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

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Withdrawal Public Assessment Report

Of the Marketing Authorisation Application for

SCINTIMUN
(Besilesomab)

EMEA/H/C/653

Applicant: CIS bio international

This Withdrawal Public Assessment Report is based on the latest assessment report adopted by the CHMP prior to the Applicant's withdrawal of the marketing authorisation application. It may not include all available information on the product in the case where the CHMP assessment of latest submitted information was still ongoing.
It should therefore be read in conjunction with the Questions and Answers Document on the withdrawal of the marketing application for this product, which provides an overview on all available information on the product at the time of the Applicant's withdrawal.

This product was later resubmitted to the EMEA. See here for information on outcome of resubmission.

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LIST OF ABBREVIATIONS

ATC	Anatomic and Therapeutic Classification
AUC	Area under the curve
CEA	Carcinoembryonic antigen
CI	Confidence interval
Cmax	Concentration maximum
CRF	Case Record Form
CT	Computed tomography
CTD	Common Technical Document
FDG	Fluorodeoxyglucose
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
HAMA	Human anti-mouse antibody
HIG	Human polyclonal immunoglobulins
HMPAO	Hexamethylproppyleneamine Oxime
^{111}In	Indium-111
MAb BW 250/183	Monoclonal antibody BW 250/183
MBq	Megabecquerel
MIRD	Medical Internal Radiation Dose Committee
MRI	Magnetic-resonance imaging
MSv	Millisievert(s)
NCA-90	Non Cross-reacting Antigen – 90
NCA-95	Non Cross-reacting Antigen – 95
NP	New manufacturing Process
OP	Old manufacturing Process
p.i.	Post injection
PTP	1,1,3,3-propane tetraphosphonic acid, tetrasodium salt, dihydrate
SAE	Serious adverse event
SPECT	Single-photon emission computed tomography
^{99m}Tc-MAb BW 250/183	Technetium-99m labelled monoclonal antibody
WBC	White Blood Cells

I. CHMP RECOMMENDATION PRIOR TO THE WITHDRAWAL

Based on the review of the data on quality, safety and efficacy, the CHMP was considering that the application for SCINTIMUN in the diagnostic imaging to determine the location of infectious or inflammatory lesions and to detect metastasis (when cancer spreads) in bone marrow was not approvable since "major objections" have been identified, which precludes a recommendation for marketing authorisation.

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II. EXECUTIVE SUMMARY

II.1 Problem statement

Confirmation of diagnosis of infections in clinical practice relies on a combination of clinical features, microbiological tests and imaging. Inflammatory diseases are associated with non-specific and specific inflammatory markers, despite varying degrees of sensitivity and specificity.

In case of suspected infectious and non-infectious inflammatory lesions, timely identification and localization of pathology might be of critical importance in the appropriate management of patients. The standard imaging tests used such as CT scan, MRI scan and ultrasound have limitations in this regard, as they provide morphological and anatomical information but not any information on the nature of pathology. Furthermore, clinical suspicion of the localization of pathology is required in order to effectively use these techniques. Where the nature of the pathology needs to be identified or where there are no clinical features to suggest the location of the disease, a product such as SCINTIMUN, which identifies clustering of neutrophils, might be helpful.

The current gold standard for labelling of neutrophils is *ex vivo* labelling using ^{111}In-oxine. This is cumbersome and carries risk of infection. There are also other radiopharmaceuticals which have been used to detect infection/inflammation: ^{67}Gallium, ^{99m}Tc-HIG, ^{99m}Tc-HMPAO labelled leucocytes and ^{18} F-FDG are some of the recognized radiopharmaceuticals. ^{67}Ga binds to transferrin and lactoferrin at the place of iron and accumulates in inflamed tissue. Unfortunately it takes 2-3 days to establish the diagnosis; and the ^{67}Ga radiation exposure is high. ^{99m}Tc-nanocolloid accumulates at the place of the inflammation due to increased capillary leakage and is taken up in macrophages of the reticuloendothelial system. This is mainly used in osteomyelitis but its uptake is non-specific.

An ideal radiopharmaceutical has the following properties: easy preparation, wide availability, low toxicity, absence of immune response and high specificity. It should also not have high background activity for a prolonged period and should be able to localize disease in a specific manner. Many of the above-mentioned radiopharmaceuticals are considered to have one or more deficiencies in this regard. SCINTIMUN has the potential advantage of labelling neutrophils specifically *in vivo*. Most clinical trials with SCINTIMUN had been carried out before 1994. An anti-NCA90 antibody (Sulesomab), which is a Fab fragment, produced in murine ascites fluid and labeled with technetium, was approved in Europe in 1997 for the determination of location and extent of infection and inflammation of the bone in suspected osteomyelitis.

Early detection of bone marrow spread of any cancer offers evidence of disseminated haematogenous spread. Since bone metastases are considered to originate from bone marrow metastases, detection of

bone marrow metastases offers advantage of earlier detection compared to bone scans. The information might also identify those who will benefit from adjuvant therapy.

In vivo labelling could also help to identify the extent of disease, to identify pathology where pre-existing structural abnormality might exist (e.g. after hip replacement) and to avoid/reduce invasive procedures e.g., bone marrow aspiration.

II.2 About the product

Mode of action
Besilesomab is a mouse immunoglobulin of IgG1 isotype that binds to antigenic structures shared by NCA-95 (non specific cross-reacting antigen 95) and the tumour marker, carcinoembryonic antigen (CEA). Besilesomab binds specifically to granulocytes and granulocyte precursors.

In infection and inflammation the accumulation of radiolabelled antibody bound to neutrophils is expected to provide radiological 'hot spots'. In the case of bone marrow metastases images, appear as 'cold spots' due to the normal surrounding neutrophils, but not the malignant cells, taking up the tracer.

Pharmacological classification
Radiopharmaceutical preparation for diagnostic use
ATC code: V09HA03

Proposed indications and posology
Proposed therapeutic indications
- Scintigraphic imaging for determining the location of infectious/inflammatory lesions.
- Scintigraphic imaging of bone marrow involvement (detection and extent of carcinoma metastasis, as cold spots).

Proposed posology and method of administration
This medicinal product is for use in hospitals or in designated Nuclear Medicine facilities only, and should be handled by persons experienced in radioisotope diagnostic imaging.

After reconstitution with sodium pertechnetate (^{99m}Tc), Technetium (^{99m}Tc)-labelled besilesomab is formed.

The single injection of Technetium (^{99m}Tc)-labelled besilesomab must be given strictly intravenously.

Dosage for adults
The recommended amount of active substance (besilesomab) to be administered is 0.25 mg. Doses up to 1 mg have been safely injected in controlled clinical trials.

The activities used are between 200 and 800 MBq of Technetium (^{99m}Tc)-besilesomab:
- 200-400 MBq (5-11 mCi) for bone marrow scintigraphy.
- 400-800 MBq (11-22 mCi) for the diagnosis of infectious/inflammatory lesions.

Special aspects
Diagnostic agent; radiolabelled monoclonal antibody of murine origin

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

This is a new centralised application (under Part A) for marketing authorisation of a murine monoclonal antibody directed against NCA-95 antigen in neutrophils. It is a complete and independent application under article 8.3(i) of Directive 2001/83/EC as amended. The product is currently authorised in Sweden, Czech Republic and Hungary.

The evidence supporting the indication for imaging of carcinomatous metastasis of bone marrow is mainly in the form of published literature.

No paediatric development is planned.

No scientific advice or recommendation was obtained from CHMP or Member States.

There has been a change in the manufacturing process since the pivotal trial, in order to comply with the European Guideline "Production and quality control of monoclonal antibodies" (3AB4a). MAb BW 250/183 manufactured with the new process was approved in 2002 in Czech Republic and Hungary.

The Applicant has provided efficacy results in terms of sensitivity, specificity and accuracy. This is consistent with the relevant CHMP guidance (Points to Consider on evaluation of diagnostic agents (CPMP/EWP/1119/98))

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

The product is manufactured at sites that have the relevant Manufacturing Authorisations. However, as noted in the pharmaceutical assessment, validation of manufacturing procedures is inadequately documented. A GMP inspection is not currently considered to be required. However, this opinion may change should the Applicant fails to respond adequately to the request for additional information regarding process validation.

The non-clinical safety studies were conducted in compliance with GLP and in accordance with the guidance that was current when the studies were undertaken. A GLP inspection is not considered necessary.

According to the Applicant, the Phase III study (1991-93) was carried out in compliance with the Declaration of Helsinki and the two comparability studies in compliance with GCP. A GCP inspection is not considered to be necessary provided that the Applicant carries out further clinical trials as required for approval. If the submitted evidence was not considered adequate by CHMP for approval, a GCP inspection would be recommended for the two major trials - 7MN-301SZ-A (phase III) and BI 71.015 (pre-phase I, pilot).

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

The evidence supporting the indication for imaging of carcinomatous metastasis of bone marrow is mainly in the form of published literature. Of the four main publications referenced, two are in German language with English abstracts. One of the two English language publications was a study in multiple myeloma, which is not strictly relevant to the assessment of efficacy as it is not an indication applied for. The expert report has not adequately justified the reasons for using published literature and has not discussed the findings in any detail. It is considered that the evidence for this indication might not be of sufficient quality to allow a proper assessment.

The clinical development of the product started in 1987. Much of the clinical evidence submitted is at least 10 years old. The Applicant acknowledges this aspect and concedes that they do not comply with current state of the art. The Applicant states that the clinical value of the product has been confirmed by clinical experience over more than 10 years, but no evidence of the value 'in use' has been provided. The phase III study was an open-label, non-randomised study with an originally intended primary objective of safety and tolerability of the product. The results have been retrospectively analysed for efficacy.

Overall, the expert report is not considered to be objective nor is the discussion in adequate detail.

III. SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 Quality aspects

Drug substance
The generation and characterisation of the hybridoma and original cell banks is well described. In 1999, cells from the original cell banks were adapted to a fully synthetic culture medium and new cell banks were generated. The manufacturing site for the antibody drug substance has changed since pivotal studies were conducted and several changes to manufacturing procedures have been introduced, Although the manufacturing procedure is generally adequately described, the validation of both the fermentation and the purification procedures is not acceptable. The relationship between individual fermentations and batch release results is unclear and process monitoring parameters are inadequately documented. During validation of purification, the majority of critical parameters were not monitored. Process yield appears to be the main parameter through which process performance was monitored. Insufficient cleaning validation data is provided. Further validation of the whole manufacturing process must be provided.

Antibodies from the old and proposed processes have been analysed by chemical and immunochemical methods. Data are presented to support the identity of the primary structure and the binding specificity. However, due to some inconsistent results during characterisation, especially glycosylation, further assurance of comparability of the product from the old and proposed process should be provided.

Immunochemical assays are directed against a number of epitopes/antigens. The Applicant should clarify the differences, relationships and specificity between the different antigens / epitopes and how the characterisation and comparability studies of immunogenicity encompass all the above named epitopes. The epitopes should be fully characterised.

Although the stability studies for the drug substance are adequate, stability of process intermediates has been inadequately discussed.

The process has been appropriately validated for removal of viral contamination, with 6-10 logs of non-enveloped virus, and 10-11 logs of enveloped virus removal being demonstrated. However, the validity of the scale down has not been proven, and further information is required. Additionally, the re-use of a virus removal filter should be justified.

Drug Product
The manufacturing facility for production of the two drug product vials has changed since pivotal clinical trials. The process for vial 1 (containing antibody) is not adequately described. In addition, the antibody is partially reduced prior to filling and freeze-drying and additional evidence of control of this procedure is required. Vial 2 contains two reagents , and manufacture is well described.

Analysis of vial 1, 2 and reconstituted product (after radiolabelling) is adequately described. Radiochemical purity is assessed by size exclusion chromatography and radioimmunoreactivity by determining the percentage of radiolabelled antibody that binds to an excess of human colonic tumour antigen. This assay demonstrates a fairly large degree of variability. However, since variable biological reagents are part of the assay (human tumour cell membrane isolates), this level of variability may be accepted. An end user assay is described, which allows detection of gross failures during reconstitution and radiolabelling procedures. No information is presented to justify the use of the clinical assays and this is required.

Stability of the drug product is adequately addressed. However, a part of the stability data for vial 2 is generated with product manufactured by the previous manufacturer and justification of the relevance of this data is required.

III.2 Non clinical aspects

Pharmacology
Binding of antibody to cryo-preserved human tissue and blood cells from cynomolgus monkey was investigated using indirect alkaline phosphatase anti alkaline phosphatase (APAAP) technique. *In vitro* binding of the antibody to granulocytes has been demonstrated in a number of normal human tissues as well as to some human carcinomas. This was shown for hybridoma supernatants (from passage 14 of master seed lot) as well as for the purified antibody and the antibody-^{99m}Tc kit product. The antibody also bound to granulocytes in peripheral blood from cynomolgus monkeys and from humans.

However the specificity of the binding has not been discussed in detail. The dossier states that the antibody is specific to granulocytes, with about 5% of binding also seen with human lymphocytes and monocytes. The evidence for this is not clear, as one study suggests that binding to granulocytes in peripheral human blood ranges from 60 to 97%. The applicant should comment on this variability and lack of specificity for the clinically relevant epitope.

Non-clinical studies were conducted in rats and dogs although there is no information about the relevance of these species in terms of whether they have the appropriate epitope for binding. This has not been discussed in the non-clinical expert report. Some of the study reports suggest that the rat does not have the epitope. The applicant should discuss the relevance of the species used in the non-clinical studies from the point of view of antibody binding and expression of epitopes.

Safety pharmacology was investigated in anaesthetised dogs, with no effect on cardiovascular or respiratory systems, haematology, coagulation or clinical chemistry parameters. ECG was not measured in this study but was not affected by treatment in the toxicity studies in rats or monkeys.
CNS effects were not investigated specifically because the high molecular weight compound will not cross the blood brain barrier. The Applicant's justification is acceptable.

Pharmacokinetics
The pharmacokinetic studies are limited and raise some additional questions.

Pharmacokinetics was evaluated in rats and cynomolgus monkeys, the former study using the kit prepared with technetium-99m (4 to 5 MBq administered), and the monkey study using the kit prepared with delayed technetium. The ELISA method used for antibody assay in the monkey study and its validation were not included in the dossier and should be provided.

In monkeys, serum levels were highest at the first time point (10 minutes), with distribution occurring within 20 minutes. The terminal half-life of the antibody was 26 and 36 hours (only 2 animals used).
In rat, plasma half-life was 30 to 35 hours, which was comparable with that in monkeys. Elimination from most organs of the rat appeared to be biphasic with the half-lives of the initial and terminal phases being 2 to 7 hours and less than 100 hours, respectively (values corrected for the decay of ^{99m}Tc).
At one hour after administration in the rat, highest levels of radioactivity were evident in the blood, followed by the liver, compact bone, kidney and small intestine. In other organs, highest levels were seen at 7h [kidney (both sexes), testes, pancreas, thymus and skeletal muscle of male rats], 17h [large intestine (both sexes), uterus] or 30h (skeletal muscle in females). Radioactivity did not appear to be distributed to the mammary gland.
Although there were no studies investigating the binding of the antibody to rat granulocytes, the study report for the rat pharmacokinetic study stated that the NCA 95 epitope is found only on human granulocytes. Therefore the Applicant should discuss what entity is being measured in this study if it is not the labelled antibody bound to the appropriate epitope on granulocytes.

Distribution in normal animals (dosimetry) was investigated in rats. The same data was used as for the rat pharmacokinetic study, but without correction for the decay of technetium-99m that was used in the pharmacokinetic study. Most of the organs showed biphasic elimination, the initial half-life being 2 to 4h, and that of the slower phase being 5 to 6h. The half-life of the slow phase is mainly determined by the half-life Tc-99m.

Using rat/man conversion factors for organ weights, the maximum organ doses expected in man are for the large intestine (18.86 µGy/MBq), kidneys (18.74 µGy/MBq), bone marrow (12.66 µGy/MBq) and the small intestine (11.78 µGy/MBq).
An effective dose of about 9 mSv is expected in man following intravenous administration of 1GBq of the compound, which is reported to be similar to that for other nuclear medical routine examinations.

No specific metabolism studies were conducted with SCINTIMUN, which is acceptable for this type of product. The antibody is expected to be broken down into individual amino acids. Different radionuclides attached to murine IgG molecules appear to have no effect on the initial uptake of the antibody into the liver, although the retention of radioactivity in the liver is dependent on the radiolabel. Selenium (^{75}Se) and indium (^{111}In) were retained for five days, but technetium (^{99m}Tc) and iodine (^{131}I) were decreasing within 2 days.

In rats, about 31-34% of the radioactivity was eliminated in the urine and 7-13% in the faeces over 30 hours. Radioactivity first appeared in the faeces at 17 hours post-dose, which corresponds to the time point at which the highest levels of radioactivity were measured in the large intestine.

Toxicology
Acute toxicity studies were conducted in mice and rats using kits made up with decayed technetium. There were no adverse affects in either species when the product was administered up to the maximum dose of 5 mg/kg. In comparison to a 1mg dose administered to a 60kg person, this represents a 300-fold safety margin.

Repeated dose studies were conducted in rats and cynomolgus monkeys. These were 30-day studies and support the single diagnostic administration of the product to humans. The product was generally well tolerated, although there were findings in the liver in both species (dose-dependent round cell infiltration in rats and accumulation of an acidophilic substance in Kupffer cells in monkeys). The Applicant should comment further on the relevance to man of these findings.

A NOAEL was not established in rats, but in monkeys the findings were restricted to the high dose and therefore the NOAEL was 0.5 mg/kg/day in this study. Toxicokinetic analysis was not undertaken in either study and therefore safety margins cannot be calculated on the basis of systemic exposure. However the maximum administered dose in man is 1mg (or 0.016mg/kg for a 60kg person), which is 30 times lower than the NOAEL (0.5mg/kg/day) in the monkey.

Antibodies to the murine IgG were not assayed in the rat study, but were present in the monkeys in the repeated dose study. HAMA have been detected in man and may affect the diagnostic ability of SCINTIMUN if present in patients.

The standard battery of genotoxicity studies is not required for biotechnology-derived pharmaceuticals. However, the Applicant conducted two genotoxicity studies in mammalian cells to test for potential mutagenic impurities in SCINTIMUN. Both tests (in CHO cells and V79 Chinese hamster cells) were negative. These studies were conducted using kit comprising antibody and PTP made by the original manufacturers. The more recent studies (Ames tests) were conducted with kit containing antibody from the proposed manufacturer and one also used PTP from the proposed supplier. These studies were also negative although the relevance of conducting such studies to assess the genotoxic potential of process contaminants has not been discussed (Note for Guidance on preclinical safety evaluation of biotechnology-derived pharmaceuticals). However the genotoxicity of the PTP has been investigated separately and also found to be negative, and although the full standard battery of tests was not used, the studies together would suggest that SCINTIMUN does not have genotoxic potential.

Carcinogenicity studies and reproductive toxicity studies have not been conducted. The absence of these studies is acceptable for this product.

Local tolerance was investigated in rabbits using SCINTIMUN containing antibody produced by the proposed manufacturer and PTP from Hoechst and made up with decayed technetium. The i.v., i.a.,

p.v. and i.m. routes were used. Only the paravenous route showed signs of irritation, although there was some evidence that the clinical signs were reversing after 7 days

The Applicant has conducted additional studies with various materials used in the manufacturing process or as excipients in the product. These were Triton X-100 (a solvent used in virus inactivation), PTP (a chelator used to couple technetium to the antibody) and Protein A (from columns used to purify the antibody). For Triton X-100, the toxicity, local tolerance, safety pharmacology and *in vitro* compatibility with human blood was investigated. Two genotoxicity studies were conducted with PTP and an acute toxicity study with Protein A.

PTP would appear to be a new excipient and therefore a full package of non-clinical studies on this agent would normally be required. However, the majority of the non-clinical studies presented in the dossier have been conducted with the kit made up as intended for the product to be marketed. The results of these studies are acceptable in place of a specific battery of studies conducted with PTP alone, as they address the toxicity of the product itself. The PTP from the proposed supplier has been shown to be chemically similar to that produced by Hoechst. Provided that the quality and clinical comparisons of the product containing the new antibody confirm that it is comparable to the product used in the non-clinical studies, there is no necessity to conduct additional studies with PTP alone for the purposes of this application.

Use of the product is not considered to pose a risk to the environment.

In summary, most of the non-clinical studies are about 15 years old, and assessment of the dossier raises a number of questions. However the package may be acceptable, provided that the applicant addresses the questions adequately, and provided that the antibody produced by the proposed manufacturer is shown to be comparable to that produced by Behringwerke AG, which was used in the majority of the non-clinical studies.

III.3 Clinical aspects

Pharmacokinetics
This is an intravenously administered, radiolabelled, novel biotechnology derived product. Full pK documentation applicable to intravenous products would be required for the commercial product for both components i.e. antibody and ^{99m}Tc.

Pharmacokinetic parameters were obtained in 3 studies involving a total of 52 patients, 47 of which are evaluable. Two studies (7D-101SZ-A and 7MN-302SZ-A) were performed with ^{99m}Tc-MAb BW 250/183 manufactured according to the “old process”. An additional study (Study 306340) for comparison of both manufacturing processes with regard to bio-distribution and kinetics was carried out on regulatory request.
Pharmacokinetic measurements were obtained in patients with suspected inflammatory processes (one of the target populations).

Studies of pharmacokinetics of ^{99m}Tc- MAb BW 250/183

Study (study period)	**Phase**	**No. of patients**	
7D-101SZ-A (4/92 – 5/93)	phase I	24	Single injection of either 0.25 or 1.0 mg of ^{99m}Tc MAb BW 250/183, parallel group design, 2 centres
7MN-302SZ-A (5/92 - 6/93)	phase III	9 (4 evaluable)	Repeated administration of ^{99m}Tc-MAb BW 250/183, 5 centres, open-label.
306340 (5/02 – 6/02)	phase I	19	Comparison between old and new manufacturing process, randomized, open-label, comparative study, 2 centres

In study 7D-101SZ-A, the analysis and results were as follows:
1. The whole blood radioactivity curves obtained in these measurements showed two phases: an early phase (0-2 h) and a late phase (5-24 h).
2. *In vivo* stability of the ^{99m}Tc labelled antibody: The single-dose study gave mostly indirect supporting evidence by demonstrating that the separately measured IgG concentrations had the same concentration time course as the measured radioactivity in the blood. In the same study, by measuring the cell-bound radioactivity the estimated rates were 10%-15% of the total radioactivity which actually binds to cells.
3. Only 13%-15% of the administered radioactivity was recovered in the urine during the first 24 hours.

The analytical methods chosen appear acceptable, but the Applicant will need to clarify whether the MAb antibody measurement was validated. The pharmacokinetics measurements appear appropriate. Since all the subjects in the studies were patients suffering from inflammatory process, it is reasonable to consider that the results would be representative of target population. The statistical aspects are acceptable. The number of patients who had pharmacokinetics measured would appear to be adequate for proper assessment of the data.

The 80-125% CI that the Applicant has used to compare the results is not necessarily applicable for IV preparations. One would expect tighter confidence intervals, for the bioavailability is 100%. Results for Cmax and AUC, when normalised to 800 MBq (see table below), appear comparable. The ratio of the means shows a slightly higher value for the "new process" product. However, taking into account that this is a diagnostic product that will be administered once or twice, at intervals, the difference in pharmacokinetics is not likely to pose any clinical problems. Urinary excretions and bio-distribution of radioactivity are similarly comparable, providing evidence of consistency and internal validity.

Ratio of geometric means (NP/OP) for C_{max} and $AUC_{0-tlast}$, and confidence intervals (CI)

		Without body weight and gender as covariates	With body weight and gender as covariates (retrospective analysis)
	Ratio of means	CI [LL, UL]	CI [LL, UL]
C_{max}	**1.1251**	**[88.32%, 143.33%]**	**[99.79%, 126.86%]**
$AUC_{0-tlast}$	**1.1010**	**[88.72%, 136.62%]**	**[95.40%, 127.06%]**

LL – lower limit of CI, UL – upper limit of CI

The parameters for the intact MAb BW 250/183 plasma concentration show large standard deviations in study 7D-101 SZ-A, however, the median values of the antibody based half-lives and clearance rates show agreement with the corresponding plasma radioactivity values. Details of the results are available in Day 70 Clinical assessment report. Applicant argues that this agreement might suggest that the labelled product is stable *in vivo.* The difference in AUC between radioactivity and antibody

concentration during the β phase, even accounting for the high standard deviation, is unexplained. Furthermore, the volumes of distribution figures for the α and the β phase are identical.

There are no notable differences between the 2 dose groups (0.25 mg and 1.0 mg) in Tc-99 pharmacokinetic parameters of relevance i.e., half-life, AUC, volume of distribution and clearance.

There is a wide inter-individual variability in results. The expert has not discussed the reasons for such variability in any detail. As this product is not likely to be used repeatedly, it is unlikely that this variability is of serious consequence, provided that efficacy (in diagnosis) and safety are convincingly demonstrated.

Tc-99 radioactivity decays, with a half-life of 6 hours. In the population studied, only about 13% is excreted in the urine in 24 hours. In the presence of impaired renal function, this might be lower. However, this is not likely to pose a clinical problem. As the antibody is a biotechnology-derived product, liver impairment is unlikely to affect the metabolism and elimination in a clinically significant manner. Liver uptake of radioactivity is minimal under trial conditions.

Variability was influenced by gender and weight in the comparative study 306340. Ideally, dosage of any pharmaceutical should be adjusted to take into account these two factors. However, that is more likely to be relevant to a therapeutic product, to ensure that sub-optimal or unsafe doses are not given. In the context of SCINTIMUN, it is not expected that there will be a serious clinical consequence of lack of dose adjustment.

All the studies have been carried out in Europe. It is likely that there is no significant exposure of non-Caucasian, non-white population to this product. This is not considered a major deficiency for this product. Apart from the lack of data/ plans for paediatric population, the available information on pharmacokinetics is considered to adequately address the special populations.

Pharmacodynamics
The evidence provided for pharmacodynamics is from a combination of 2 studies in patients, 2 published papers and 4 *in vitro* studies.

No evidence is available to support the dose of antibody chosen for use. No preliminary dose finding study was carried out. Dose-response was assessed in the Phase III study retrospectively. There was no difference between different doses of antibody administered, ranging from 0-0.25 mg, 0.25-0.5mg and 0.5-1.0 mg. Applicant has recommended one of the lower doses studied. A non-effective or sub-optimal dose needs to be identified in order to keep the dose of this murine antibody to the minimum.
As for the dose of radioactivity, 0-400 (47 patients), 400-600 (272), 600-800 (187) and >800MBq (169) were administered. The lowest had a sensitivity of 73% while other doses had a comparable sensitivity of 89-91%. The rationale for the choice of the dose of radioactivity has not been adequately addressed in the clinical expert report. The phase III study was in patients with infection/ inflammation. One would have expected, on the basis of evidence provided, for it to be kept to a maximum of 600 MBq.

Applicant will also need to show that the effect *in vivo* is indeed specific. A comparison with a labelled colloid, for example, might be necessary.

The potential for an adverse effect on neutrophil function has not been completely resolved. This could have safety implications as commented in the safety section. The potential for *in vivo* binding to cells other than neutrophils has not been assessed for the new product.

Clinical efficacy
Information is available from a total of 7 studies (see table below), out of which 2 might be considered pivotal for assessment purposes.

Available evidence is not considered sufficient for a proper assessment of efficacy of the intended commercial product. The clinical development started in 1987. Pivotal trial data is 12 years old.

Pivotal trial and most other trials in support of efficacy were carried out with 'old' product. Eighteen patients have received the 'new' product. The comparative imaging techniques used such as CT scan, MRI might not be considered state-of-the-art by current standards.

No dose-response study was carried out to determine the lowest effective dose. Main studies were not randomised, controlled, blinded studies. The primary end-point of the pivotal study was safety. The analysis of efficacy was carried out retrospectively. The dose of antibody and radioactivity administered in the main trials were arbitrary and not pre-defined.

For the two main studies, the final assessment of the investigator was used as the 'gold standard'. This is not satisfactory. Furthermore, planar imaging was the primary technique. SPECT imaging is currently considered state-of-the-art but was used in a minority of patients at 24 hours. The Tc-99 dose in Study BI-71.015 was too wide.

It is not possible to determine whether the sample sizes were appropriate for assessing diagnostic efficacy. However, it would appear that the number of patients would appear to be sufficient for a proper evaluation

The number of deviations and exclusions was high. The clinical expert acknowledges that the studies did not comply with current state-of-the-art. Applicant was not able to retrieve all the CRFs. If these studies were to be accepted as sufficient evidence for a positive opinion, a GCP inspection would be warranted.

The efficacy results were, however, provided for the full analysis set for Study 7MN-301SZ-A. Antibiotic treatment was not specifically included in the exclusion criteria, but such usage was determined to be a protocol deviation. Antibiotics would not be expected to affect results, if an active ongoing infection is suspected in spite of such therapy. The results appear to be encouraging especially for detection of osteomyelitis, joint prosthesis and intestinal inflammation (sensitivity rates ≥ 80 %). Because of the open-label nature of the studies, assessment and analysis bias cannot be excluded.

Clinical studies conducted with SCINTIMUN

Study ID	No. of study centres / locations	Design	Study Posology of 99mTc-MAb BW 250/183	Study Objective	No. of subjects.	Duration	Gender M/F Median Age	Diagnosis (Inclusion criteria)	Primary Endpoint
BI 71.015	10/ EU	open-label, non-randomized	Single or repeated injection 0.1 - 1.0 mg	diagnostic efficacy and safety	379	5/87- 9/90	207/169 (3 unknown)		detection of inflammatory lesions and bone marrow metastasis
7D-101SZ-A	2	parallel group design	Single injection of either 0.25 or 1.0 mg	pharmacokinetic parameters, safety, and diagnostic efficacy	24	4/92– 5/93	15/9; 48 yrs	Infection/ inflammation/ bone marrow metastasis	Pharmacokinetics and radiation exposure
306340	1	randomized, open-label, comparative study	Single injection of old or new product	Comparison between old and new manufacturing process	19	5/02– 6/02	9/10; 45		distribution of radioactivity in regions of interest
7D-201 SZ-A	4	open-label, non-randomized	Single injection 0.25 to 1.0 mg	diagnostic efficacy and safety	49	7/92 – 12/93	33/16; 51		Original: safety and tolerability Retrospective: sensitivity and specificity of immunoscintigraphy
7MN-301SZ-A	42/ EU	open-label, non-randomized, uncontrolled	Single injection 0.1 - 1.0 mg	safety and efficacy (Retrospectively – diagnostic sensitivity and specificity)	690	12/91 – 12/93	391/299; 52		Original: safety and tolerability Retrospective: sensitivity and specificity of immunoscintigraphy
7MN-302SZ-A	5	Repeated administration	Single injection 1.0 mg	pharmacokinetic parameters, safety, and diagnostic efficacy	9 (4 evaluable)	5/92 – 6/93	3/1; 29-61 yrs		safety and tolerability
AG-NP	2	Randomised, open-label, comparative study (old versus new manufacturing process)	Single injection up to 1.0 mg	To assess uptake of radioactivity in pathological and physiological sites	20	7/00 – 12/00	13/8; 66		Comparison of uptake

The selection of patients in the main trials is considered appropriate and reasonably representative of the target indication. The 41 patients with 'other inflammation' (in Study 7MN-301SZ-A) are a sizable group that has not been adequately discussed. Ideally, for each indication i.e., infection, inflammation and bone marrow metastasis, at least two different clinical conditions should be studied to be able to apply the results for a broad indication.

Unusual accumulation was found in 120 of 690 patients in the pivotal trial at 5 or 24 hours in one or more organs – bone marrow, spleen, liver, kidneys, bowels etc. This is likely to be related to either binding to granulocytes or to excretion. The clinical significance of this finding is not clear. It is possible that this may decrease the specificity of the procedure in diagnosing infections in these

organs. Accumulation was also seen in great arteries. The significance of this finding needs to be explored.

The comparability between SCINTIMUN and ^{111}In-oxine-labeled leukocytes is reassuring and promising. The numbers of patients are small. A prospective comparison of the 'new' product SCINTIMUN with ^{111}In-oxine-labeled leukocytes that is adequately powered would likely provide evidence of efficacy, if comparable results are reproduced. The majority of positive results were detected at 5h. In practice, this might mean that only those negative at 5 h. is likely to need 24 h. imaging. There is also a reasonable concordance between Planar and SPECT imaging.

The Applicant has not provided data to substantiate the claim about the efficacy being proven in-use. The literature data would provide support if pivotal evidence is robust. Depending on how frequently HAMA can be pre-existing, routine testing might be necessary prior to first use.

The trials available are methodologically flawed. In particular, there is no justification for the trial designs and no clear, prospectively identified trial objectives. There is no systematically defined or implemented control arm and hence reliable comparisons with a recognised standard are not available. Furthermore, no assessment 'by lesion' is possible and there are concerns over the retrospective nature of the assessments, over the formulation and the dose of the product tested in the trials and over adherence to the trial protocols in the pivotal studies. It is not clear whether the readers of imaging were trained properly and whether the results reproducible across different observers.

This indication for use of SCINTIMUN is too "broad". SCINTIMUN is not suitable for detection of infectious/inflammatory lesions in the central skeleton. Its use cannot also be recommended in chronic IBDs (Inflammatory Bowel Disease) because of the safety of the repeated use of the antibody had not yet been proven.

There is some evidence for effectiveness and reasonable evidence for the quality of the image. Nevertheless, the major design flaws preclude the conclusion that the trials presented provide confirmatory evidence of diagnostic capability. Further clinical work appears to be required.

Clinical safety

A summary of safety has been provided as part of the clinical expert report. Serious adverse events and deaths have not been discussed in any detail. SAEs were retrospectively classified as per ICH criteria.

In clinical studies, over a 1000 patients have been exposed to the original 'old' product and only 18 patients have been exposed to the 'new' (proposed commercial) product. In the repeat dose study nine patients received it more than once, 4 of these being evaluable. Six other patients received 2 or more doses in the pilot study. These data are insufficient for a proper assessment of repeat use. The product was not administered to healthy volunteers.

It is estimated that 63,000 patients have been administered with the "old" product between Jan. 1996 and Aug. 2002 according to the PSUR of Jan. 2003. There appears to be sufficient exposure of single administration of the 'old' product, to assess its safety. Regarding the "new" (proposed commercial) product, and according to the PSUR of July 2005 provided during the clarification meeting of 14 July 2005, it is estimated that 19,000 patients have received the new product between August 2002 and May 2005. Nevertheless, the Applicant will need to conduct a further safety study with an adequate number of patients.

The presentation by the Applicant is not considered balanced. All SAEs, deaths and any significant event (e.g. Quincke's oedema) should have been discussed in more detail rather than uncritically accepting investigator assessment of causality in these open-label studies conducted in 1992 - 1993.

In general, the product appears to have been well tolerated. Two of the 4 non-serious AEs in the pivotal study 7MN-301SZ-A have vascular basis and another patient might also have had such a basis. This raises concern about cardiovascular safety of the product, especially in susceptible individuals. The study report for BI 71.015 states that no side effects were reported. 125 patients could not be

evaluated for lack of proper documentation. It is very unusual that a study with over 500 patients did not reveal a single adverse event. The Applicant should clarify the level of documented evidence available.

Of the 7 deaths/SAE, there were 3 myocardial infarctions, 1 cardiovascular failure, 1 pulmonary embolus and 2 internal haemorrhages all occurring between 5 and 27 days after product administration. There appears to be a preponderance of vascular related events. A role for the intravenously administered murine protein in these cannot be totally excluded at present as there is a high number of such events. Also, it has been shown *in vitro* that the product specifically binds to granulocytes. At the time the SAE events were reported, no in-depth investigation was made by the sponsor to totally exclude the fact that the SAE events were not product related. Even if no other type of such SAE have been observed outside these clinical trials, a safety surveillance should be performed by the Applicant to totally exclude product responsibility for such potential cardiovascular events.
The decline in RBCs and WBCs is a cause for concern. The explanation for the drop in WBCs is equally weak in the absence of a comparator arm. Applicant should provide detailed analysis of haematological laboratory parameters such as cell counts, Hb from the studies. If these are not available appropriate prospective studies are required to provide evidence for the lack of haematological adverse effects.

In the indications sought i.e. infections and inflammatory conditions, any adverse effect on neutrophil function could easily outweigh potential benefits. In the case of CEA producing tumours with metastasis, the risk is considered lower although a susceptibility to bacterial infections is a theoretical possibility. The *in vivo* demonstration of lack of adverse effect on white cell count is not sufficient, as it provides no information on the function, which is the more important aspect requiring investigation. The *in vitro* data provides partial reassurance.

Presence of pre-existing antibody might increase risk of anaphylaxis to first administration. It might therefore be necessary, as for efficacy reasons, to test all individuals prior to administration.

In the context of clinical use, this product is likely to be used more than once. The immunogenicity is an important issue in this regard. The rate of around 5% in the appearance of HAMA does not appear high. But it is difficult to be certain that the assay reliably reproduces actual clinically important incidence of antibody formation. Furthermore, the type of antibody (IgG or IgM) and the potential for each type to affect safety (allergy, anaphylactoid reactions) and efficacy (neutralising antibodies) will need to be further explored with state-of-the-art technology.

The incidence of HAMA after single injection of SCINTIMUN is slightly below 5%. HAMA usually become apparent within 30 days after injection but may, in few patients, also develop at later time points. Patients who are HAMA positive may have a greater risk for hypersensitivity reactions and this accounts for HAMA tests to be carried out on the patient's serum before each repeat administration of mouse monoclonal antibodies. It appears, based on the small numbers of patients studied, that the 'new' commercial product is no more immunogenic than the old product and possibly less so. Larger studies are needed to confirm this. Post-marketing data should also be gathered as part of pharmacovigilance planning.

There does not appear to be a high rate of clinical immunological events of immediate-type hypersensitivity. Whether the vascular events seen were immunologically mediated or a direct toxic effect remains to be established. Further clinical trials and additional post-marketing pharmacovigilance data will be necessary to clarify this.

Radiation exposure after injection of SCINTIMUN is 0.0106 mSv/MBq (0.0104 mSv/MBq after recalculation with more up-to-date software MIRDOSE3) which is in the range of other diagnostic nuclear medicine techniques. After IV injection of 800 MBq SCINTIMUN, an effective dose of 8.5 mSv is reached which is comparable to respective values for 1 CT examination or the values reached after injection of ^{111}In-labeled white blood cells (0.590 mGy/MBq; ICRP report 53; recommended activity according to the Society of Nuclear Medicine: 10-18.5 MBq). The radiation dose after

SCINTIMUN is not considered to constitute a safety concern, however, in pregnant women the use of SCINTIMUN should be avoided.

A pharmacodynamic drug/ disease interaction is possible. The Applicant should discuss whether there are drugs or diseases that can influence binding of the antibody to other cells and/or impair the function/ structure of neutrophils.

IV. BENEFIT RISK ASSESSMENT

A technique for specific imaging of clustering of neutrophils is likely to provide important information in the management of patients. The need is well established in the case of diagnosis of suspected infections and inflammatory diseases. The use of such techniques to identify bone marrow metastasis is a novel concept. The current gold standard of imaging accumulation of neutrophils is through *ex vivo* labelling using ^{111}In-oxine. This is cumbersome and carries risk of infection. SCINTIMUN has the potential advantage of labelling neutrophils specifically *in vivo*. In small study comparing the two techniques in a cohort of 22 patients, there was reassuring concordance of findings on imaging.

The clinical studies conducted by the sponsor are seriously methodologically flawed, rendering the results to be of poor quality. Efficacy and safety have not been demonstrated with robust evidence. Furthermore, the manufacturing process has changed, making the findings even less valuable as most of the clinical information was obtained with the old product.

The pharmacokinetic studies and the comparative studies provide some evidence to support the stability of the product (old) *in vitro* and a reasonable similarity between the old and the new products. The specificity of *in vivo* binding to neutrophils and lack of any interference with the functional integrity of neutrophils has not been adequately demonstrated for the commercial product.

It is not possible to approve SCINTIMUN for marketing authorisation at the present time, as benefit/risk assessment is considered unfavourable. Further clinical evidence showing positive benefit/risk profile would be required prior to approval.

This Withdrawal Public Assessment Report is based on the latest assessment report adopted by the CHMP prior to the Applicant's withdrawal of the marketing authorisation application. It may not include all available information on the product in the case where the CHMP assessment of latest submitted information was still ongoing.
It should therefore be read in conjunction with the Questions and Answers Document on the withdrawal of the marketing application for this product, which provides an overview on all available information on the product at the time of the Applicant's withdrawal.