulect = 1.3 %, placebo = 1.4 %).

Among the post-marketing clinical studies assessed (ITT population, n = 1161), the bolus injection of Simulect, compared with the intravenous infusion over 20–30 minutes, was well tolerated, with a comparable incidence of adverse events reported on the days of Simulect administration. There was no limiting acute intolerance to the administration of Simulect as an IV bolus injection. Furthermore there was no evidence of cytokine-release syndrome or anaphylaxis in any of the studies.
In a pooled analysis of the two five-year extension B201 and B352 pivotal studies, the incidence of LPD and cancer was found to be equal with Simulect 7% (21/295) and placebo 7% (21/291). Long-term safety data also showed that the incidence and cause of death remained similar in both treatment groups, (Simulect 15 %, placebo 11 %), the primary cause of death being cardiac-related disorders (Simulect 5 %, placebo 4 %).

First 5 year renewal

During the period cover by the eight PSUR the main safety concerns described were hypersensitivity reactions. However, the frequency of these events is in the range of what could be accepted from hospitalised patients and section 4.4 of the SPC currently states a warning regarding the rarely occurrence of severe acute hypersensitivity reactions including anaphylactoid type reactions. These reactions have to continue to be closely monitored including suspicious cases of cytokine release syndrome in the yearly safety update reports.

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Risk/benefit assessment

The applicant has demonstrated, in two Phase III clinical trials, that the addition of Simulect to a standard immuno-suppressive regimen reduces the number of acute graft rejection episodes. There were no significant differences between the two arms in patient or graft survival after 6 and 12 months. Beside the significant improvement in the primary endpoint, other factors also had demonstrated the superiority of Simulect over the used standard immunosuppressive regimen. The data demonstrated a good safety profile of Simulect during the 12-months follow-up period. The marketing authorisation has been therefore recommended, waiting for the results of 5-years follow-up of the Phase III trials.

Further to the assessment of the 5-years follow-up safety and efficacy data, as well the clinical data related to the use of Simulect in triple immunosuppressive regimen, the risk-benefit ratio was considered unchanged.

5. Conclusions

On the basis of the assessment of the dossier as described in this assessment report, the CPMP evaluated in depth the risk-benefit balance and amended the Summary of Product Characteristics in order to ensure that all considerations were properly reflected. A positive opinion was adopted for Simulect for the following indication:

Simulect is indicated for the prophylaxis of acute organ rejection in *de novo* allogeneic renal transplantation in adult and paediatric patients. It is to be used concomitantly with ciclosporin for microemulsion- and corticosteroid-based immunosuppression, in patients with panel reactive antibodies less than 80%, or in a triple maintenance immunosuppressive regimen containing ciclosporin for microemulsion, corticosteroids and either azathioprine or mycophenolate mofetil.

Based on the CPMP review of data on quality, safety and efficacy at the time of the first 5 year renewal, the CPMP considered by consensus that the benefit/risk profile of Simulect remain favourable in the approved therapeutic indication.

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