European Medicines Agency
Evaluation of Medicines for Human Use

Doc.Ref.: EMEA/CHMP/100434/2009

ASSESSMENT REPORT

FOR

Removab

International Nonproprietary Name: catumaxomab

Procedure No. EMEA/H/C/000972

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

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1. BACKGROUND INFORMATION ON THE PROCEDURE

1.1 Submission of the dossier

The applicant Fresenius Biotech GmbH submitted on 24 December 2007 an application for Marketing Authorisation to the European Medicines Agency (EMEA) for Removab, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004.

The legal basis for this application refers to:

A - Centralised / Article 8(3) / New active substance.

The application submitted is a complete dossier composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

The applicant applied for the following indication: the intraperitoneal treatment of malignant ascites in patients with epithelial cancers where no standard therapy is available or no longer feasible.

Scientific Advice
The applicant received Scientific Advice from the CHMP on 18 November 2004, on 17 January 2005 and on 30 June 2006.The Scientific Advice pertained to the clinical aspects of the dossier.

Licensing status:
The product was not licensed in any country at the time of submission of the application.

The Rapporteur and Co-Rapporteur appointed by the CHMP were:
Rapporteur: **Tomas P Salmonson** Co-Rapporteur: **Jens Ersbøll**

1.2 Steps taken for the assessment of the product

- The application was received by the EMEA on 24 December 2007.
- The procedure started on 30 January 2008.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 18 April 2008. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 22 April 2008
- During the meeting on 27-29 May 2008 the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 30 May 2008.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 22 August 2008.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 3 October 2008.
- During the CHMP meeting on 20-23 October 2008 the CHMP agreed on a list of outstanding issues to be addressed in writing and in an oral explanation by the applicant.
- The applicant submitted the responses to the CHMP list of outstanding issues on 17 November 2008.
- During the CHMP meeting on 17-20 November 2008 the CHMP agreed on an addendum to the list of outstanding issues to be addressed in writing by the applicant.
- The applicant submitted the responses to the addendum to the CHMP list of outstanding issues on 27 November 2008.
- The Rapporteurs circulated the updated Joint Assessment Report on the applicant's responses to the list of outstanding issues to all CHMP members on 2 December 2008.

- During a meeting of a SAG Oncology on 4 December 2008, experts were convened to address questions raised by the CHMP.
- During the CHMP meeting on 15-18 December 2008 the CHMP agreed on a second list of outstanding issues to be addressed in writing and in an oral explanation by the applicant.
- The applicant submitted the responses to the CHMP second list of outstanding issues on 22 December 2008.
- The Rapporteurs circulated the updated Joint Assessment Report on the applicant's responses to the second list of outstanding issues to all CHMP members on 5 January 2009.
- During the CHMP meeting on 19-22 January 2009 outstanding issues were addressed by the applicant during an oral explanation before the CHMP.
- During the meeting on 16-19 February 2009 the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Removab on 19 February 2009. The applicant provided the letter of undertaking on the follow-up measures to be fulfilled post-authorisation on 18 February 2009.

2 SCIENTIFIC DISCUSSION

2.1 Introduction

Malignant Ascites

Malignant ascites is a sign of advanced and often metastatic malignancy. In general, the following major mechanisms for the development of malignant ascites are known:

1. Tumour cells seeding along the peritoneal wall obstruct lymphatic drainage, resulting in a decreased fluid efflux from the peritoneal cavity.
2. Tumour cells produce factors (e.g. vascular endothelial growth factor (VEGF)) leading to
    - tumour neovascularisation
    - increased permeability of the capillaries of the tumour and the peritoneum.

Nonmalignant causes of ascites in cancer patients are recognized as well: These include cirrhosis, nephrosis, congestive heart failure and peritonitis secondary to pyogenic organisms and tuberculosis. These involve different mechanisms often unrelated to the above mentioned mechanism of malignant ascites.

Symptoms commonly reported by malignant ascites patients are abdominal bloating, permanent feeling of fullness, abdominal pain, nausea, early satiety, abdominal swelling, anorexia, dyspnea, insomnia, fatigue and respiratory distress.

If the patient's malignant disease is sensitive to chemotherapy, reduction of ascites production and relief of symptoms may be achieved. However, most of the patients with ascites have already been treated with several lines of treatment, and their disease has become refractory to chemotherapy. For such patients, Currently, the standard treatment method of treatment of malignant ascites is paracentesis To date, no drug therapy, specific for the treatment of malignant ascites, has been approved in the European Union.

The Medicinal Product

Removab contains catumaxomab, a monoclonal antibody. The antibody possesses 2 different antigen binding sites that target the human epithelial cell adhesion molecule (EpCAM), human CD3 expressed on T-lymphocytes, respectively. The Fc region binds to the Fcγ-receptor-type I (CD64), -type IIa and -type III (CD16), which are expressed on positive accessory cells

EpCAM is overexpressed in the majority of epithelial tumours. Binding of catumaxomab to EpCAM-positive tumour cells, T cells and accessory cells is thought to bring them in close proximity and induce simultaneous recruitment and activation of different types of immune effector cells at the tumour cell site via a complex "crosstalk" between T cell and accessory cell. This crosstalk includes cytokines and co-stimulatory signalling necessary for a physiological T cell activation cascade and ultimately, via multiple tumouricidal mechanisms, tumour cells could be eliminated.

The initially proposed indication for Removab was: intraperitoneal treatment of malignant ascites in patients with epithelial cancers where no standard therapy is available or no longer feasible. Following the CHMP scientific assessment, this indication was subsequently modified to "intraperitoneal treatment of malignant ascites in patients with EpCAM positive carcinomas where standard therapy is not available or no longer feasible", in order to reflect the clinical data that formed the basis of the assessment.

Removab must be administered under the supervision of a physician experienced in the use of anti-neoplastic medicinal products. Prior to the intraperitoneal infusions, a premedication with antipyretic / antiphlogistic medicinal products is recommended. Removab dosing schedule comprises the following four intraperitoneal infusions: 1st dose: 10 µg on day 0; 2nd dose: 20 µg on day 3; 3rd dose: 50 µg on day 7; 4th dose: 150 µg on day 10. An interval of at least two days must elapse between infusions. The interval between the infusion days can be prolonged in case of relevant adverse reactions (see SPC section 4.2).

Removab must be administered as an intraperitoneal infusion only. Removab must not be administered by intraperitoneal bolus or by any other route of administration. Before administration of Removab the concentrate for solution for infusion is diluted in sodium chloride 9 mg/ml (0.9%) solution for injection. The diluted Removab solution for infusion is administered intraperitoneally via a constant infusion pump system. The SPC section 6.6 provides detailed instructions on dilution prior to administration and for instructions for administration.

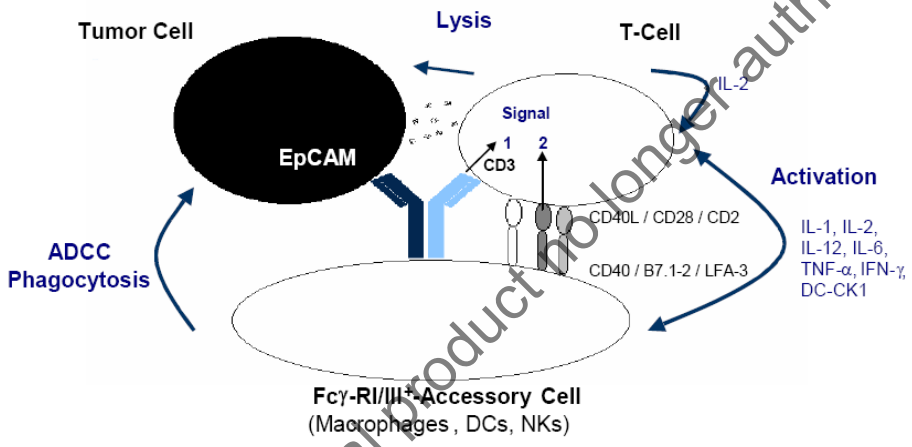
2.2 Quality aspects

Introduction

Removab is intended for the treatment of malignant ascites in patients with EpCAM-positive carcinomas where standard therapy is not available or no longer feasible.

Removab contains catumaxomab, an engineered intact trifunctional bispecific monoclonal antibody (trAb) consisting of a mouse kappa light chain, a rat lambda light chain, a mouse IgG2a heavy chain and a rat IgG2b heavy chain. In addition to the mouse and rat Fab fragments enabling bispecific binding to human EpCAM and human CD3 receptors, respectively, the hybrid Fc region provides a third functional binding site which preferentially binds the activating receptors FcγRI (CD64), FcγRIIA and FcγRIII (CD16) (see figure 1 below).

Figure 1



Binding of catumaxomab to EpCAM-positive tumour cells, T cells and accessory cells results in a simultaneous recruitment and activation of different types of immune effector cells at the tumour cell site. The tumour cells and immune effector cells are brought into close proximity, and a complex "crosstalk" between T cell and accessory cell can occur, which includes cytokines and co-stimulatory signalling necessary for a physiological T cell activation cascade resulting in killing of tumour cell. Since EpCAM is overexpressed in the vast majority of all epithelial tumours, catumaxomab is expected to be effective across a variety of epithelial tumours.

Catumaxomab is formulated in a 0.1 M sodium citrate buffer solution (pH 5.6) containing 0.02% polysorbate 80. Catumaxomab is provided as a concentrate for solution for infusion in prefilled syringe. The product is presented in two different presentations, with the same formulation, containing a 10 µg and a 50 µg dose of catumaxomab at 100 µg/mL in pre-filled 1 mL glass syringes with a nominal volume of 100 µl and 500 µl, respectively.

The concentrate is diluted in sterile isotonic saline solution (0.9%) and administered to the patient by intraperitoneal infusion.

Active Substance
Catumaxomab is the active substance of Removab. Catumaxomab is a trifunctional antibody consisting of a mouse kappa light chain (220 aa), a rat lambda light chain (215 aa), a mouse IgG2a heavy chain (450 aa) and a rat IgG2b heavy chain (451 aa). Mouse IgG2a and rat IgG2b represent highly homologous IgG subclasses.

Catumaxomab has three different binding sites:

- the rat Fab fragment binding to human CD3
- the mouse Fab fragment binding to human EpCAM
- the hybrid Fc-region binding to Fcγ receptor-type I (CD64), -type IIa and -type III (CD16) positive accessory cells.

- Manufacture

The drug substance is manufactured according to Good Manufacturing Practice (GMP) at Trion Pharma GmBH facilities in Munich (DE).

Catumaxumab is produced by fermentation in a rat/mouse hybrid hybridoma (quadroma) cell line. The quadroma cell line was obtained by the fusion of two parental cell lines: a hybridoma cell line which expressed anti-human EPCAM antibody and a hybridoma cell line producing anti-human CD3 antibody.

A MCB was produced by cell culture of a selected single clone. The establishment, characterization and control of the Master Cell Bank were described and are adequate. A strategy for providing a continuous supply of cells by producing a new Working Cell Bank on a regular basis has been described. The genetic stability of the sequences of catumaxomab encoding cDNA of the cell banks was appropriately demonstrated.

The manufacturing process starts with the culture and expansion of a single vial of WCB. The medium containing the antibodies is filtered to remove any cells and purified by two chromatographic steps: a protein A chromatography and a cation-exchange. The eluate is diafiltered and nanofiltered to exchange buffers and to adjust protein concentration.

The active pharmaceutical ingredient is formulated by dilution with 0.1 M sodium citrate buffer at pH 5.6 to a final target concentration 100 µg/mL of catumaxomab and addition of 0.02% polysorbate 80.

Materials used in the manufacturing process are adequately controlled. Apart from the WCB, no materials of primary animal origin are used.

The manufacturing process of the drug substance is well defined. In-process controls and in-process parameters are based on experience gained during development of the manufacturing process and are in general considered appropriate.

Validation studies presented demonstrate clearance of process related impurities and consistency of the drug substance manufacturing process.

Manufacturing process development and validation
Process development involves the use of 4 different processes. During process development, process changes including the introduction of serum free fermentation process, changes in the nanofiltration/diafiltration membranes and chromatographic steps as consequence of the up-scale.

Pivotal studies were performed using process II. The comparability package showing comparability with the proposed commercial process (advanced III) was updated with appropriate additional data during the procedure and found to be acceptable for the proposed commercial scale.

Characterisation

A thorough characterisation program for catumaxomab has been performed to address the physicochemical and biological properties of the product and to evaluate the impurity and heterogeneity profiles.

A) Physicochemical characterisation
The primary, secondary and tertiary structures of catumaxomab were analysed by various techniques.

The complete amino acid sequence of catumaxomab was determined.
The different isoforms of catumaxomab were characterized with respect to origin and biological activity.

The isoforms isolated present equal biological activities in the activity assay and appear at the same levels in the characterisation batches of catumaxomab tested. Deamidation is expected to be the root cause of the isoform distribution in catumaxomab, however this has not been possible to conclude up to now. The applicant has demonstrated control of mismatched variants during production.

Characterisation of glycosylation indicated that catumaxomab is N-glycosylated. No sialylated structures were detected.

The secondary and tertiary structure of catumaxomab was analysed. All the structural features are in agreement with that expected of an IgG molecule.

A2) Biological activity
Biological activity of catumaxomab was analysed. A dose response relation of both (EpCAM and CD3) binding specificities has been demonstrated. The Applicant has provided data showing that the activity assay is specific for catumaxomab.

B) Impurities
Product related impurities.
The Applicant has provided data documenting the clearance of product related impurities at different steps during the manufacturing process of catumaxomab.

Process related impurities.
The applicant has demonstrated in the process validation the reduction of process related impurities to an acceptable level in the drug substance. The clearance of product related impurities was consistent.

- Specification

The specifications for the drug substance have been adequately justified and are acceptable and batch results demonstrate consistency. The methods were appropriately validated and in compliance with pharmacopoeial requirements when applicable.

For the control of the active substance, the list of specifications has been updated during the procedure. The proposed initial limits for the potency assay were considered too wide since the drug requires a careful escalating dosing regimen. During the procedure they have been slightly tightened but should be further evaluated after an appropriate amount of batches. The company commits to re-evaluate the approved limits of the potency method after the manufacture of 5, 10, 15 batches of catumaxomab.

- Stability

Catumaxomab is stored in flexible bags and the claimed stability is 6 months at 2-8^{o}C.

During the procedure, the applicant provided additional data on real time real conditions to show that catumaxomab DS is stable over the claimed period. It was recommended that the company performs an evaporation study of the formulation buffer within flexible bags using conditions actually encountered during production. The company has provided the protocol and a commitment to perform the evaluation study and to report the results at the end of the study.

Medicinal Product

Removab is intended to be marketed in two presentations of drug product, corresponding to a 10 µg and a 50 µg dose of catumaxomab, respectively. They are supplied in pre-filled 1 mL glass syringes containing a nominal value of 100 µL and 500 µL, respectively.

Catumaxomab 100 µg/mL is supplied as a concentrate for solution for infusion. The concentrate is diluted in sterile isotonic saline solution. The infusion set are standard medical items for parental use and are not part of the drug product presentation.

Removab is formulated in a 0.1 M sodium citrate buffer solution (pH 5.6) containing 0.02% polysorbate 80.

The container closure system consists of a siliconised glass barrel, a siliconised plunger stopper, and a closure system composed of a siliconised tip cap, a luer lock and a tamper-evident seal. The syringes are filled with an appropriate overfill which is justified to ensure the withdrawal of the nominal volume.

- Pharmaceutical Development

The drug product formulation is the same as the drug substance formulation and has been fully described and justified. The different catumaxomab drug products used during clinical development have been described. The differences relate primarily to the primary packaging materials, the sterile filtration conditions and the fill volume for the filling process.

The Applicant has provided information on losses of catumaxomab with infusion systems and the compatibility of catumaxomab with different tested infusion materials (catheters, perfusion tubings, perfusion syringes, and infusion valves/Y-connections). A consistent dose delivery is considered assured.

- Manufacture of the Product

Catumaxomab drug product is formulated at the drug substance stage and the manufacturing process for the bulk medicinal product thus consists of only two main steps: sterile in-line filtration of the formulated drug substance solution followed by filling and stoppering of the syringes.

The manufacturing process together with the IPC has been sufficiently described. Critical steps have been defined and are adequately controlled. Validation of the manufacturing process has been provided.

- Product Specification

The specifications for the drug product have been adequately justified and are acceptable and batch results demonstrate consistency. The methods were appropriately validated and in compliance with pharmacopoeial requirements when applicable.

- Stability of the Product

The stability data has been provided to cover 18 months of storage for two batches and 15 months for a third batch and the results show a good stability for the product at storage conditions protected from light. A shelf life of 18 months when stored at 5 C is acceptable, provided a commitment is given to submit the 18 month data for batch 101I02 within an agreed time frame.

- Adventitious Agents

The cell line was characterized according to the ICH Q5A requirements for microbial contamination, the presence of retroviruses, and contamination with adventitious viruses. Results were typical for a

murine hybridoma cell line and confirmed that the cell line is suitable. Cell line testing was confirmed by testing of PPCB.

Adventitious viruses were not detected by *in-vitro* and *in-vivo* assays and also the extensive testing of MCB and PPCB cells as well as unprocessed bulk provided no evidence of contamination with bovine viruses. In addition, MCB and PPCB cells were tested for the presence of BPyV (bovine polyoma DNA) with negative result.

The virus validation studies and the risk analysis have shown that the manufacturing process of Catumaxomab contains four steps of removal/inactivation of enveloped viruses. Two of these steps are also effective for removal of non-enveloped viruses. The different manufacturing steps complement each other in the mode of action of removal/inactivation. The data demonstrate that the virus safety of Catumaxomab meets the pre-specified requirement.

Discussion on chemical, pharmaceutical and biological aspects

Overall, information on development, manufacture and control of the drug substance and drug product have been presented in a satisfactory manner. The results of tests carried out indicate satisfactory consistency and uniformity of important quality characteristics.

At the time of the opinion, there were some minor unresolved quality issues having no impact on the Risk-benefit balance of the product. The applicant gave a Letter of Undertaking and committed to resolve them after the opinion within an agreed timeframe.

2.3 Non-clinical aspects

Introduction

The non-clinical programme was adapted to the fact that catumaxomab is a protein, and its binding properties are essentially specific for humans.

The pharmacokinetic studies did not fully comply with principles of Good Laboratory Practice (GLP). The remaining studies were conducted in accordance with GLP.

The most notable consequence of the inability to find a relevant species is that the present application does not contain repeated dose toxicology studies of catumaxomab. A number of other pharmacokinetic and safety studies are also not included, which is common for biological substances.

Pharmacology

Catumaxomab (or TPBs01) is an intact trifunctional bispecific monoclonal antibody produced from rat/mouse hybrid-hybridoma cells. This antibody possesses three different binding sites: 1) The rat Fab fragment targets human cluster of differentiation CD3, expressed on T-lymphocytes, 2) the mouse Fab fragment is directed against the human epithelial cell adhesion molecule (EpCAM), a tumour-associated antigen that is expressed on most adenocarcinomas and 3) The hybrid Fc region provides a third functional binding site, which is able to selectively bind and activate Fcγ receptors.

EpCAM (also known as ESA or EGP-2) is a transmembrane 40-kDa glycoprotein that is encoded by the GA733-2 gene. It mediates Ca^{2+}-independent homotypic cell-cell adhesions. In human, EpCAM is expressed only in epithelium and neoplasias derived from epithelia (Balzar et al., 1999). EpCAM is strongly expressed in carcinomas of various origins including colon, rectum, prostate, liver, oesophagus, lung, pancreas, breast, head and neck (Went et al., 2004). A differential attachment of sugar residues to the extracellular moiety of EpCAM was observed in healthy versus tumour tissues (Pauli et al., 2003). The intracellular part is responsible for the signalling properties of EpCAM including the induction of cell proliferation and the upregulation of the proto-oncogene c-Myc (Munz, 2004).

The interaction of different immune effector cells at the tumour site is postulated to result in elimination of tumour cells by several killing mechanisms:

- T-cell-mediated lysis through perforin or granzyme B-driven mechanisms
- Cytotoxicity by released cytokines, such as TNF-α and IFN-γ
- Phagocytosis via activation of FcγR I and III positive accessory cells
- Antibody dependent cellular cytotoxicity following activation of FcγR I, IIa and III positive accessory cells

A targeted non-clinical testing strategy was developed to obtain relevant information from scientifically justified pharmacological, pharmacokinetic and toxicological model systems.

- *In vitro* effects of catumaxomab were assessed in models using human cells where catumaxomab is able to exert its full pharmacological activity.
- A surrogate antibody (BiLu), which is of equivalent structure to catumaxomab and has the same principal target specificity but binds to mouse CD3 instead of human CD3, was used for pharmacology, pharmacokinetic and toxicology studies in mouse models.

- Primary pharmacodynamics

The primary pharmacology studies have assessed the trifunctional mechanism of action. In these studies binding, T-cell activation, and the importance of T-cells and FcγR-positive accessory cells in anti-tumour activity was demonstrated.

In vitro

Specificity of binding of catumaxomab to CD3 and EpCAM ()

Human peripheral blood mononuclear cells (PBMC) from healthy donors were incubated with catumaxomab and a commercially available anti-CD3 antibody. Binding was analyzed by fluorescence activated cell sorter (FACS). EpCAM binding experiments were performed with an EpCAM-positive colon cancer cell line, and an EpCAM-specific antibody.

Determination of the antibody binding site on EpCAM ()

Mutants of EpCAM were generated and expressed in a human cell line in order to determine the binding site on EpCAM.

Binding properties of catumaxomab to various human tumour cell lines. Anti-tumour activity against human tumour cells from different tissue.

Binding to lymphocytes was assessed using PBMC from healthy donors, which were incubated with various concentrations of catumaxomab or parental antibody (anti-CD3). Bound catumaxomab and bound parental antibody were analyzed by FACS. There was similar binding of catumaxomab (anti-EpCAM x anti-CD3) and the parental anti-CD3 antibody to T-cells.

The antitumour efficacy correlated to the binding efficacy.

Replacing catumaxomab with the parental antibody which binds to EpCAM only (no CD3 binding) did not result in antitumour activity. Several other studies studied the *in vitro* tumouricidal effects of catumaxomab.

Binding of catumaxomab to human Fcγ receptors of monocytes, NK cells and granulocytes.

PBMC and granulocytes were isolated from blood, and binding to Fcγ receptor was investigated on monocytes (CD14+), T-cells (CD4+ or CD8+), B-cells (CD19+) and NK cells (CD56+). The different cell types were identified by FACS. Additional samples of cells were co-stained with specific antibodies against CD surface markers plus the Fcγ receptor I and Fcγ receptor III. A concentration-dependent binding of catumaxomab to monocytes (CD14+), T-cells (CD4+ or CD8+), NK cells (CD56+) and granulocytes was observed; there was only minimal binding to B-cells (CD19+). When cells were pre-incubated with an anti-CD3 antibody, the binding of catumaxomab to CD4+ and CD8+ cells was reduced, suggesting that binding of catumaxomab to T-cells is mainly dependent on CD3.

Binding of catumaxomab to human mononuclear cells was demonstrated. Binding to Fcγ-receptor positive cells was observed although the binding varied considerably between donors..

Activation of human T-cells by catumaxomab

Granzyme B is a protease released by NK-cells and cytotoxic T-cells, which also release perforin. Granzyme B and perforin enter target cells via the mannose 6-phosphate receptor and cause apoptosis of these cells. Catumaxomab, in contrast to the parental anti-EpCAM antibody, induced granzyme B release by PBMC from healthy donors contributing to the catumaxomab antitumour effect.

Antibody-dependent cellular phagocytosis observed that activated peripheral blood monocytes, incubated with catumaxomab and calcein-loaded EpCAM-positive tumour cells, phagocytosed the tumour cells.

Complement-dependent cytotoxicity showed that catumaxomab induced cytotoxicity towards EpCAM-positive gastric tumour cells in the presence of complete human serum, but not in the absence of serum or in the presence of heat-inactivated serum. in study *HD-Catu-201206 (not GLP)* EpCAM-positive colon tumour cells were lysed as a result of complement activation in the presence of normal serum and high catumaxomab concentrations but not in the presence of therapeutic catumaxomab concentrations. T-lymphocytes were not lysed, apparently due to the presence of membrane bound complement regulatory proteins, since neutralisation of the latter did result in T-cell lysis.

In vivo

The variant antibody BiLu (anti-human EpCAM & anti-mouse CD3) was used to demonstrate proof of concept in a syngeneic mouse tumour model expressing human EpCAM. Anti-tumour activity of catumaxomab was observed in a human ovarian carcinoma xenograft study. The mouse-CD3-specific antibody BiLu was more effective in a mouse tumour model (Ruf et al., 2001).

- Secondary pharmacodynamics

Cytokine and histamine release in vitro)

Blood samples from healthy human donors were incubated with catumaxomab in the presence or absence of EpCAM-positive human colon tumour cells .. Catumaxomab-induced production of pro-inflammatory cytokines was only observed in significant amounts when catumaxomab was incubated with blood cells in the presence of EpCAM-positive tumour cells. The greatest stimulatory effect of catumaxomab was seen for TNF-α and IL-6, and a smaller stimulatory effect was seen for IL-2. Only insignificant effects were observed for IL-12 and IL-1. In all cases, the stimulation was greater after incubation for 24 h compared to 2 h. In several cases, the release of TNF-α, IL-2 and IL-6 was inversely correlated to the concentration of catumaxomab.

Histamine release was analysed in a similar way, using whole blood incubated with various concentrations of catumaxomab (but no tumour cells). No significant induction of histamine release by catumaxomab was detected.

For complement activation, C3 or C4 was added to the blood sample. No activation of complement (formation of C3a or C4a) by catumaxomab was showed after incubation with PBMC alone.

A significant induction of PBMC proliferation was observed at all catumaxomab concentrations. The induction was similar to that of the positive control. A slight induction of proliferation of the tumour cell lines Jurkat (CD3+), HCT-8 and SKBR-3 (EpCAM+) was observed in the absence of PBMC. A demonstrated proliferation induction by catumaxomab has not been observed.

BiLu application was associated with a transient decrease in CD3+ cells. However, the doses used in this study were high compared to the clinical dose.

- Safety pharmacology programme

The safety pharmacology programme was defined by the accessibility of intact monoclonal antibodies in vivo to EpCAM positive tissue. EpCAM in normal tissues can be reached only at inflamed and injured sites. An exception is the vascular system of the liver, which may permit contact of catumaxomab with the EpCAM-positive bile duct cells in cases of increased permeability if the antibody enters the circulation following IP administration. Potential effects on hepatocytes have therefore been investigated in *in vitro* models.

Cross-reactivity

Two GLP studies have investigated the potential cross-reactivity of catumaxomab and the parental anti-EpCAM antibody with normal human tissues.

The first study found that catumaxomab bound to the epithelia of various tissues (adenoid tissue, the urogenital system, the alimentary tract and mamma). Binding of the antibody was also found on lymphocytes. Results suggested that the antibody was mainly membrane bound. and a nuclear binding was not observed. In the peripheral blood in the parenchyma of the cerebellum and the cerebral cortex, in the cardiac muscle, in the placenta, in the skin as well as in the skeletal muscles and in the uterus (area of the cervix) no binding of antibody could be detected.

The results of the second study were similar. In this study, comparison was made to the anti-EpCAM parent antibody. Binding to epithelium, via the EpCAM binding arm, with both antibodies was comparable, and was found for tissues for which EpCAM expression has been described in the literature (Balzar et al. 1999. Went et al. 2004)

Binding and effects on freshly harvested or cultured human hepatocytes.

There was no binding to hepatocytes and no functional impairment (albumin release, UDP formation or urea production; increases in AST and LDH were seen but considered minor). Binding to bile duct cells in liver tissue was seen, since these cells are EpCAM positive.

- Pharmacodynamic drug interactions

Pharmacodynamic drug interactions were investigated *in vitro* due to the lack of suitable animal models.

Influence of steroids on antibody activity

Cytokine release after administration of therapeutic antibodies *in vivo* may induce side effects, which might be alleviated by the concomitant use of anti-inflammatory drugs. Since catumaxomab was shown to increase cytokine release *in vitro* the influence of steroids (dexamethasone, hydrocortisone) on in *vitro* immune stimulation by catumaxomab was investigated. Dexamethasone dose-dependently and markedly inhibited Removab-induced cytokine release and granzyme B release. Catumaxomab-induced tumour cell killing was inhibited by dexamethasone at all tested concentrations in conditions of a low catumaxomab concentration. Hydrocortisone showed weaker inhibition of cytokine and granzyme B release and had no effect on catumaxomab-induced tumour cell killing.

The influence of chemotherapeutic drugs on catumaxomab activity was studied in vitro in order to investigate potential synergistic effects.

Pharmacokinetics

Pharmacokinetic studies were performed with catumaxomab and the variant antibody BiLu, which is of equivalent structure but binds to mouse CD3 instead of human CD3. Since BiLu binds specifically to mouse CD3, its pharmacokinetic profile in mice is a more relevant model for the pharmacokinetics of catumaxomab in humans.

Methods of analysis

ELISA methods were developed for sensitive measurement of catumaxomab (ng/mL range).

Absorption

Intravenous pharmacokinetics of catumaxomab in male mice. The animals were treated with a bolus dose. Blood samples collected were analysed using ELISA. The elimination was initially fast, the plasma concentration decreased during the first hours, followed by a terminal slow elimination phase Similar to the study above, using BiLu instead, which differs from catumaxomab by binding to mouse CD3 no slow terminal elimination phase was seen.

In a different study i.p. and i.v. administration of BiLu to mice were compared. The bioavailability after i.p. administration was complete.

Another s*tudy* investigated the effects of catumaxomab on SCID-mice intraperitoneally injected with human EpCAM-positive tumour cells in combination with human PBMC The amount of binding

partners (EpCAM-positive tumour cells, CD3-positive T-cells and FcγR-positive immune cells) determines the retention and transfer of catumaxomab.

Distribution

Single-dose

Binding and distribution of ^{123}I-labelled catumaxomab in SCID-mice bearing flank-injected human EpCAM-positive tumours

Catumaxomab localised to the tumour. The time-activity course for both catumaxomab and a control antibody without tumour specificity in non-target organs was similar.

Metabolism

No metabolism studies were submitted.

Excretion

No excretion studies were submitted.

Pharmacokinetic drug interactions

No pharmacokinetic drug interaction studies were submitted.

Other pharmacokinetic studies

No other pharmacokinetic studies were submitted.

Toxicology

- Single dose toxicity

A number of common laboratory animal species, including the three monkeys marmoset (*Callitrix* sp.), cynomolgus (*Macaca fascicularis*) and rhesus (*Macaca mulatta*) were tested histologically for catumaxomab binding, but none showed a binding pattern similar to that of human tissues, and were consequently considered non-relevant. In the few studies performed in rats, mice and one cynomolgus monkey, no acute toxicity was seen even at very high doses of catumaxomab.

A single dose toxicology study as well as a number of other preclinical studies was performed with the antibody BiLu, which is specific for mouse CD3, in contrast to catumaxomab, which is specific for human CD3. However, both BiLu and catumaxomab are specific for human EpCAM. BiLu may thus not have similar toxicological and dynamic effects in the mouse as catumaxomab has in the human leaving the safety assessment of catumaxomab largely to the clinical studies. Effects seen with BiLu may thus not be relevant for catumaxomab.

- Repeat dose toxicity.

Repeat-dose toxicity studies have not been submitted.

- Genotoxicity

Genotoxicity studies have not been submitted.

- Carcinogenicity

Carcinogenicity studies have not been submitted.

- Reproduction Toxicity

Reproductive and developmental toxicity studies have not been submitted.

- Toxicokinetic data

See Pharmacokinetics.

- Local tolerance

Local tolerance of catumaxomab (of the formulation used in humans)

In rabbits, i.a. and p.v. application resulted in a well defined reversible erythema formation. Histopathological mild to marked subcutaneous haemorrhages at the application site occurred after p.v. administration. Subcutaneous application resulted in a slight reversible erythema formation in one animal. Intramuscular administration caused no erythema or edema formation.

Administration of 150 µg i.p. catumaxomab showed an histopathological moderate subchronic inflammation of skin and abdominal muscle after administration of the test item in one animal.

In Cynomolgus monkey, no catumaxomab-related intolerance reactions were observed.

Evaluation of the local tolerance of the mouse-CD3-specific analogue BiLu showed no test item-related local reactions at the injection sites in any of the treated mice. No histological findings were detected that could be attributed to an intolerability of the test item.

- Other toxicity studies

Antigenicity

Single dose toxicity study in the cynomolgus monkey. The development of anti-mouse and anti-rat antibodies was detected in serum samples after the last dose.

Immunotoxicity

Single dose toxicity study in the cynomolgus monkey. No changes were seen in the serum cytokine levels following i.v. infusions of catumaxomab at escalating dose levels. In addition, no influence on the plasma levels of complement was observed.

Dependence

No dependence studies have been submitted.

Metabolites

No studies on metabolites have been submitted.

Studies on impurities

No studies on impurities have been submitted.

"Since no animal model is available which permits toxicological testing of the full pharmacological activity of catumaxomab, toxicity studies with trace impurities were not performed."

Other studies

A number of cross-reactivity studies were conducted using mouse, monkey, rabbit and dog tissues to evaluate the suitability of animals for pharmacology and toxicology studies.

Ecotoxicity/environmental risk assessment

A justification for not providing an environmental risk assessment has been submitted.

Discussion on the non-clinical aspects

The application has been assessed in accordance with the current guidelines on pre-clinical evaluation of anticancer medicinal products (CPMPP/SWP/997/96) and pre-clinical safety evaluation of biotechnology-derived pharmaceuticals (ICH S6). Although not fully complying with GLP, most pharmacokinetic studies were subjected to quality assurance evaluation. The absence of many non-clinical studies is considered acceptable for an antibody, given the absence of suitable animal models.

Based on the non-clinical programme submitted, the CHMP raised the following concerns:

The CHMP requested clarifications about the binding of catumaxomab to different Fcγ receptors. In addition to the data submitted in the initial dossier the applicant provided further studies to clarify binding of catumaxomab to the high affinity Fcγ-receptor I (CD64) and to the low affinity Fcγ-receptor IIa (CD32a) and its inhibitory counterpart Fcγ-receptor IIb (CD32b). The CHMP considered that the data submitted indicates that catumaxomab binds to human Fcγ receptor I, IIa and III .

The applicant was asked to provide a critical assessment with regards to safety concerns due to T- and B-cell cross talk. Although no animal models were available to permit toxicological testing of the full

pharmacological activity of the medicinal product, the applicant stated that no significant toxicities were found after repeated i.v. infusion of escalating doses of catumaxomab in cynomolgus monkeys, and the applicant also provided data from BiLu in mice.

Following CHMP review, the applicant was asked to investigate the binding potential of catumaxomab towards the human GA733-1 gene product, a protein with high homology to EpCAM. The applicant therefore provided data indicating that the interaction of catumaxomab with GA733-1 gene product , a protein with high homology to EpCAM is very unlikely.

In addition, the CHMP raised other concerns with regards to the non-clinical pharmacokinetic data and toxicology data submitted. The applicant was asked to elaborate on the initial rapid elimination of catumaxomab from the plasma of i.v.-injected mice which was surprising, including an account for the distribution of the injected material. After the applicant's responses, the CHMP considered that the distribution of catumaxomab and the mechanism behind the rapid elimination of catumaxomab remains obscure. Generally, knowledge of these topics is essential for the assessment of toxicological data. However, due to the unavailability of relevant models for the toxicological testing of catumaxomab, further data were not requested.

The single-dose toxicity studies with BiLu indicate that catumaxomab may cause liver toxicity. The applicant was therefore asked to justify the wording of the SPC regarding potential effects on the liver toxicity. As argued by the applicant, the toxicity findings obtained with the surrogate antibody BiLu were considered of limited value. Due to the lack of a relevant animal model, safety assessment of catumaxomab mainly depend on the clinical safety assessment. Therefore, an amendment of the SPC was not considered necessary. with regards to the hepatotoxicity observed with BiLu.

In addition to the concerns raised by the CHMP, the following information was included in the SPC based on the data submitted:

The medicinal product is contraindicated in patients with hypersensitivity to murine (rat and/or mouse) proteins (see section 4.3)

No interaction studies with other medicinal products or other forms of interaction have been performed (see section 4.5)

The medicinal product should not be used during pregnancy unless clearly necessary, given that is unknown whether catumaxomab is excreted in human breast milk: "A decision must be made whether to discontinue breast-feeding or to discontinue / abstain from Removab therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman" (see section 4.6)

Section 5.1 of the SPC was updated to include the following text on pharmacodynamic effects:

The anti-tumour activity of catumaxomab has been demonstrated in vitro and in vivo. Effective catumaxomab-mediated killing of tumour cells in vitro was observed for target cells with low and high expression of the EpCAM antigen, independent of the primary tumour type. The in vivo anti-tumour activity of catumaxomab was confirmed in an immunologically compromised mouse model of ovarian carcinoma, where tumour development was delayed by an intraperitoneal treatment with catumaxomab and human peripheral blood mononuclear cells.

No ERA is included in the dossier, which is acceptable for a protein, based on CHMP guidance (EMEA/CHMP/SWP/4447/00).

2.4 Clinical aspects

Introduction

The development program for the indication treatment of malignant ascites consists of one Phase I/II dose finding study (STP-REM-01), one pharmacokinetic study (IP-REM-PK-01-EU) and one pivotal Phase II/III study (IP-REM-AC-01). The clinical program is supported by 3 additional phase I and II studies (AGO-OVAR-2.10, IP-REM-PC-01-DE, IP-REM-GC-01) which provide additional safety information. A total of 270 patients were treated in all completed studies.

Table 7. Studies included in the catumaxomab development program for the indication malignant ascites

Study Number	Indication	Phase	Study Design	No. of Treated Patients
Studies in patients with malignant ascites				
IP-REM-AC-01	Malignant ascites due to epithelial cancer	II/ III	Multicenter, multinational, 2-arm randomized, open-label	157
STP-REM-01	Malignant ascites due to ovarian cancer	I/II	Multicenter, multinational, open-label, uncontrolled, sequential dose-escalating	23
IP-REM-PK-01-EU	Malignant ascites due to epithelial tumours	II	Multicenter, open-label pharmacokinetic	13
Supportive studies in patients with other indications				
AGO-OVAR-2.10	Ovarian cancer	IIa	Multicenter, multinational, 2-arm randomized, open-label	41
IP-REM-PC-01-DE	Peritoneal carcinomatosis due to epithelial gastro-intestinal malignancies	I	Multicenter, uncontrolled, open-label, sequential dose-escalating Addendum 1: Comparison of efficacy and safety with dose group III Addendum 2: Dose above MTD plus 10 mg dexamethasone	Total: 24 14 7 3
IP-REM-GC-01	Intra-abdominal epithelial tumour	I	Single-center, uncontrolled, open-label, dose-escalation	12
There were 270 total treated patients in completed clinical studies with i.p. administration. i.p.: intraperitoneal				

Scientific advice concerning the clinical development of catumaxomab was sought from the EMEA in June 2004 (see discussion on Clinical Efficacy). A follow-up scientific advice regarding modifications in the clinical development plan of catumaxomab in the indication treatment of malignant ascites was received on 30 June 2006.

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

Pharmacokinetics

Only one clinical study with pharmacokinetic data from 11 patients is discussed in the application (study IP-REM-PK-01-EU). Very limited pharmacokinetic data are also available from dose-finding phase I/II studies. All studies were performed in patients with malignant ascites. There are no data on catumaxomab from healthy volunteers. In study IP-REM-PK-01-EU, catumaxomab concentrations in ascites fluid as well as in plasma were evaluated.

Analysis of free catumaxomab in plasma and ascites was made using a validated ELISA method. Analysis of late plasma samples was confounded by the presence of anti-catumaxomab antibodies, but this could be partly overcome by using an antibody-blocking agent in the analysis method. The

antibody-blocking agent was not used during analysis of ascites samples, as there were no ascites sampling after day 10 (the 4th dose) of treatment.

- Absorption

No studies were submitted.

- Distribution

Plasma and ascites data from 11 patients receiving the proposed four doses of catumaxomab but as 6h peritoneal infusions (instead of 3h, see SPC section 6.6) were submitted.

Catumaxomab was detectable in plasma in 10 of 11 patients after the 3rd and 4th peritoneal infusions (50 µg and 150 µg). The mean plasma exposure over the total treatment period ($AUC_{0\text{-}tlast}$) was 3.7 ng*day/mL (range 0 to 13.4 ng*day/mL). The mean C_{max} in plasma was 0.76 ng/ml (range 0 to 2.3 ng/ml).

In ascites, only predose (C_{trough}) concentrations of free catumaxomab were measured, and only until before the fourth infusion. Predose catumaxomab concentrations in ascites varied considerably from 0.27 to 39.9 ng/ml.

- Elimination

No studies were submitted.

- Dose proportionality and time dependencies

No studies were submitted.

- Special populations

No studies were submitted.

- Pharmacokinetic interaction studies

No studies were submitted.

- Pharmacokinetics using human biomaterials

No studies were submitted.

Pharmacodynamics

- Mechanism of action

No studies were submitted.

- Primary and Secondary pharmacology

For the investigation of the pharmacodynamics of catumaxomab a large number of tentative PD biomarkers have been measured across studies. These included measurements of EpCAM +/- tumour cell load in ascites fluid, measurement of leukocyte load in ascites fluid and surface expression of activation markers, measurement of tumour cell/leukocyte ratio in ascites fluid (EpCAM+/CD45+ cell ratio), systemic cytokine production, in vitro clonogenic and proliferation assays for tumour cells and leukocytes isolated from ascites fluid and determination of anti drug antibody (ADA) titers [Human Anti-Mouse Antibodies (HAMA) and Human Anti-Rat Antibodies (HARA)]

EpCAM+/CD45+

The result of the cross study analysis of EpCAM/CD+45 ratios in ascites fluid are tabulated below:

Table 8 EpCAM+ tumour cell / CD45+ leukocyte ratio in ascites in patients treated with catumaxomab (Study IP-REM-PK-01-EU and randomized part of Study IP-REM-AC-01)

Timepoint	Statistic	EpCAM+ tumour cell / CD45+ leukocyte ratio		
		Study IP-REM-PK-01-EU	Study IP-REM-AC-01	
			Ovarian cancer	Non-ovarian cancer
Screening	N Median Range	12 0.464 0.008 - 4.740	73 0.1709 0.000 - 48.333	63 0.6910 0.000 - 17.370
Before 2nd infusion	N Median Range	6 0.000 0.0 - 0.010	46 0.0001 0.000 - 583.000	48 0.0000 0.000 - 6.844
Before 4th infusion	N Median Range	9 0.000 0.0 - 0.119	- -	- -
After 4th infusion	N Median Range	- -	42 0.0000 0.000 - 0.160	33 0.0000 0.000 - 0.129
Puncture visit	N Median Range	2 0.031 0.0 - 0.061	17 0.1371 0.000 - 1.662	15 0.5940 0.000 - 355.721
EpCAM: epithelial cell adhesion molecule, N: number of patients with values at a given timepoint.				

The above data are supported by in vitro incubation of malignant ascites fluid with and without catumaxomab:

Table 9 EpCAM+ cell and CD45+ leukocyte counts in ascites after incubation with and without catumaxomab (in vitro long-term clonogenic assay, Studies IP-REM-PK-01-EU and IP-REM-AC- 01)

Study/ Variable	Median (range) number of cells per 10^6 ascites cells			
	Catumaxomab group		Control group	
	Without catumaxomab	With catumaxomab	Without catumaxomab	With catumaxomab
Study IP-REM-PK-01-EU				
N	6	6	-	-
EpCAM+	4415.00 (464.0 - 21373.0)	9195.00 (6.0 - 15904.0)	-	-
CD45+	19214.00 (2150.0 - 32252.0)	21777.00 (994.0 - 32094.0)	-	-
Study IP-REM-AC-01 (patients with ovarian cancer)				
N	55	55	31	31
EpCAM+	1609.0 (0 - 32045)	17.5 [a] (0 - 30120)	3331.0 [b] (1 - 24562)	107.0 (0 - 32003)
CD45+	6170.5 [a] (35 - 32269)	10117.0 (0 - 32249)	4470.0 (0 - 32243)	6754.0 (0 - 32080)
Study IP-REM-AC-01 (patients with non-ovarian cancer)				
N	62	62	24	24
EpCAM+	2548.0 [c] (0 - 32026)	11.5 [d] (0 - 25476)	4734.0 (0 - 32248)	80.0 (0 - 23790)
CD45+	6284.0 (0 - 32276)	4935.5 (0 - 32082)	10217.5 (2 - 32212)	10122.5 (0 - 32200)
N: number of samples. [a] N= 54. [b] N= 30. [c] N= 61. [d] N= 60.				

Activation markers

The results of the cross-study analysis of activation markers in cells of ascites fluid are tabulated below:

Table 10 Activation markers CD25, HLADR, and CD69 on immune cells in patients with malignant ascites after i.p. administration of catumaxomab (Study IPREM- PK-01-EU and randomized part of Study IP-REM-AC-01)

Study Timepoint (no. of patients)	Median (range) percentage of cells showing activation marker (%)				
	CD25		HLADR	CD69	
	CD45+ CD4+ T cells	CD45+ CD11c+ monoc./ macroph.	CD45+ CD8+ T cells	CD45+ CD4+ T cells	CD45+ CD8+ T cells
IP-REM-PK-01-EU					
Screening (N=12)	5.50 (0.05 - 15.31)	4.05 (0.15 - 7.11)	42.15 (10.19-56.00)	3.49 (0.30 - 32.41)	4.01 (0.35 - 34.54)
Before 2nd infusion (N=9)	7.29 (0.73 - 49.82)	5.07 (0.29 - 27.78)	51.76 (38.80-79.76)	12.28 (0.65 - 33.88)	21.04 (1.27 - 43.79)
Before 4th infusion (N=10)	12.71 (1.90 - 52.25)	8.89 (1.12 - 30.00)	74.97 (33.26-78.81)	23.63 (1.73 - 55.62)	24.19 (1.59 - 49.89)
Puncture visit (N=4)	8.63 (1.88 - 29.69)	9.92 (0.43 - 24.61)	67.31 (32.26-73.46)	12.55 (2.87 - 25.43)	14.29 (1.41 - 29.76)
IP-REM-AC-01 (patients with ovarian cancer)					
Screening (N=69)	15.330 (0.06-49.26)	9.845 (0.27-29.34)	52.930 (9.10-95.76)	6.090 (0.21 - 62.64)	15.270 (0.32 - 90.89)
Before 2nd infusion (N=63)	16.910 (0.06-76.58)	10.440 (0.10-61.29)	62.670 (0.00-96.73)	14.470 (0.12 - 58.68)	24.250 (0.14 - 78.71)
After 4th infusion (N=42)	14.670 (1.51-68.52)	4.700 (0.20-46.87)	66.25 (26.78-95.99)	28.425 (0.38 - 73.73)	38.180 (0.12 - 82.61)
Puncture visit (N=20)	9.030 (1.60-35.22)	8.990 (1.34-26.95)	47.070 (0.64 - 93.80)	4.440 (0.91 - 34.21)	11.715 (1.18 - 45.93)
IP-REM-AC-01 (patients with non-ovarian cancer)					
Screening (N=57)	11.240 (0.0-32.47)	7.460 (0.06-38.02)	51.780 (0.10-94.07)	7.240 (0.00 - 31.50)	11.290 (0.00 - 59.54)
Before 2nd infusion (N=58)	14.020 (1.18-59.09)	7.455 (0.00-39.50)	66.980 (13.03-89.80)	15.760 (1.00-58.55)	23.345 (0.39 - 75.07)
After 4th infusion (N=37)	9.380 (0.10-56.15)	4.865 (0.15-48.38)	71.210 (21.59-89.95)	17.780 (0.20 - 62.85)	26.640 (1.94 - 83.52)
Puncture visit (N=12)	10.605 (1.23-44.67)	6.950 (0.64-28.93)	58.615 (2.51-78.38)	9.700 (1.07 - 32.08)	24.990 (1.88 - 49.52)
N: number of patients with values at a given timepoint; monoc.: monocytes; macroph.: macrophages.					

Tumour load in ascites fluid was also studied in the pivotal trial IP-REM-AC-01 (data not shown).

No secondary pharmacology studies were performed *in vivo*. Systemic cytokine production was analysed in all studies. In the pharmacokinetic study (study IP-REM-PK-01-EU), a clear trend towards increasing values (although variable) shortly after infusions were detected for IL-6, IL-10 and IFN-γ, while values for IL-2 and IL-4 were only slightly increased and TNFα was largely unchanged.

In the pivotal study (IP-REM-AC-01), IL6 was measured in serum before and after catumaxomab infusion. In patients the IL-6 concentration in serum (catumaxomab group only) increased at 24 hours after each infusion, and returned to the baseline value before the next infusion and at Visit 6 (8 days after last infusion). The most pronounced increase occurred after the first infusion.

In another study (STP-REM-01) both IL-6 and TNF-α were measured. At baseline, 17 patients (74%) had normal serum levels of IL-6 and TNF-α, while 6 patients (26%) had values above the upper limit of normal (ULN) for both cytokines. The proportion of patients with elevated IL-6 values increased from 26% to about 80% on the days after infusion and decreased to almost baseline values before the next infusion. The proportion of patients with elevated TNF-α values on the infusion days was about 60%. The tendency to shift back to normal values decreased with the number of infusions.

The safety pharmacology program was limited to *in vitro* binding of catumaxomab to human tissues. As some catumaxomab will leak to the blood through tumour vasculature, systemic exposure will occur. Therefore potential effects on hepatocytes derived from biopsies were investigated (with parental EpCAM-antibody HO-3) without significant binding of catumaxomab. However, in a second

in vitro binding study in human liver tissue there was significant binding to bile duct cells. A selection of human tissues which have a potential to cross-react with catumaxomab is presented below.

Table 11 Catumaxomab-binding to human tissue

++ = moderately positive, +++=strongly positive

Tissue	Intensity
Colon, Mucosal, absorptive and goblet cells; lymphoid tissue	+++
Breast, epithelium lining mammary acini Alveoli Ductal Epithelium	 + ++
Duodenum, mucosa	++
Ileum, Mucosa, mucus secreting goblet cells	++
Kidney, Bowman's capsule Tubules Collecting ducts	+ ++/+ ++
Liver, hepatocytes Bile canaliculi Bile ducts	- +/- ++
Lung, Bronchial mucosa Alveolar pneumocytes and ducts, Ciliated bronchiolar epithelium	++ + +
Prostate epithelial lining acini cells	++
Pituitary, all cell types	++
Thyroid, follicular epithelium C cells	++ +
Parathyroid	++
Uterine cervix	++
Uterus. endometrium, epithelium and glands	++
Pancreas, Ductal epithelium Acini Islets	++ ++ +
Ovary, Oocytes	++

Immunogenicity

Across studies the development of HAMA was observed within days or weeks after the treatment period in the majority of treated patients. In most patients, anti-catumaxomab antibodies were not detectable in plasma until some time after the last infusion. However, in a small proportion of patients anti-catumaxomab antibodies were detectable in plasma before the 4th infusion (data not shown).

Discussion on clinical pharmacology aspects

It is difficult to draw conclusions regarding concentrations of free catumaxomab in ascites during the treatment period. Only C_{trough} values were measured, and only until before the 4th dose. Concentrations after the fourth infusion are likely much higher. The detected free concentrations varied more than 100-fold and the analysis might be confounded by the presence of anti-drug antibodies, which might decrease the actual catumaxomab free concentration by binding catumaxomab and increasing its elimination. On the other hand, anti-drug antibodies might have confounded the analysis method, leading to falsely high concentrations. However, there was no analysis of presence of anti-catumaxomab antibodies in ascites. The variability in free catumaxomab concentrations in ascites fluid might be due e.g. to different amounts of tumour and immune effector cells that bind catumaxomab, to variable amounts of ascites fluid at sampling, and possibly to variable anti-catumaxomab antibody titres.

There are no studies on absorption, distribution, and elimination mechanisms or studies investigating intrinsic factors and special populations. The variability in plasma concentrations introduced by disease factors is likely largely overweighing any variability due to intrinsic factors such as age, gender or race.

There are no pharmacokinetic interaction studies, which are considered acceptable for an antibody.

Proof of principle of primary pharmacodynamics *in vivo* in cancer patients has not been convincingly established. One of the problems is the lack of evaluable target lesions in the clinical studies presented. Although leukocyte activation markers and cytokine release can be documented *in vitro* using human malignant ascites (long term clonogenic assays) and *in vivo* (measuring cytokines in plasma, cytokine release symptoms), sampling methods for measurement of decrease of tumour load is flawed by the mode of catumaxomab administration (repeated lavage and possible dilution) and by the fact that catumaxomab can alter the proportion of leukocytes by stimulation of proliferation.

Despite the claimed interaction of catumaxomab exclusively with abnormal tissue, systemic exposure and interaction with EpCAM positive normal tissues is possible and constitutes another concern. Only very little data is at hand regarding the magnitude of systemic exposure following intraperitoneal administration. Certain reported adverse events (such as hepatotoxicity, cholangitis, see clinical safety results) could result from binding of catumaxomab to relevant tissues.

The cytokine release stimulation of catumaxomab on effector cells constitutes a safety concern. The data presented provide support to some of the manifested adverse events reported in the clinical trials (symptoms of cytokine release, see clinical safety results). Moreover, cytokines as well as EpCAM-binding to bile ducts may cause hepatotoxicity. TNFα tended to accumulate with increasing number of infusions, which is the same pattern as for liver enzyme elevations in the pivotal clinical trial. Therefore, section 4.5 of the SPC was updated to include more information on this warning (see clinical safety discussion)

Catumaxomab is a rodent hybrid monoclonal antibody and the development of neutralizing HAMA/HARA antibodies is expected. This was confirmed in several studies by identification of neutralizing antibodies in plasma, in some patients already before the last dose. The applicant committed to evaluate more patients in a planned phase IIIb clinical study in order to gain additional data on HAMA/HARA positive patients receiving catumaxomab treatment and toxicity. Summary of safety concerns and planned pharmacovigilance actions of the Risk Management Plan (RMP) were revised accordingly.

Based on the clinical pharmacology data submitted, the CHMP updated section 5.2 of the SPC as follows:

Pharmacokinetics of catumaxomab during and after four intraperitoneal infusions of 10, 20, 50 and 150 microgram catumaxomab were investigated in 13 patients with symptomatic malignant ascites due to EpCAM positive carcinomas.

The variability between subjects was high. The geometric mean plasma C_{max} was approximately 0.5 ng/ml (range 0 to 2.3), and the geometric mean plasma AUC was approximately 1.7 day* ng/ml (range < LLOQ (lower limit of quantification) to 13.5). The geometric mean apparent terminal plasma elimination half-life ($t_{1/2}$) was approximately 2.5 days (range 0.7 to 17).

Catumaxomab was detectable in the ascites fluid and in plasma. The concentrations increased with the number of infusions and the doses applied in most patients. Plasma levels tended to decline after achieving a maximum after each dose.

Clinical efficacy

The efficacy claim is primarily based on data from one pivotal Phase II/III clinical study (Study IP-REM-AC-01) investigating patients with malignant ascites due to epithelial cancers. This was the only controlled study in which treatment with catumaxomab was compared to the current standard treatment with paracentesis alone.

In addition, data supporting the efficacy claim are provided from the following studies:

- Phase I/II, dose finding study (Study STP-REM-01) and a Phase II pharmacokinetic (PK) study (Study IP-REM-PK-01-EU) in the same indication supporting the results from the pivotal study.
- Phase IIa Study AGO-OVAR-2.10 in patients with **ovarian** cancer supporting the efficacy of catumaxomab.

Table 12 Studies supporting the efficacy claim are shown in the following table

Study Identifier/ Phase	Indication	Study Design and Type of Control	Number of Patients	Test Product; Dosage Regimen; Route and Duration of Administration
Pivotal study				
IP-REM-AC-01 Phase II/III	Malignant ascites	Multicenter, multinational, 2-arm randomized, open label, controlled	Treated: 157 Control: 88	Catumaxomab; 4 doses: 10-20-50-150 µg I.p. infusions over 6 hours on Days 0, 3, 7 and 10 Premedication: 1000 mg Paracetamol
STP-REM-01 Phase I/II	Malignant ascites due to ovarian cancer	Multicenter, multinational, open label, sequential dose-escalating, uncontrolled	Treated: 23	Catumaxomab; 4(5) doses in 6 escalating dose groups I: 5-10-10-10 µg IIa: 10-50-50-50 µg IIb: 10-20-50-50 µg III: 10-20-50-100 µg IV: 10-20-50-200 µg V: 10-20-50-200-200 µg I.p. infusions over 6 hours on Days 0, 3, 6, 9, (13 for group V) Premedication: 1000 mg Paracetamol
IP-REM-PK-01-EU Phase II	Malignant ascites	Multicenter, multinational, 2-arm randomized, open label, uncontrolled	Treated: 13	Catumaxomab; 4 doses: 10-20-50-150 µg I.p. infusions over 6 hours on Days 0, 3, 7 and 10 Premedication: 1000 mg Paracetamol
AGO-OVAR-2.10 Phase IIa	Ovarian cancer	Multicenter, multinational, 2 arm randomized, open label, uncontrolled	Treated: 41	Catumaxomab; 4 doses in 2 dose groups: I: 10-10-10-10 µg II: 10-20-50-100 µg I.p. infusion over 6 hours on Days 0, 3, 7 and 10 Premedication: 1000 mg Paracetamol

- Dose response studies

STP-REM-01

This Phase I/II, multi-center, dose-escalation study with up to 5 i.p. infusions of catumaxomab established the maximum tolerated dose (MTD) in patients with malignant ascites due to ovarian carcinoma and investigated the safety, tolerability and preliminary efficacy of catumaxomab. Each infusion lasted 6 h. Overall, 23 patients were treated.

The actual doses the patients received in each dose groups until the MTD was reached were as follows:

Table 13

Dose group	Loading dose	Consecutive doses			
	Day 0	**Day 3**	**Day 6**	**Day 9**	**Day 13**
I	5 µg	10 µg	10 µg	10 µg	
IIa	10 µg	50 µg	50 µg	50 µg	
IIb	10 µg	20 µg	50 µg	50 µg	
III	10 µg	20 µg	50 µg	100 µg	
IV	10 µg	20 µg	50 µg	200 µg	
V	10 µg	20 µg	50 µg	200 µg	200 µg

Maximum tolerated dose: Two dose limiting toxicities (DLTs) occurred in Dose Group V (1 Grade 3 large bowel obstruction after a dose of 200 µg and 1 Grade 4 increase in gamma-glutamyltransferase [GGT] after a dose of 50 µg). Therefore, the dose steering board decided that the MTD was reached in Dose Group V at 10-20-50- 200-200 µg of catumaxomab.

Study IP-REM-PK-01_EU

This Phase II, multi-center, open-label PK study in male and female patients with malignant ascites due to epithelial cancers requiring therapeutic ascites puncture was designed to determine the systemic exposure during and after 4 i.p. infusions with increasing doses and to characterize the PK of catumaxomab after i.p. administration (four 6-hour constant-rate i.p. infusions of catumaxomab at escalating doses of 10, 20, 50, and 150 µg) and to obtain further safety and efficacy data. A total of 13 patients received catumaxomab in this study.

Study AGO-OVAR-2.10

This Phase IIa, multi-center, randomized, open-label, 2-dose-level study was designed to select a better dose level of catumaxomab based on the overall response rate (complete response [CR] or partial response [PR]) according RECIST administered by i.p. infusion to ovarian cancer patients refractory to platinum-based chemotherapy. A total of 41 patients were treated with catumaxomab in this study.

Escalating doses of catumaxomab (10-20-50-100 µg) were associated with higher anti-tumour activity without compromising the safety profile when compared to the low-dose constant treatment group (10-10-10-10 µg). The overall response rate in the escalation treatment group was 4.6 % (one patient with a partial response) vs. 0.0% in the low-dose constant treatment group.

Based on the results of the dose response studies the Applicant chose the following dosing scheme: Day 0: 10 µg, Day 3: 20 µg, Day 7: 50 µg, Day 10: 150 µg. The intervals between doses (Day 0, 3, 7 and 10) were chosen to allow for sufficient recovery of the patients from symptoms and laboratory abnormalities following each infusion, as intraperitoneal administration of catumaxomab is associated with symptoms attributed to cytokine release.

- Main study

The main study (IP-REM-AC-01) conducted to support the claim was a randomized open-label phase II/III study. The treatment arms included catumaxomab as add-on to two peritoneal ascites paracenteses (drainage to dryness) performed before and after completion of dose escalation schedule over a period of 11 days (active arm) versus only one ascites paracentesis (drainage to dryness) in the control arm. The treatment period in the active arm could at the most be extended to 21 days, but not longer.

METHODS

Study Participants

Ovarian cancer patients were recruited at 53 centres (municipal and university hospitals specializing in gynaecology and/or oncology) in 11 countries in Eastern and Western Europe, as well as the Russian Federation and Ukraine.

Non-ovarian cancer patients were recruited at 70 centres (municipal and university hospitals, specializing in oncology) in 11 countries in Eastern and Western Europe, as well as the Russian Federation and Ukraine. The need for increased number of centres recruiting patients in the non-ovarian cohort is reflected in amendment 3-1, November 2005.

The main inclusion criteria were as follows:

1. Histologically confirmed diagnosis of cancer.

2. EpCAM+ tumour cells in the ascites fluid.

3. Symptomatic malignant ascites requiring therapeutic ascites puncture.

4. Refractory/resistant to chemotherapy or where the standard chemotherapy was no longer feasible. This was defined as resistance/recurrence while on first line treatment with platinum based regimens or recurrence within 3 months after such treatment for ovarian cancer. For colorectal cancer patients resistance to first line platinum or irinotecan-based chemotherapy and for pancreatic and gastric cancer resistance to first line chemotherapy treatment, were eligibilility criteria.

5. Karnofsky Index ≥60.

6. Life expectancy >8 weeks.

7. At least 1 therapeutic ascites puncture within 5 weeks before screening puncture.

Exclusion criteria were as follows:

1. Acute or chronic infections

2. Exposure to investigational product, cancer chemo- or radiotherapy within the last 28 days, (6 weeks for nitrosureas or mitomycin C) before first infusion

3. Previous treatment with mouse or rat monoclonal antibodies

4. Known or suspected hypersensitivity to catumaxomab or similar antibodies

5. Inadequate renal function (creatinine >1.5 x ULN

6. Inadequate hepatic function (AST, ALT, GGT >5 ULN, bilirubin > 1.5 ULN

7. Platelets <80000 cells/mm^3; absolute neutrophil count (ANC) < 1500 cells/mm^3

8. BMI <17

9. Patients with a reduced nutrional status requiring predominantly parenteral nutrition (>50% of energy intake)

10. Patients with gastric or small bowel feeding tube at study entry

11. Patients with ileus within the last 30 days

12. Patients with any other severe disease that would have rendered participation in the study an undue risk

13. Known brain metastases

14. Pregnant or nursing women, or women with childbearing potential and males who were not using an effective contraceptive method during the study and for at least 3 months after the last infusion

15. History of myocardial infarction

16. Signs or symptoms of relevant cardiovascular disease, congestive heart failure or cardiac arrythmias (NYHA class >II)

17. History of cerebrovascular accident

18. Patients with portal vein obstruction or portal vein thrombosis diagnosed by CT at screening

19. Patients with extensive liver metastases (> 70% of liver metastasised)

20. Inadequate respiratory function in the opinion of the investigator,

21. Any further condition, which according to the investigator resulted in an undue risk of the patient by participating in the present study**.**

Treatments

In the catumaxomab-group patients were premedicated with 1000 mg paracetamol 30 minutes before each infusion. After the ascites fluid was discharged before each infusion, the patients in the catumaxomab group received 4 infusions of catumaxomab via an indwelling i.p. catheter. as follows: 10 µg on Day 0, 20 µg on Day 3, 50 µg on Day 7, and 150 µg on Day 10, in a total volume of 750-800 ml. Before the first infusion (Day 0), and after the last infusion (Day 10) drainage to dryness was performed in the catumaxomab-group. Dose reductions were not permitted. The infusion time was 6 hours at constant rate. Patients in the catumaxomab group were hospitalized for 24 hours on the days of infusion. The treatment period was not to exceed 21 days.

The control group was treated by paracentesis only (drainage to dryness). However, an optional single-arm cross-over period was added to enable patients in the control group to be treated with catumaxomab after the end of their participation in the randomized part of the study. Before the patients were permitted to continue to the single-arm cross-over period, they were required to have had 1 (Amendment 1) or 2 (Amendment 2) protocol-conforming therapeutic ascites punctures after Day 0.

Premedication with antihistamines or corticosteroids was prohibited. All concomitant medications were continued throughout the study at a conventional dose and schedule. Maintenance anti-hormonal treatment was permitted before and during catumaxomab treatment, if it had been initiated for at least 3 months before first infusion. Local radiation of bone metastases was permitted throughout the study.

In case of adverse events suggested rescue medication was restricted to bronchodilators (inhaled β2 sympaticomimetics, theofyllamine IV), paracetamol or metamizol IV and antihistamines. Administration of other medications to treat AEs depending on symptoms, was left to the investigators discretion. Corticosteroids were not mentioned.

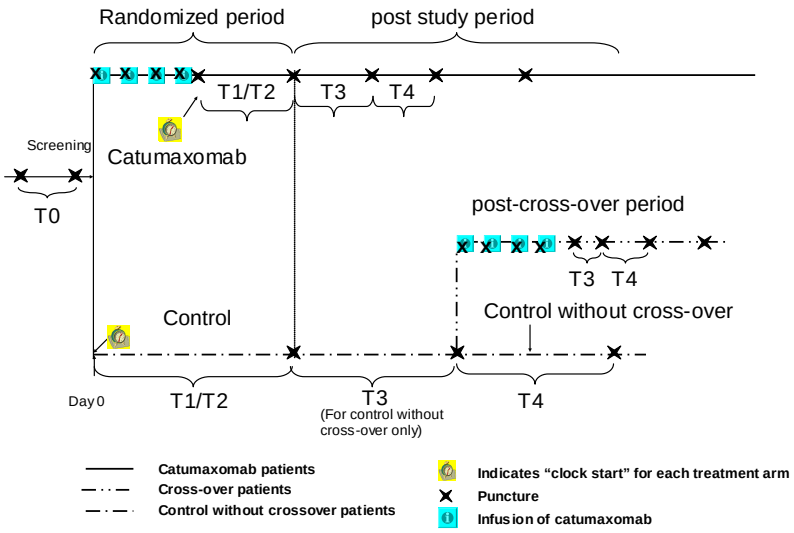
Objectives
The objective was to demonstrate the superiority of a treatment with paracentesis plus catumaxomab over a treatment with paracentesis alone.

Outcomes/endpoints

The primary efficacy endpoint was puncture-free survival. For its definition, an event was defined as (need for) therapeutic ascites puncture or death, whichever occurred first. The rationale for the use of the word ‘need for’ was that therapeutic puncture was performed only when it was deemed necessary as objectively as possible. For the purposes of the endpoint, time to the actual puncture was used.

For patients in the catumaxomab group, puncture-free survival was defined as the time after drainage to dryness following the last infusion (planned on Day 11, 1 day after the last infusion) until the first need for therapeutic puncture or death, whichever occurred first. For patients in the control group puncture-free survival was defined as the corresponding time after the therapeutic ascites puncture on Day 0.

Figure 3 Schematic illustration of the design of primary endpoint and clockstart



T0: Time from last puncture before screening until screening puncture.

T1: Time during randomized part from clock start to first therapeutic puncture for all patients who had a puncture.

T2: The same time as in T1 but only for patients who had at least 1 post-study puncture.

T3: { For catumaxomab and controls without cross-over: Time from first therapeutic puncture in the randomized part of the study to first puncture in the post-study.

For cross-over: Time after first therapeutic puncture in cross-over to first therapeutic puncture at post-cross-over.

T4: Time between first and second puncture at post-study.

Secondary endpoints measured included:

– Overall survival, defined as time from randomization until death.

– Progression-free survival, defined as time from randomisation to disease progression or death (whichever occurred first).

– Tumour response according to RECIST for patients with measurable disease

– Assessment of ascites signs and symptoms

Moreover, secondary/additional endpoints included the following (results are not shown in this report): time to first/next need of therapeutic ascites puncture, time to death without therapeutic ascites puncture, time to progression, body weight and abdominal girth, volume of collected/calculated ascites fluid, total protein concentration in ascites collected during therapeutic ascites punctures, tumour cell load in ascites fluid, tumour markers, quality of life, number of ascites punctures, anti cancer medications.

Overall survival (and time to progression) was analyzed using 2 approaches. These approaches differed in the handling of the corresponding events either as events or censored observations at the time of cross-over.

Progression-free Survival was only analysed in the randomised part of the study.

Pooled analyses for the ovarian and non-ovarian cancer strata were performed for selected efficacy parameters (puncture-free survival, time to first need for therapeutic ascites puncture, time to death without therapeutic ascites puncture, overall survival, and time to progression).

Sample size
Based on the original assumptions, a total of 108 patients (catumaxomab: 72, control: 36) had to be randomized in each of the ovarian and non-ovarian cancer subgroups to achieve a power of 90% in

detecting at least a doubling of puncture free survival between catumaxomab and control, after rounding up to allow an appropriate block size.

According to the procedures in the protocol, when a total of 148 patients (ovarian and non-ovarian) were randomized, the proportion of patients censored for the primary variable prior to Month 7 was determined among all patients who at this time had undergone a therapeutic ascites puncture, had died, had terminated the study prematurely or had completed the study after 7 months without therapeutic ascites puncture. This was done separately within the 2 cancer groups

Randomisation

Patients were allocated by central randomization, 2:1 ratio (catumaxomab: control) stratified by cancer entity (ovarian versus non-ovarian) and country.

Blinding (masking)

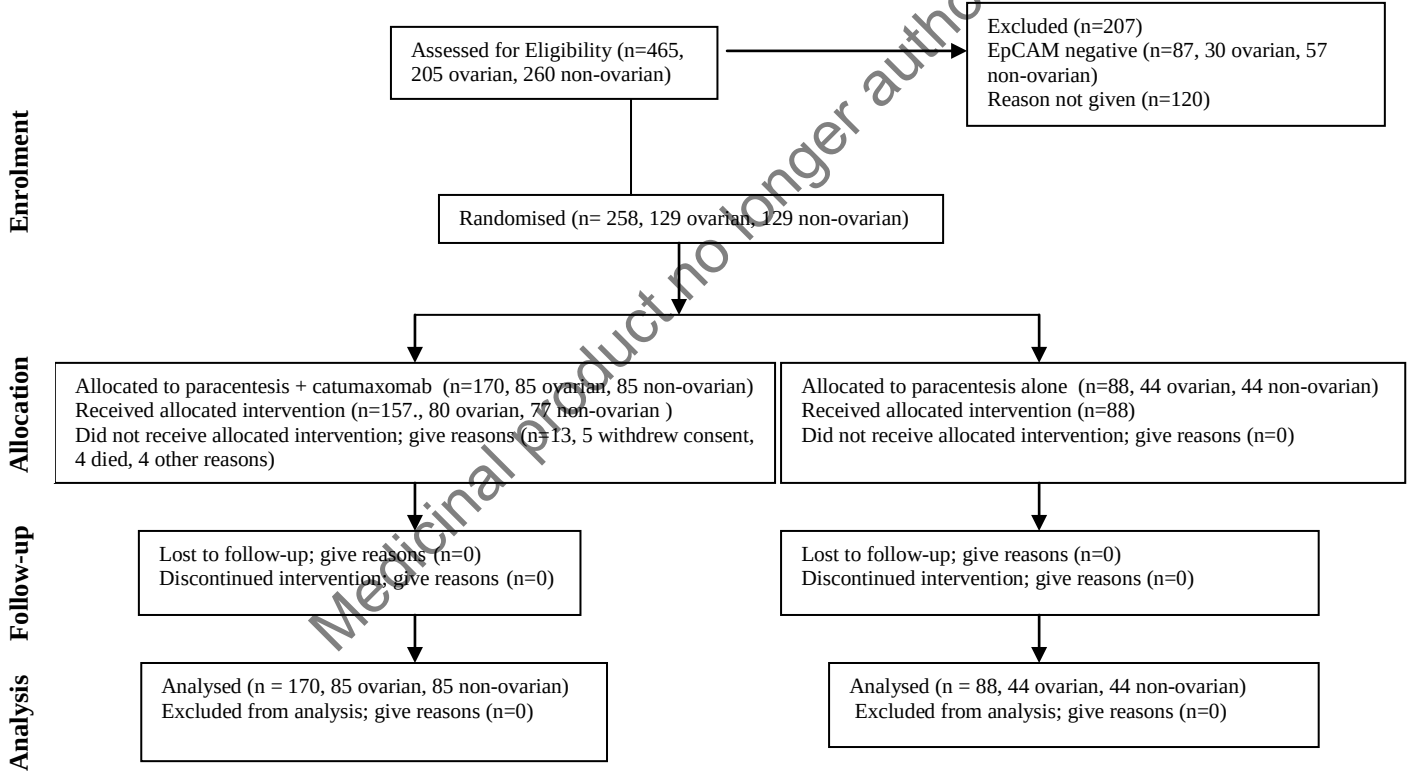
This was an open-label trial.

Statistical methods

Standard statistical tests were employed.

RESULTS

Participant flow



In the ovarian cancer group, five (5.9%) of the patients assigned to catumaxomab did not receive treatment (4 patients withdrawal of consent, 1 patient not able to perform paracentesis). In the non-ovarian group, eight (9.4%) of the patients assigned to catumaxomab did not receive treatment (4 patients died, 3 patients because of SAE and 1 patient not eligible).
The sample size readjustment (see sample size) resulted in a sample size adjustment of total of 126 ovarian cancer patients (catumaxomab: 84, control: 42) and 120 non-ovarian cancer patients (catumaxomab: 80, control: 40) to be randomized.

Recruitment

The pivotal study included the first patients in both ovarian and non-ovarian cohorts on September 6, 2004. The accrual of non-ovarian cancer patients was slower and therefore the number of centres

recruiting those patients was increased. Also, because of different completion dates two separate reports were to be prepared for the two cancer categories and the sponsor instigated recruitment of gastric cancer patients only to the non-ovarian cancer group (In amendment 4-1, May 2006.) The ovarian cancer study was completed on September 29, 2006 and the non-ovarian study on November 3, 2006.

Conduct of the study

During the study five amendments with 90 changes of study conduct, statistics and accrual were implemented.

Most major protocol violations concerned administration of fewer than 3 catumaxomab infusions (13 patients in the ovarian cancer stratum and 17 patients in the non-ovarian cancer stratum). These were dealt with in the sensitivity analyses.

Baseline data
Statistical tests of key baseline characteristics indicated that randomization resulted in balanced treatment groups as all p-values were >0.05.

Most patients were enrolled after Amendment 2. For the ovarian cancer group, 27 patients were included before the implementation of Amendment 2 (20 catumaxomab, 7 control) and 107 thereafter (65 catumaxomab, 37 control). For the non-ovarian cancer group, 28 patients were enrolled before Amendment 2 (18 catumaxomab, 10 control) and 101 thereafter (67 catumaxomab, 34 control).

A total of 465 patients were screened for EpCAM-positivity. The threshold for positivity was set at 400 EpCAM-positive cells/10^6 cells.

Table 14 EpCAM positivity results

	Pooled analysis	**Ovarian cancer**	**Non-ovarian cancer**
Total number screened patients	465	205	260
Number of EpCAM negative patients	87 / 71*	30 / 20*	57 / 51*
% of EpCAM negative patients	19 / 15*	15 / 10*	22 / 20*
* excluding patients <400 cells			

Concerning baseline disease characteristics, in the ovarian cancer stratum > 80% of the patient population had FIGO-stageing IIIc or IV. Over half of the patients had experienced one previous paracentesis (56.6%) and one fifth (20.2%) had experienced two previous paracenteses at screening.

Table 15 Baseline disease characteristics ovarian cancer group

Ovarian cancer	**Catumaxomab group (n=85)**	**Control group (n=44)**
Age years mean (STD)	58.6 (10.2)	58.2 (11.7)
Median time since first cancer diagnosis (months)	19 (0-188)	23.5 (0-102)
Median number of previous antineoplastic treatments (range)	3 (0-8)	3 (1-10)
Time since diagnosis, months (range)	7 (0-62)	6.5 (0-82)
Time since last therapeutic puncture, days (range)	17 (1-46)	19.5 (3-36)
Ascites volume at last puncture before inclusion, mL (mean ± SD)	3523.3 ±2269.69	3436.9 ±2033.9

In the non-ovarian cancer stratum over half of the patients had experienced one previous paracentesis (62.8%) and one fifth (20.9%) two previous paracenteses at screening.

Table 16 Baseline disease characteristics non-ovarian cancer group (I)

	Non-ovarian cancer (overall population)
Gastric carcinoma	51%
Breast cancer	< 10%
Other tumour	< 10%
TNM staging	69% T3, T4 60,9% N1, N2, N3 61% Distant metastasis
1 surgical procedure	34.9%
2 surgical procedures	48.8%
Number of previous therapeutic ascites punctures	1 (62.8%) 2 (20.9%)

In general the gastric cancer subpopulation had a worse TNM classification than the other non-ovarian subpopulations. For gastric cancer patients 60.9% in the catumaxomab group and 78.9% in the control group had distant metastases. For the non-gastric non-ovarian cancer patients 64.5% in the catumaxomab group and 40.9% of the patients in the control group had distant metastases.

Concerning differences between treatment groups in terms of baseline disease characteristics, see table below.

Table 17 Baseline disease characteristics non-ovarian cancer group (II)

Non-ovarian cancer	**Catumaxomab group (n=85)**	**Control group (n=44)**
Time since last therapeutic puncture (days)	14 (2-63)	17.5 (2-35)
Median time since first cancer diagnosis (months)	11 (0-229)	11 (0-343)
Ascites volume at last puncture before inclusion mL (mean ± SD)	4368.9 ±2871.7	4812.8. ±3077.9

Finally, both ovarian and non-ovarian cancer patients had symptomatic ascites at screening and most had a Karnofsky Index between 70 and 90, similar in both treatment groups.

Numbers analysed

For the efficacy analyses all randomized patients were analyzed.

Outcomes and estimation

Primary efficacy endpoint: puncture-free survival

In all analysis groups, puncture-free survival was significantly longer ($p<0.0001$) in the catumaxomab group compared to the control group (Figure 9, Table 9). In the pooled analysis, the median difference between the groups was 35 days (95% CI: 25; 45). For ovarian cancer patients, the median difference between the groups was 41 days (95% CI: 32; 50) and for all non-ovarian cancer patients 23 days (95% CI: 8; 38) (Figure 4).

Figure 4 Kaplan-Meier estimates of puncture-free survival in the pooled population (full analysis set)

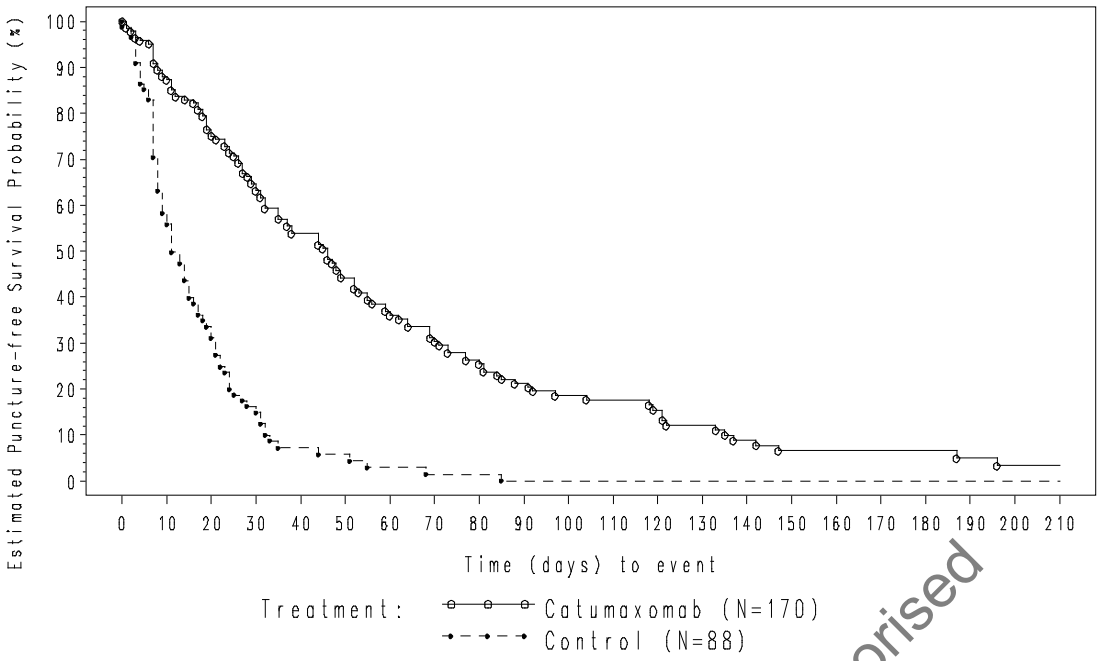


Table 18 Puncture-free survival in Study IP-REM-AC-01 (full analysis set)

	Pooled analysis		**Ovarian cancer patients**		**Non-ovarian cancer patients**	
	Catumaxomab (N=170)	**Control (N=88)**	**Catumaxomab (N=85)**	**Control (N=44)**	**Catumaxomab (N=85)**	**Control (N=44)**
% of patients with event [a]	70%	93%	66%	95%	74%	91%
Median puncture-free survival [days]	46	11	52	11	37	14
95% CI	[35; 53]	[9; 16]	[38; 62]	[9; 20]	[27; 49]	[8; 17]
p-value (log-rank test)	<0.0001		<0.0001		<0.0001	

[a] Designates therapeutic puncture or death, whichever occurred first.
N: Total number of patients; CI: confidence interval.

Secondary endpoints

Overall survival

The results for Overall Survival are presented below:

Figure 5 Post-study: Kaplan-Meier estimates of overall survival: pooled analysis, full analysis set

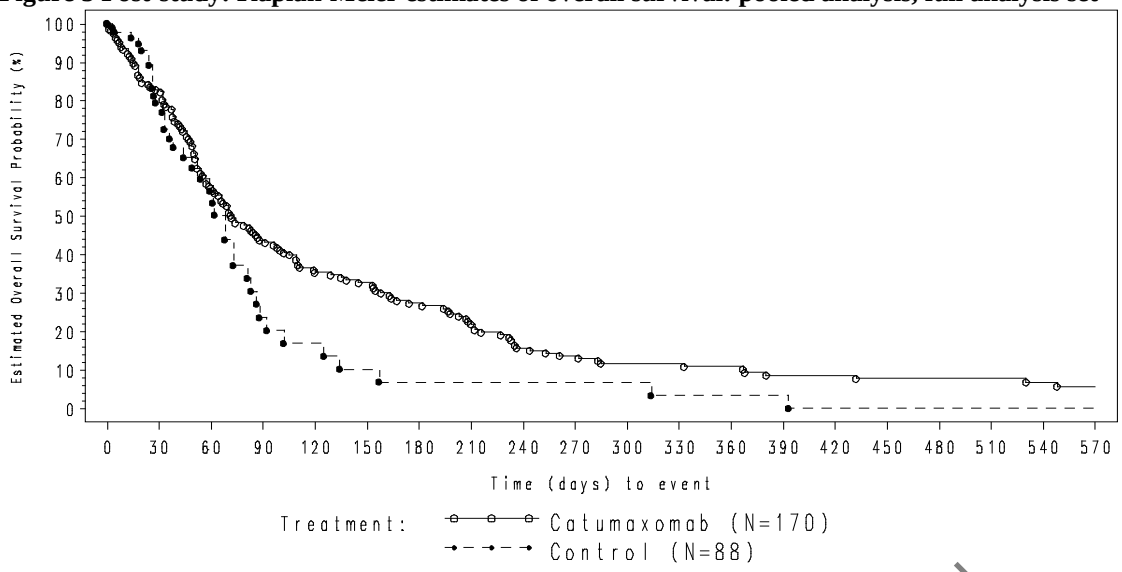


Table 19 Post-study: overall survival in the 2-group analysis (full analysis set)

	Pooled analysis		Ovarian cancer patients		Non-ovarian cancer patients	
	Catumaxomab (N=170)	**Controls without cross-over (N=88)**	**Catumaxomab(N=85)**	**Controls without cross-over (N=44)**	**Catumaxomab (N=85)**	**Controls without cross-over (N=44)**
2-group analysis						
Median overall survival (days)	72	68	110	81	52	49
95% CI	[61; 98]	[49; 81]	[70; 164]	[68; 134]	[44; 74]	[33; 68]
p-value, log-rank test	0.0846		0.1543		0.4226	
CI: confidence interval						

Table 20 Post-study: overall survival in the 3-group analysis (full analysis set)

	Pooled analysis			Ovarian cancer patients			Non-ovarian cancer patients		
	Catuma-xomab (N=170)	**Controls without cross-over (N=43)**	**Controls switched to catuma-xomab (N=45)**	**Catuma-xomab (N=85)**	**Controls without cross-over (N=16)**	**Controls switched to catuma xomab (N=28)**	**Catuma xomab (N=85)**	**Controls without cross-over (N=27)**	**Controls switched to catuma-xomab (N=17)**
3-group analysis									
Median overall survival (days)	72	54	95	110	71	134	52	44	70

Progression-free survival

No pooled analysis was carried out for this efficacy parameter.

For ovarian cancer patients, the median progression-free survival was significantly longer in the catumaxomab group than in the control group (p<0.0001). For all non-ovarian cancer patients, no statistically significant difference was observed.

Table 21 Median progression-free survival (full analysis set)

	Ovarian cancer patients		**Non-ovarian cancer patients**	
	Catumaxomab (N=85)	**Control (N=44)**	**Catumaxomab (N=85)**	**Control (N=44)**
Median progression-free survival (days)	64	35	53	33
p-value, log-rank test	<0.0001		0.1530	

Tumour response rate

No pooled analysis was carried out for this efficacy parameter.

For ovarian cancer patients and non-ovarian cancer patients, results on tumour response rates according to RECIST were inconclusive due to low number of patients with measurable disease and the short time of follow up in the control group

Ascites signs and symptoms

Table 22 Number of patients without clinical signs or symptoms of ascites at Visit 6 (full analysis set)

	Number (%) of patients					
	Ovarian cancer patients			**Non-ovarian cancer patients**		
	Catumaxomab (N=85)	**Control (N=44)**	**p-value[a]**	**Catumaxomab (N=85)**	**Control (N=44)**	**p-value[a]**
Number of patients at Visit 6, n (%)	67 (100.0)	24 (100.0)		54 (100.0)	26 (100.0)	
Symptoms assessed by interview as "none"						
Abdominal pain	41 (61.2)	7 (29.2)	0.0021	34 (63.0)	10 (38.5)	0.0033
Nausea	43 (64.2)	10 (41.7)	0.0202	36 (66.7)	12 (46.2)	0.0311
Early satiety	37 (55.2)	6 (25.0)	0.0294	32 (59.3)	13 (50.0)	0.2298
Abdominal swelling	39 (58.2)	9 (37.5)	0.0319	30 (55.6)	11 (42.3)	0.0649
Anorexia	40 (59.7)	9 (37.5)	0.0364	31 (57.4)	11 (42.3)	0.1381
Vomiting	46 (68.7)	14 (58.3)	0.1800	38 (70.4)	18 (69.2)	0.5086

Heartburn	43 (64.2)	13 (54.2)	0.2304	39 (72.2)	19 (73.1)	0.9199
Fatigue	42 (62.7)	17 (70.8)	0.3211	33 (61.1)	15 (57.7)	0.4745
Swelling ankles	31 (46.3)	8 (33.3)	0.5050	23 (42.6)	7 (26.9)	0.1032
Dyspnoea	39 (58.2)	13 (54.2)	0.7073	33 (61.1)	8 (30.8)	0.0027
Signs assessed by abdominal examination as "none"						
Shifting dullness	39 (58.2)	5 (20.8)	0.0004	33 (61.1)	8 (30.8)	0.0005
Fluid thrill	42 (62.7)	7 (29.2)	0.0008	34 (63.0)	12 (46.2)	0.0051
Abdominal distension dull to percussion	33 (49.3)	4 (16.7)	0.0013	30 (55.6)	8 (30.8)	0.0091
Bulging flanks	39 (58.2)	9 (37.5)	0.0556	33 (61.1)	12 (46.2)	0.0537

n (%): number and percentage of patients with a given assessment of none, N: number of patients per treatment group.

Note: Data are sorted by p-values for ovarian cancer patients.

[a] p-value refers to overall categorization of signs/symptoms by severity ("missing", "none", "mild", "moderate" and "severe") by Cochran-Mantel-Haenszel row mean scores test.

Ancillary analyses

Due to concerns with the censoring of events (deaths and progressions) in the planned 2-group survival analysis, a number of sensitivity analyses were performed upon request by the CHMP (data not shown).

Additional variables to objectify the need for therapeutic ascites puncture

As the need to perform a therapeutic ascites puncture (based on ascites signs and symptoms assessment and ascites volume estimated via CT) might be subjective due to the open-label design, ascites volume was estimated by local radiologists from CT scans and by central blinded CT scan readers and collected ascites volumes were measured.

Based on these data the following analyses were performed: correlation analysis of ascites volume collected at puncture and time to puncture, comparison between ascites volume estimated by the local radiologist and the volume calculated by the blinded reader, comparison of adherence to schedule for assessment of burden of ascites in the pooled population based on the presence of collected clinical and radiological data and, finally, comparison of number of punctures within and outside the visit schedule (data not shown).

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

No pooled analyses or meta-analyses were performed.

- Clinical studies in special populations

No clinical studies in special populations were performed.

- Supportive study(ies)

Study STP-REM-01

This Phase I/II, multi-center, dose-escalation study with up to 5 i.p. infusions of catumaxomab established the maximum tolerated dose (MTD) in patients with malignant ascites due to ovarian carcinoma and investigated the safety, tolerability and preliminary efficacy of catumaxomab. Each infusion lasted 6 h. Overall, 23 patients were treated.

Ascites flow rate: The ascites flow rate showed a decrease by 52 mL/h from a median of 105 mL/h at baseline to a median of 23 mL/h on Day 1 after the fourth infusion. Necessity of peritoneal puncture: From the last infusion until the last individual visit (28 ±4 days after start of last infusion), only 1 of 23 patients needed a peritoneal puncture. Tumour cell load: Tumour cell elimination in the ascites occurred rapidly (Figure 7). The mean value of epithelial tumour cells was reduced from 539 per 10^6 screened cells before treatment to 39 per 10^6 at the last individual measurement, resulting in a mean reduction of 99.9%. In 6 out of 23 patients, tumour cell elimination to levels below the detection limit was observed. Tumour markers: The tumour marker CA 72-4 decreased in 3 patients (by 18%, 19%, and 49%) and increased in 10 patients (by a range of 20% to 158%) between pre-treatment and EoS. The tumour marker CA 125 decreased in 3 patients (by 22%, 32%, and 43%), remained stable in 1 patient, and increased in 9 patients (by a range of 21% to 852%) between pre-treatment and EoS. For 10 patients values were missing at EoS.

Maximum tolerated dose: Two dose limiting toxicities (DLTs) occurred in Dose Group V (1 Grade 3 large bowel obstruction after a dose of 200 µg and 1 Grade 4 increase in gamma-glutamyltransferase [GGT] after a dose of 50 µg). Therefore, the dose steering board decided that the MTD was reached in Dose Group V at 10-20-50- 200-200 µg of catumaxomab.

Study IP-REM-PK-01_EU

This Phase II, multi-centre, open-label PK study in male and female patients with malignant ascites due to epithelial cancers requiring therapeutic ascites puncture was designed to determine the systemic exposure during and after 4 i.p. infusions with increasing doses and to characterize the PK of catumaxomab after i.p. administration (four 6-hour constant-rate i.p. infusions of catumaxomab at escalating doses of 10, 20, 50, and 150 µg) and to obtain further safety and efficacy data. A total of 13 patients received catumaxomab in this study.

Need for peritoneal puncture: After the treatment phase, a therapeutic puncture was performed in 5 patients up to EoS (1 month after the last infusion) with volumes of 200 mL, 500 mL, 1700 mL and 2000 mL (the volume of 1 patient is unknown); no therapeutic puncture was performed in 7 patients and 1 patient died without the necessity of therapeutic puncture. Abdominal ultrasound was performed at EoS in 9 (69%) patients and revealed ascites in 7 patients. In 3 of these patients, a therapeutic puncture was performed. Ascites volume: The mean drained ascites volume decreased considerably from screening (mean of 2546 mL) to Day 3 (before 1st infusion) (mean of 900 mL) and remained stable thereafter. Tumour cell load: The tumour cell load (EpCAM+ cells) in the ascites fluid decreased already after the first infusion. Whereas a median of 9362 EpCAM+ cells/106 ascites cells was determined at screening, the median number was 49 before the second infusion and decreased further to 0 before the fourth infusion (no tumour cells were detectable in 5 [56%] patients).

Additional efficacy results: There was no consistent change in the Karnofsky index between screening and EoS. Body weight decreased during the treatment period, but increased again thereafter, reaching the screening values at EoS.

Study AGO-OVAR-2.10

This Phase IIa, multi-centre, randomized, open-label, 2-dose-level study was designed to select a better dose level of catumaxomab based on the overall response rate (complete response [CR] or partial response [PR]) according RECIST administered by i.p. infusion to ovarian cancer patients refractory to platinum-based chemotherapy. A total of 41 patients were treated with catumaxomab in this study.

Escalating doses of catumaxomab (10-20-50-100 µg) were associated with higher anti-tumour activity without compromising the safety profile when compared to the low-dose constant treatment group (10-10-10-10 µg). The overall response rate in the escalation treatment group was 4.6 % (one patient with a partial response) vs. 0.0% in the low-dose constant treatment group.

- Discussion on clinical efficacy

Scientific advice was sought by the applicant from the CHMP. The CHMP agreed upon the open label design, paracentesis as standard of care for the control arm and the primary endpoint “puncture-free survival”. Means to objectify the need for therapeutic puncture was requested by the CHMP. The cross-over design was discussed as a potential problem which could introduce bias. Therefore, the

CHMP recommended that patients continue to cross-over period only after the second therapeutic puncture. The applicant was also requested to support the claim for the indication “malignant epithelial ascites” by providing separate analyses of ovarian and non-ovarian cancer patients. Group wise analysis (ovarian and non-ovarian cancer) was also encouraged by the CHMP for the evaluation of a potential bias affects the reliability of the primary endpoint.

During the evaluation of catumaxomab, the CHMP raised a major objection with regards to the benefit – risk relationship of the medicinal product given that a precise estimate of PFS was hard to obtain due to frequent premature study termination, and the increase in puncture-free survival (PFS) needed to be balanced against frequent, commonly severe, adverse reactions. The CHMP Scientific Advisory Group for Oncology was also consulted to identify if efficacy could be considered established taking into consideration the data submitted, and to determine a minimum clinically relevant level of efficacy in this indication.

Due to the design of the study, the SAG agreed that significant biases might affect the estimated efficacy endpoints, including the primary endpoint, favouring catumaxomab. For instance, patients in the control arm received just one puncture and this may well have resulted in suboptimal drainage of ascites and a higher residual volume leading to a relatively shorter time to puncture. In contrast, patients randomised to catumaxomab received 4 times a drainage at baseline and this may have resulted in a lower residual volume, prolonging the time to puncture. Due to the open design of the study, important ascertainment bias could be expected. Furthermore, a number of important points still remained outstanding with the available data, such as the impact on the life-time number of punctures, the long-time efficacy, or the impact on the quality of life of the patients and of the effect on symptoms such as ascites ileus.

The SAG disagreed on whether efficacy can be considered established. For some, the impact of potential biases hindered any conclusion on the efficacy in the claimed indication or any subpopulation, and that the benefits do not outweigh the risk. Some argued that despite the biases, the observed effect was such that a benefit in a subpopulation was considered established (although such population is still undefined). Others argued that the efficacy had been established in the claimed indication, and that the benefits outweigh the risks.

Finally, the SAG agreed that further studies should be encouraged in order to compare catumaxomab against best available treatment These recommendations were put forward to the CHMP. The CHMP considered this proposal as being of scientific interest but did not deem it a requirement for the granting of the marketing authorisation.

To further clarify the benefit/risk relationship of catumaxomab, the CHMP identified the following salient points that needed further discussion.

The applicant was asked to present median duration of hospital stay in relation to reason for hospitalization, discussing possible impact on the "hospitalization" analysis of imbalanced withdrawal. From the data submitted, in the experimental group, hospitalization was to an important part due to catumaxomab administration. The increased withdrawal rate in the experimental arm was largely explained by longer period of observation. In patients withdrawn from therapy more grade 3/4 events were reported and they stayed for longer time in hospital. However, the CHMP considered that the apparent increase in withdrawn patients in the experimental arm did not bias the assessment of hospitalization to an important degree. At the request of the CHMP, section 5.1 of the SPC was updated to include the median days of hospitalisation for patients in the main study: In the pivotal study IP-REM-AC-01 98.1% of patients were hospitalised for a median of 11 days.

The applicant was asked to present time to puncture, counting withdrawal as event. From the data submitted, counting withdrawal as events in the time-to-puncture analysis shortened the apparent benefit from 64 to 41 days. The CHMP considered this a conservative estimate of patient benefit, which would correspond to about 4 punctures less.

The applicant was asked to address the possible bias related to four draining procedures to dryness in the experimental arm versus one in the control arm. The data presented, collectively indicate that the

asymmetric design with respect to drainage until dryness did not introduce a bias of importance put in relation to the estimated activity of catumaxomab. This conclusion was based on the pattern over time of drained volumes compared with infused volumes, the total net increase in drained volume comparing experimental and control arms put in relation to accumulation over time in control and experimental arms, the similarity between infused and drained volume at last drain, and weight changes.

Fully acknowledging that some subgroups are small or very small, available data do not indicate that "histology" is an important determinant of catumaxomab activity in terms of hazard ratios for PFS should be reported per diagnosis (gastric cancer, breast cancer, etc.).

The applicant was asked to report patient outcome for the subgroup of patients with a history of at least one therapeutic puncture per week prior to enrolment. Based on the evidence submitted, the number of patients with frequent punctures prior to inclusion was small and the prognostic and predictive value with respect to time to puncture was not considered overwhelming. The CHMP noted that the absolute benefit of catumaxomab therapy appears similar in both groups of patients.

The applicant was asked to report the time to next puncture after first therapeutic puncture (control not crossing-over, experimental arm). However, due to cross-over, early deaths and patients lost to follow-up, the CHMP could not draw any meaningful conclusions with respect to time to puncture and puncture-free survival comparing experimental and control arms.

The CHMP requested that the safety of repeated courses of treatment with Removab (i.e. off-label use) be reviewed within PSURs, and the RMP be update accordingly.

- Patient exposure

The ISA (Integrated Safety Analysis) for catumaxomab contains pooled patient safety data from five completed studies investigating the i.p. administration (Overall Population), all of whom received at least 1 dose of catumaxomab (N=258). The pivotal phase II/III study IP-REM-AC-01 accounts for almost 2/3 of the overall population.

Table 23

Trial	Design	Study population
IP-REM AC-01	Phase II/III, randomized, controlled open-label Intraperitoneal administration, 10, 20, 50, 150 µg, 6 hrs constant rate	N= 157 (ovarian cancer N=80, non-ovarian cancer N=77)
STP-REM-01	Phase I/II uncontrolled sequential dose escalation to MTD Intraperitoneal administration, 6 hrs constant rate	N=23 malignant ascites due to ovarian cancer
IP-REM-PK-01-EU	Phase II open label PK (dosing as in pivotal study) Intraperitoneal administration, 6 hrs constant rate	N=13 malignant ascites
AGO-OVAR-2.10	Phase II a, randomised open label Two-dose level 10 µg constant or dosing at 10, 20, 50 and 100µg Intraperitoneal administration, 6 hrs constant rate	N=41 platinum refractory ovarian cancer
IP-REM-PC-01-DE	Phase I, uncontrolled, sequential dose escalation to MTD, Intraperitoneal administration, 6 hrs constant rate.	N=14 (Main study) Peritoneal carcinomatosis GI-cancer
IP-REM-PC-01-DE Addendum 1	Phase I, uncontrolled, sequential dose escalation to MTD, intraperitoneal administration,	N=7 Peritoneal carcinomatosis GI-cancer

	3 hrs constant rate at dose 10, 20, 50, 200 µg (MTD)	
IP-REM-PC-01-DE Addendum 2	Phase I, uncontrolled, intraperitoneal administration, doses at above MTD (20, 50, 100, 400 µg), 3 hrs constant rate with 10 mg IV dexamethasone as premedication (3 patients).	N=3 Peritoneal carcinomatosis GI-cancer

A total of 258 patients were treated in the Overall Population and 207 (80.2%) patients completed the treatment. Most patients (79.5%) received all 4 infusions of catumaxomab as specified in the study protocol, although 4 patients in Study STP-REM-01 received a fifth infusion of catumaxomab.

In all the studies included in the ISA, patients were premedicated with 1000 mg paracetamol 30 minutes before infusions.

The extent of exposure in the overall population is shown in the table below:

Table 24 Synopsis of exposure in the Overall Population and in Pivotal Study IP-REM_AC-01

Parameter	**Overall Population**	**Study IP-REM-AC-01**
Number of patients who received at least 1 dose of catumaxomab, N (%)	**258 (93.8[a])**	**157 (92.4)**
Actual number of infusion, N (%)		
1	13 (5.0)	7 (4.5)
2	18 (7.0)	10 (6.4)
3	18 (7.0)	9 (5.7)
4	205 (79.5)	131 (83.4)
5	4 (1.6)	NA
Mean percentage of planned dose (%)	85.2	86.3
Mean total dose, µg (SD)	186.1 (98.2)	198.5 (71.1)
Median total dose, µg (range)	230 (10 – 570)	230 (10 – 230)
Median dose at each infusion, µg		
1	10.0	10.0
2	20.0	20.0
3	50.0	50.0
4	150.0	150.0
5	200.0	NA

[a] This percentage reflects the percentage of enrolled patients (i.e., 258/275).

[b] Patients not receiving all planned infusions were counted as having no treatment completion.

NA=not applicable; SD = standard deviation

Infusion rate

The claim for MAA is catumaxomab administration as a single treatment cycle with 4 infusions infused at 3 hours. However, in the single pivotal study (IP-REM-AC-01) catumaxomab doses were infused over 6 hours. Studies IP-REM-PC-01 and Study IP-REM-GC-01 are included in the dossier to support the 3 hours infusion rate.

At submission a total of 12 patients had been exposed to catumaxomab at the intended dose escalation levels at a 3 hours infusion rate (IP-REM-GC-01). These patients were first treated intra-abdominally in ascending doses, and later by intraperitoneal infusions at doses as in the pivotal trial.

An additional 10 patients were treated at higher doses with a 3 hours infusion rate i.p: 7 patients at MTD: 10-20-50-200 µg and 3 patients above MTD: 20-50-100-400 µg (IP-REM-PC-01-DE Addendum 2).

- Adverse events

In the control arm (paracentesis only), 58% of patients had adverse events (AEs) and 29.3% had TEAEs of grade 3 or higher. Dominating TEAEs were abdominal pain (11.4%), nausea (10.2%), vomiting (9.1%) and malignant neoplasm progression (15.9%), symptoms all related to the underlying disease.

Adverse events in the catumaxomab treated patients are summarised in the tables below:

Table 25 Overview of TEAEs by group (ISA)

Category	**Number of patients (%)**			
	Overall TEAEs		**TEAEs related to treatment**	
	Overall Population (N=258)	**Study IP-REM-AC-01 (N=157)**	**Overall Population (N=258)**	**Study IP-REM-AC-01 (N=157)**
TEAE	255 (98.8)	154 (98.1)	233 (90.3)	133 (84.7)
TEAE of CTCAE Grade ≥3	200 (77.5)	125 (79.6)	127 (49.2)	74 (47.1)
Serious TEAE	132 (51.2)	91 (58.0)	39 (15.1)	23 (14.6)
Serious TEAE of CTCAE Grade ≥3	119 (46.1)	87 (55.4)	31 (12.0)	19 (12.1)
TEAE leading to discontinuation of treatment	28 (10.9)	11 (7.0)	18 (7.0)	6 (3.8)
TEAE leading to study discontinuation	14 (5.4)	1 (0.6)	14 (5.4)	1 (0.6)
Deaths	84 (32.6)	71 (45.2)	1 (0.4)	0

Table 26 TEAEs considered related to study treatment occurring in ≥5% of patients in either group by preferred term (ISA)

Preferred Term	Number of patients (%)	
	Overall Population (N=258)	Study IP-REM-AC-01 (N=157)
Patients with at least 1 TEAE considered related to study treatment	**233 (90.3)**	**133 (84.7)**
Pyrexia	166 (64.3)	95 (60.5)
Abdominal pain	124 (48.1)	67 (42.7)
Nausea	106 (41.1)	52 (33.1)
Vomiting	101 (39.1)	43 (27.4)
Fatigue	35 (13.6)	17 (10.8)
Chills	33 (12.8)	21 (13.4)
CRP increased	31 (12.0)	23 (14.6)
GGT increased	31 (12.0)	18 (11.5)
Lymphopenia	30 (11.6)	22 (14.0)
Pain	28 (10.9)	8 (5.1)
Diarrhoea	27 (10.5)	16 (10.2)
Constipation	24 (9.3)	4 (2.5)
Blood AP increased	23 (8.9)	14 (8.9)
Leukocytosis	21 (8.1)	16 (10.2)
Anaemia	20 (7.8)	14 (8.9)
Anorexia	20 (7.8)	14 (8.9)
AST increased	18 (7.0)	12 (7.6)
ALT increased	16 (6.2)	10 (6.4)
Tachycardia	16 (6.2)	15 (9.6)
Hypotension	15 (5.8)	13 (8.3)
Dyspnoea	15 (5.8)	5 (3.2)
Dyspepsia	13 (5.0)	7 (4.5)
Ileus	11 (4.3)	10 (6.4)

Note: Columns are not additive, as patients may have had more than 1 event. Data are sorted by the Overall Population.

Source: Module 5, Section 5.3.5.3, Report Cat-ISA-01, Table 5.4.2

Immunological events

The majority of the most common AEs were related to cytokine release in response to the antibody infusion. Such symptoms are presented in the following table:

Table 27 Cytokine release-related symptoms in ≥1% of patients in either group by preferred term (ISA)

Preferred Term	Number of patients (%)			
	All TEAEs		TEAEs of CTCAE Grade ≥3	
	Overall Population (N=258)	Study IP-REM-AC-01 (N=157)	Overall Population (N=258)	Study IP-REM-AC-01 (N=157)
Pyrexia	168 (65.1)	97 (61.8)	13 (5.0)	9 (5.7)
Nausea	133 (51.6)	71 (45.2)	10 (3.9)	8 (5.1)
Vomiting	124 (48.1)	59 (37.6)	16 (6.2)	8 (5.1)
Dyspnoea	45 (17.4)	28 (17.8)	6 (2.3)	3 (1.9)
Chills	35 (13.6)	22 (14.0)	2 (0.8)	2 (1.3)
Hypotension	26 (10.1)	21 (13.4)	6 (2.3)	5 (3.2)
Tachycardia	25 (9.7)	24 (15.3)	2 (0.8)	1 (0.6)
Hypertension	10 (3.9)	3 (1.9)	4 (1.6)	-
Hyperthermia	3 (1.2)	3 (1.9)	-	-
Influenza-like illness	4 (1.6)	4 (2.5)	-	-
Note: Columns are not additive, as patients may have had more than 1 event. Data are sorted by the Overall Population.				

- Serious adverse event/deaths/other significant events

Overall, 76.7% of patients in the Overall Population had at least 1 TEAE of CTCAE Grade ≥3. Malignant neoplasm progression (24.8%), abdominal pain, (12.4%) and lymphopenia (9.3%) were the most frequently reported TEAEs of CTCAE Grade ≥3 in the Overall Population.

Serious adverse events are summarised in the following tables:

Table 28 Overview of patients with serious TEAEs (ISA)

Category	Number of patients (%)			
	Overall TEAEs		TEAEs related to study treatment	
	Overall Population (N=258)	Study IP-REM-AC-01 (N=157)	Overall Population (N=258)	Study IP-REM-AC-01 (N=157)
Serious TEAE	132 (51.2)	91 (58.0)	39 (15.1)	23 (14.6)
Serious TEAE of CTCAE Grade ≥3	119 (46.1)	87 (55.4)	31 (12.0)	19 (12.1)

Table 29 TEAEs of CTCAE Grade ≥3 considered related to study treatment in >3% of patients in either group by preferred term (ISA)

Preferred Term	Number of patients (%)	
	Overall Population (N=258)	Study IP-REM-AC-01 (N=157)
Patients with at least 1 TEAE of CTCAE Grade ≥3 considered related to study treatment	**127 (49.2)**	**74 (47.1)**
Abdominal pain	25 (9.7)	15 (9.6)
Lymphopenia	18 (7.0)	11 (7.0)
GGT increased	17 (6.6)	9 (5.7)
Pyrexia	13 (5.0)	9 (5.7)
Vomiting	10 (3.9)	4 (2.5)
Blood AP increased	9 (3.5)	4 (2.5)

Preferred Term	Number of patients (%)	
	Overall Population (N=258)	Study IP-REM-AC-01 (N=157)
CRP increased	9 (3.5)	7 (4.5)
Ileus	6 (2.3)	5 (3.2)
Lymphocyte count	6 (2.3)	6 (3.8)
Nausea	6 (2.3)	5 (3.2)
Fatigue	5 (1.9)	5 (3.2)
Anorexia	5 (1.9)	5 (3.2)
Note: Columns are not additive, as patients may have had more than 1 event. Data are sorted by the Overall column.		

Table 30 Serious TEAEs considered related to treatment in ≥1% of patients in either group by preferred term (ISA)

Preferred term	Number of patients (%)	
	Overall Population (N=258)	Study IP-REM-AC-01 (N=157)
Patients with at least 1 serious TEAE considered related to study treatment	**39 (15.1)**	**23 (14.6)**
Ileus	8 (3.1)	7 (4.5)
Pyrexia	6 (2.3)	4 (2.5)
Subileus	4 (1.6)	2 (1.3)
Abdominal pain	3 (1.2)	3 (1.9)
Vomiting	2 (0.8)	2 (1.3)
Hypotension	2 (0.8)	2 (1.3)
Note: Columns are not additive, as patients may have had more than 1 event. Data are sorted by the Overall Population. Source: Module 5, Section 5.3.5.3, Report Cat-ISA-01, Table 5.5.2		

Table 31 Categorized reasons for hospitalization, IP-REM-AC-01, safety set (N=245)

	Catumaxomab (N=157)		Control (N=88)	
	N (%)	E	N (%)	E
Patients (%) hospitalized	154 (98.1)	305	58 (65.9)	96
Reasons (%)				
Due to AE	46 (29.3)	59	14 (15.9)	16
Due to screening procedure	14 (8.9)	15	15 (17.0)	15
Due to social reasons	10 (6.4)	14	8 (9.1)	8
Due to study related procedures other than catumaxomab infusions e.g., puncture visit	43 (27.4)	53	36 (40.9)	49
Due to application of catumaxomab infusion	127 (80.9)	164	5 (5.7)*	8

N= patients with at least one hospitalization

% percentage of patients with event based on the safety set

E= number of hospitalizations

* control group patients crossing-over to catumaxomab

None of the AEs with outcome of death that occurred after start of first infusion was considered related to catumaxomab. There were no deaths in Study IP-REM-GC-01.

- Laboratory findings

Table 32 Laboratory abnormalities reported as TEAEs occurring in ≥5% of patients in either group by preferred term (ISA)

Preferred Term	Number of patients (%)	
	Overall (N=258)	Study IP-REM-AC-01 (N=157)
Patients with at least 1 TEAE	**255 (98.8)**	**154 (98.1)**
CRP increased	38 (14.7)	27 (17.2)
GGT increased	34 (13.2)	21 (13.4)
Blood AP increased	25 (9.7)	16 (10.2)
AST increased	20 (7.8)	14 (8.9)
ALT increased	17 (6.6)	11 (7.0)
Lymphocyte count decreased	9 (3.5)	9 (5.7)
Note: Columns are not additive, as patients may have had more than 1 event. Data are sorted by the overall column. Source: Module 5, Section 5.3.5.3, Report Cat-ISA-01, Table 5.2.2		

Hepatic and hepatobiliary disorders

Hepatic and hepatobiliary disorders included TEAEs such as increase of hepatic enzymes, increase of transaminases, hepatic failure, hepatitis toxic, hyperbilirubinaemia, and jaundice. Overall, 27.1% of patients experienced hepatic and hepatobiliary disorders without showing clinical signs or symptoms. Liver function tests displayed a transient increase (in general fully reversible). GGT and AP showed a tendency of accumulation over the 4 infusions.

Table 33 WBC disorders (TEAEs) occurring in ≥1% of patients in either group by preferred term (ISA)

Preferred Term	Number of patients (%)			
	All TEAEs		TEAE of CTCAE Grade ≥3	
	Overall Population (N=258)	Study IP-REM-AC-01 (N=157)	Overall Population (N=258)	Study IP-REM-AC-01 (N=157)
Lymphopenia	39 (15.1)	30 (19.1)	24 (9.3)	16 (10.2)
Leukocytosis	27 (10.5)	19 (12.1)	3 (1.2)	2 (1.3)
Neutrophilia	11 (4.3)	8 (5.1)	-	-
Lymphocyte count decr.	9 (3.5)	9 (5.7)	8 (3.1)	8 (5.7)
Leukopenia	6 (2.3)	4 (2.5)	-	-
Note: Columns are not additive, as patients may have had more than 1 event. Data are sorted by the Overall Population.				

Immunogenicity of catumaxomab: development of human anti-mouse and anti-rat antibodies (HAMA and HARA)

Across studies, the majority of patients developed HAMA/HARA. Please refer to the pharmacodynamics section (including discussion on clinical pharmacology).

- Safety in special populations

The proportion of treated patients ≥65 years was 81 (31%). The percentage of patients who discontinued treatment due to TEAEs was slightly higher in this population. Overall, the incidence in elderly and non-elderly was similar, but 10.2% of younger patients (<65 years) had ileus compared to 4.9% of older patients (≥65 years). The incidence of AEs of ≥ Grade 3 in the two age-groups was also similar, where slightly more TEAEs with hyponatremia (8.6%) and anemia (6.2%) occurred in the elderly.

No other studies in special populations were conducted. Patients with massive liver metastasis or other hepatobiliary conditions, as well as renal dysfunction were excluded in the pivotal study.

- Safety related to drug-drug interactions and other interactions

No interactions were presented.

- Discontinuation due to adverse events

Table 34 TEAEs leading to study discontinuation in ≥1% of patients in either group by preferred term (ISA)

Preferred term	**Number of patients (%)**	
	Overall Population (N=258)	**Study IP-REM-AC-01 (N=157)**
Patients with at least 1 TEAE leading to study discontinuation	**14 (5.4)**	**1 (0.6)**
Pyrexia	11 (4.3)	1 (0.6)
Abdominal pain	8 (3.1)	0
Vomiting	8 (3.1)	0
Blood AP increased	4 (1.6)	0
Constipation	4 (1.6)	0
CRP increased	4 (1.6)	1 (0.6)
Nausea	4 (1.6)	0
Ileus	3 (1.2)	0
Hepatic enzyme increased	3 (1.2)	0
Oedema	3 (1.2)	0
Note: Columns are not additive, as patients may have had more than 1 event. Data are sorted by the Overall Population.		

- Post marketing experience

No post marketing data have been submitted.

- Discussion on clinical safety

The CHMP raised concerns with regards to the higher death rate in the catumaxomab-groups compared to the control group (55 vs. 13 deaths). This concern was addressed by the applicant during the procedure. The differences in death rates can be explained by the 2:1 randomization and the longer observation time in the catumaxomab arm. Furthermore, none of the death cases in the randomized part of the study was related to catumaxomab. Nevertheless, the CHMP considered that as a treatment administered for palliative intent, the high incidence and the severity of adverse reactions were major drawbacks. To further evaluate this matter, the following issues were discussed at the SAG-Oncology:

1. The frequent and commonly severe adverse reactions associated with catumaxomab treatment, including need for hospitalization. The applicant was asked to provide more details about durations of grade 3/4 events and hospitalisation. Based on the evidence provided, the SAG was of the opinion that the safety profile could be considered as adequately defined. However, it was difficult to assess whether a safety profile is generally acceptable (without taking efficacy into account). In general, the safety profile could be considered as acceptable provided that a clear benefit is shown. In the absence of a clear benefit, the observed safety profile would be considered unacceptable.

2. The identification of measures that could be taken to reduce the severity and frequency of the adverse events reported with catumaxomab (nausea, abdominal pain, asthenia, constipation and pyrexia). The SAG concluded that it was not possible to identify any measures or concomitant medications that might be used to reduce the toxicity because there is always a potential for interaction with catumaxomab (e.g., pharmacodynamic interaction with corticosteroids).

In addition to these issues, the CHMP raised other concerns with regards to the clinical safety data submitted:

3. Data on systemic exposure upon intraperitoneal administration were considered too scarce for safety evaluation. The applicant was therefore requested to discuss the potential risks of systemic bioavailability of catumaxomab, including e.g. the risk for effects of catumaxomab in EpCAM-positive normal tissue at disruption of capillary barriers (e.g. local infiltration of tumour or infectious processes). After a review of the safety database for signs compatible with toxicity in EpCAM posive norma-tissue, the CHMP considered that the available safety findings were sufficient to enable a benefit-risk assessment.

Section 4.2 of the SPC was updated to note that catumaxomab is not recommended for use in children below the ages of 18 years due to the lack of data on safety and efficacy.

The applicant committed to evaluate more patients in a planned phase IIIb clinical study in order to gain additional data on HAMA/HARA positive patients receiving catumaxomab treatment and toxicity. Summary of safety concerns and planned pharmacovigilance actions of the Risk Management Plan (RMP) were revised accordingly.

In addition, the applicant committed to providing the results of a two-arm, randomized, open label, phase IIIb study investigating the safety of the 3hours i.p infusion of catumaxomab with and without prednisolone premedication in patients with malignant ascites due to epithelial cancers, which began in December 2008.

As a result of the clinical safety data submitted, the following sections of the SPC were amended:

Section 4.4 of the SPC was updated to include the following special warnings and precautions for use:

Cytokine release related symptoms

As release of pro-inflammatory and cytotoxic cytokines is initiated by the binding of catumaxomab to immune and tumour cells, cytokine release related clinical symptoms such as fever, nausea, vomiting and chills have been commonly reported during and after the Removab administration (see section 4.8). Dyspnoea and hypo-/ hypertension are less commonly observed. In the clinical studies in patients with malignant ascites, 1000 mg paracetamol intravenously was routinely administered prior to Removab infusion for pain and pyrexia control. Despite this premedication, patients experienced the adverse reactions described above with an intensity of up to grade 3, according to the Common Terminology Criteria for Adverse Events (CTCAE) of the US National Cancer Institute. Other or additional standard pre-medication with analgesic / antipyretic / nonsteroidal antiphlogistic medicinal products is recommended.

Systemic Inflammatory Response Syndrome (SIRS), which may also occur uncommonly due to the mechanism of action of catumaxomab, develops, in general, within 24 hours after Removab infusion, showing symptoms of fever, tachycardia, tachypnoea and leucocytosis (see section 4.8). Standard therapy or premedication, e.g. analgesic / antipyretic / nonsteroidal antiphlogistic is appropriate to limit the risk.

Abdominal pain

Abdominal pain was commonly reported as an adverse reaction. This transient effect is considered partially a consequence of study procedures such as the intraperitoneal route of administration.

Performance status and BMI

A solid performance status expressed as Body Mass Index (BMI) > 17 (to be assessed after drainage of ascites fluid) and Karnofsky Index > 60 is required prior to Removab therapy.

Acute infections

In presence of factors interfering with the immune system, in particular acute infections, the administration of Removab is not recommended.

Ascites drainage

Appropriate medical management of ascites drainage is a prerequisite for Removab treatment in order to assure stable circulatory and renal functions. This must at least include ascites drainage until stop of

spontaneous flow, and, if appropriate, supportive replacement therapy with crystalloids and / or colloids. Conditions such as hypovolaemia, hypoproteinaemia, hypotension, circulatory decompensation and acute renal impairment should be resolved prior to each Removab infusion.

Hepatic impairment or portal vein thrombosis / obstruction

Patients with hepatic impairment of a higher severity grade than moderate and / or with more than 70% of the liver metastasized and / or portal vein thrombosis / obstruction have not been investigated. Treatment of these patients with Removab should only be considered after a thorough evaluation of benefit / risk.

Renal impairment

Patients with renal impairment of a higher severity grade than mild have not been investigated. Treatment of these patients with Removab should only be considered after a thorough evaluation of benefit / risk.

Perfusion system

Only the following material must be used for the application of Removab:

- 50 ml polypropylene syringes
- polyethylene perfusion tubing with an inner diameter of 1 mm and a length of 150 cm
- polycarbonate infusion valves / Y connections
- polyurethane, polyurethane silicon coated catheters

Section 4.7 of the SPC was updated to reflect the lack of studies performed on the effects on the ability to drive and use machines. Patients experiencing infusion-related symptoms should be advised not to drive and use machines until symptoms abate.

Section 4.8 of the SPC was updated to include the nature and frequency of adverse reactions analysed in an integrated safety analysis on the basis of 5 clinical studies consisting of 258 patients in the indications malignant ascites (193 patients), peritoneal carcinomatosis (24 patients) and ovarian cancer (41 patients) with intraperitoneal application of Removab.

Approximately 90% of patients experienced adverse reactions. In tabular format, adverse reactions reported with catumaxomab were listed in the SPC and classified according to frequency and System Organ Class. Adverse reactions of special interest included cytokine release-related symptoms, SIRS, and abdominal pain:

Cytokine release related symptoms:

Very commonly reported acute infusion-related reactions due to release of cytokines included fever, nausea, vomiting and chills. These reactions were frequently observed during and after Removab infusions with a severity of grade 1 and 2 and were fully reversible. Grade 3 pyrexia (5%), vomiting (3.9%), nausea (2.3%), dyspnoea (1.6%) hypotension (1.2%), hypertension (0.8%) and chills (0.8%) were reported. Grade 4 dyspnoea and hypotension were also reported in one patient each. Symptoms of pain and pyrexia can be ameliorated or avoided by pre-medication (see sections 4.2 and 4.4).

Systemic Inflammatory Response Syndrome (SIRS):

In 0.8% of the patients symptoms of SIRS were observed within 24 hours after Removab infusion, such as grade 3 tachycardia and fever and grade 4 dyspnoea. These reactions resolved under symptomatic treatment.

Abdominal pain:

In 48.1% of patients abdominal pain was reported as an adverse reaction reaching grade 3 in 9.7% of patients, but it resolved under symptomatic treatment.

Section 4.9 of the SPC was amended to include that no case of overdose had been reported. Patients receiving a higher than recommended dose of catumaxomab experienced more severe (grade 3) adverse reactions.

2.5 Pharmacovigilance

Detailed description of the Pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

Risk Management Plan

The MAA submitted a risk management plan.

Table 35 Summary of the risk management plan

Safety concern	Proposed pharmacovigilance activities	Proposed risk minimization activities
Cytokine release related symptoms	Monitoring and evaluation in future Periodic Safety Update Reports	Guidance in the SPC, Section 4.4. As release of pro-inflammatory and cytotoxic cytokines is initiated by the binding of catumaxomab to immune and tumour cells, cytokine release related clinical symptoms such as fever, nausea, vomiting and chills have been commonly reported during and after the Removab administration (see section 4.8). Dyspnoea and hypo-/ hypertension are less commonly observed.
Systemic inflammatory response syndrome	Monitoring and evaluation in future Periodic Safety Update Reports	Guidance in the SPC, Section 4.4. Systemic Inflammatory Response Syndrome (SIRS), which may also occur uncommonly due to the mechanism of action of catumaxomab, develops, in general, within 24 hours after Removab infusion, showing symptoms of fever, tachycardia, tachypnoea and leucocytosis (see section 4.8). Standard therapy or premedication, e.g. analgesic / antipyretic / nonsteroidal antiphlogistic is appropriate to limit the risk.
Hepatic and hepatobiliary disorders	Monitoring and evaluation in future Periodic Safety Update Reports	Guidance in the SPC, Section 4.4. Patients with hepatic impairment of a higher severity grade than moderate and / or with more than 70% of the liver metastasized and / or portal vein thrombosis / obstruction have not been investigated. Treatment of these patients with Removab should only be considered after a thorough evaluation of benefit / risk.
Transient decrease in peripheral lymphocyte count	Monitoring and evaluation in future Periodic Safety Update Reports	Mentioned in the SPC, Section 4.8.

Safety concern	Proposed pharmacovigilance activities	Proposed risk minimization activities
Early occurrence of HAMA/HARA	Further clinical investigation of potential risk for patients in Phase IIIb clinical study.	Guidance in the SPC, Section 5.1. The induction of human anti murine (rat and / or mouse) antibodies (HAMAs/HARAs) is an intrinsic effect of murine monoclonal antibodies. Current data on catumaxomab derived from the pivotal study show that only 5% of patients (7/132 patients) were HAMA positive before the 4th infusion. HAMAs were present in 87% of patients one month after the last catumaxomab infusion. No data about clinical effects due to the presence of HAMAs/HARAs are available to date. No hypersensitivity reactions were observed.
Limited scope of recommended premedication paracetamol with regard to cytokine release related symptoms	Further clinical investigation of potential risk for patients in PIII study	Guidance in the SPC, Section 4.4. In the clinical studies in patients with malignant ascites, 1000 mg paracetamol intravenously was routinely administered prior to Removab infusion for pain and pyrexia control and is therefore recommended. Despite this premedication, patients experienced the adverse reactions described above with an intensity of up to grade 3, according to the Common Terminology Criteria for Adverse Events (CTCAE) of the US National Cancer Institute. Other or additional standard pre-medication with analgesic / antipyretic / nonsteroidal antiphlogistic medicinal products is recommended.
Gastric hemorrhage/upper GI hemorrhage	Monitoring and evaluation in future Periodic Safety Update Reports	Mentioned in the SPC, Section 4.8.
Doses higher than the recommended dose of catumaxomab per infusion	Monitoring and evaluation in future Periodic Safety Update Reports	Guidance in the SPC, Section 4.9. No case of overdose has been reported. Patients receiving a higher than recommended dose of catumaxomab experienced more severe (CTCAE grade 3) adverse reactions.
Off-label use	Monitoring and evaluation of safety and efficacy in future Periodic Safety Update Reports	N/A
Ileus, intestinal perforation, intra-abdominal infection, catheter-related infection	Monitoring and evaluation in future Periodic Safety Update Reports	Mentioned in the SPC, Section 4.8.

Safety concern	Proposed pharmacovigilance activities	Proposed risk minimization activities
Patients with hepatic dysfunction and/or extensive liver metastases not investigated	Collect important missing information using a specific questionnaire in the context of spontaneous reporting Monitoring and evaluation in future Periodic Safety Update Reports	Guidance in the SPC, Section 4.4. Patients with hepatic impairment of a higher severity grade than moderate and / or with more than 70% of the liver metastasized and / or portal vein thrombosis / obstruction have not been investigated. Treatment of these patients with Removab should only be considered after a thorough evaluation of benefit / risk.
Patients with renal dysfunction not investigated	Collect important missing information using a specific questionnaire in the context of spontaneous reporting Monitoring and evaluation in future Periodic Safety Update Reports	Guidance in the SPC Section 4.4. Patients with renal impairment of a higher severity grade than mild have not been investigated. Treatment of these patients with Removab should only be considered after a thorough evaluation of benefit / risk.
Patients with portal vein thrombosis/ obstruction not investigated	Collect important missing information using a specific questionnaire in the context of spontaneous reporting Monitoring and evaluation in future periodic safety update reports	Guidance in the SPC Section 4.4. Patients with hepatic impairment of a higher severity grade than moderate and / or with more than 70% of the liver metastasized and / or portal vein thrombosis / obstruction have not been investigated. Treatment of these patients with Removab should only be considered after a thorough evaluation of benefit / risk.
Non-Caucasian population not investigated		Guidance in the SPC, Section 4.2. Patients of non-Caucasian origin have not been included in clinical studies.

The CHMP, having considered the data submitted in the application, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information.

2.6 Overall conclusions, risk/benefit assessment and recommendation

Quality

The different aspects of the chemical, pharmaceutical and biological documentation comply with existing guidelines. The fermentation and purification of the drug substance, have been adequately described, controlled and validated. The drug substance has been well characterised with regard to its physicochemical and biological characteristics, using state-of the-art methods, and appropriate specifications have been set. The manufacturing process of the drug product has been satisfactorily described and validated. The results of tests carried out indicate satisfactory consistency and uniformity of important quality characteristics. The quality of the drug product is controlled by adequate test methods and specifications. The viral safety and the safety concerning other adventitious agents including TSE have been sufficiently assured.

Non-clinical pharmacology and toxicology

Administration of catumaxomab in animal models did not result in any signs of abnormal or drug-related acute toxicity or signs of local intolerance at the injection/infusion site. However, these findings are of limited value due to the high species-specificity of catumaxomab.

Repeated-dose toxicity, genotoxicity, carcinogenicity, reproductive and developmental toxicity studies have not been performed.

Efficacy

The efficacy of catumaxomab was demonstrated in a two-arm, randomized, open-label clinical trial (IP-REM-AC-01) in 258 patients with symptomatic malignant ascites due to EpCAM positive carcinomas of whom 170 were randomized to catumaxomab treatment. This study compared paracentesis plus catumaxomab *versus* paracentesis alone (control).

Catumaxomab was applied in patients where standard therapy was not available or no longer feasible and who had a Karnofsky performance status of a least 60. Catumaxomab was administered as four intraperitoneal infusions with increased doses of 10, 20, 50 and 150 micrograms on day 0, 3, 7 and 10, respectively.

In this study, the primary efficacy endpoint was puncture-free survival, which was a composite endpoint defined as the time to first need for therapeutic ascites puncture or death, whichever occurred first. In all analysis groups, puncture-free survival was significantly longer ($p<0.0001$) in the catumaxomab group compared to the control group. In the pooled analysis, the median difference between the groups was 35 days (95% CI: 25; 45). For ovarian cancer patients, the median difference between the groups was 41 days (95% CI: 32; 50) and for all non-ovarian cancer patients 23 days (95% CI: 8; 38). After reviewing a number of sensitivity analyses, the CHMP considered that the expected puncture-sparing effect for a patient is likely to be of about 4 punctures (see risk-benefit assessment).

Safety

The nature and frequency of adverse reactions were described in section 4.8 of the SPC and were analysed in an integrated safety analysis on the basis of 5 clinical studies consisting of 258 patients in the indications malignant ascites (193 patients), peritoneal carcinomatosis (24 patients) and ovarian cancer (41 patients) with intraperitoneal application of Removab.

Approximately 90% of patients experienced adverse reactions. Adverse reactions reported with catumaxomab were listed in the SPC and classified according to frequency and System Organ Class. Frequency groupings were defined according to the following convention: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100).Within each frequency grouping, undesirable effects were presented in order of decreasing seriousness. The following adverse reactions were of special interest.

Cytokine release related symptoms:

Very commonly reported acute infusion-related reactions due to release of cytokines included fever, nausea, vomiting and chills. These reactions were frequently observed during and after Removab infusions with a severity of grade 1 and 2 and were fully reversible. Grade 3 pyrexia (5%), vomiting (3.9%), nausea (2.3%), dyspnoea (1.6%) hypotension (1.2%), hypertension (0.8%) and chills (0.8%) were reported. Grade 4 dyspnoea and hypotension were also reported in one patient each. Symptoms of pain and pyrexia can be ameliorated or avoided by pre-medication (see sections 4.2 and 4.4).

Systemic Inflammatory Response Syndrome (SIRS):

In 0.8% of the patients symptoms of SIRS were observed within 24 hours after Removab infusion, such as grade 3 tachycardia and fever and grade 4 dyspnoea. These reactions resolved under symptomatic treatment.

Abdominal pain:

In 48.1% of patients abdominal pain was reported as an adverse reaction reaching grade 3 in 9.7% of patients, but it resolved under symptomatic treatment.

An Annual Safety Report (ASR) was received by the EMEA on 16 February 2008, covering the reporting period of 05 January 2008 through 04 January 2009. Based on this report, the benefit-risk ratio of catumaxomab remains favourable.

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

Having considered the safety concerns in the risk management plan, the CHMP considered that the proposed activities described in section 3.5 adequately addressed these.

- User consultation

The Applicant performed a readability testing ("user consultation") and a satisfactory report has been provided.

Risk-benefit assessment

A treatment effect has been demonstrated in terms of prolonged puncture-free survival in patients with malignant ascites due to ovarian and non-ovarian cancer. While statistically convincing, the treatment effect is difficult to reliably estimate due to premature study termination, mainly in the experimental arm. Based on a weighed review of alternative analysis, however, the median delay in paracentesis puncture is approximately 1 month. Number of paracenteses avoided is considered a reasonable overall measure of patient benefit. Due to the cross-over design this benefit can only be estimated, but about 4 punctures seem to be a reasonable estimate. This is considered to be a relevant reduction in number of paracenteses needed until death. The indication sought has been restricted to treatment of EPCAM positive tumours as catumaxomab is highly unlikely to be active in tumours not expressing the target antigen.

There are certain risks and uncertainties associated with catumaxomab. During the discussion of the benefit/risk balance of this medicinal product, no significant increase in overall survival was noted, despite the demonstrated increased in puncture-free survival from 11 days to 46 days. Administration of catumaxomab was associated with frequent grade 3/4 events, but the vast majority of symptomatic severe events were of short duration and infusion-related. Number of days at hospital was increased from 4 days to 18 days, but remained similar if corrected for observation time (median 18/42 and 4/11). The increased number of withdrawn patients in the experimental arm is also mainly accounted for by increased time of observation.

The study design (cross-over) impacts on the possibility to properly assess efficacy and safety over time. With respect to number of paracenteses avoided it has been assumed that the frequency will remain stable in the control arm over time. Adverse events and hospitalizations have also been assumed to remain stable. With respect to hospitalization, it is not unreasonable to assume that need for hospitalization will increase over time, in relation to punctures, as performance status deteriorates. Taking into consideration the palliative nature of this treatment in terminally-ill cancer patients, and in the absence of a significant survival advantage, the increase in puncture-free survival should always be weighed against the need for hospitalisation for the administration of catumaxomab.

Important biases in relation to clock start, puncture and time to event analyses were not been identified or have been possible to handle through sensitivity analyses.

In conclusion, the benefit as estimated based on reduced need for paracenteses is considered to outweigh treatment associated adverse reactions. The prolonged time to need for puncture conferred by this medicinal product is approximately 40-60 days, and grade 3/4 adverse reactions are common but of short duration. Patients receiving catumaxomab should expect to remain in hospital for the duration of treatment (In the pivotal study IP-REM-AC-01 98.1% of patients were hospitalised for a median of 11 days, SPC section 5.1).

A risk management plan was submitted. The CHMP, having considered the data submitted, was of the opinion that:

- routine pharmacovigilance was adequate to monitor the safety of the product.
- no additional risk minimisation activities were required beyond those included in the product information.

Therefore, the overall benefit/risk of catumaxomab for the intraperitoneal treatment of malignant ascites in patients with EpCAM positive carcinomas where standard therapy is not available or no longer feasible, is considered to be positive.

Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus decision that the risk-benefit balance of Removab in the treatment of malignant ascites in patients with EpCAM positive carcinomas where standard therapy is not available or no longer feasible, was favourable and therefore recommended the granting of the marketing authorisation.