17 October 2024
EMA/551738/2024
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Korjuny

International non-proprietary name: catumaxomab

Procedure No. EMEA/H/C/005697/0000

Note

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

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List of abbreviations

ADA	Anti-drug antibody
ADCC	Antibody-dependent cell-mediated cytotoxicity
ADCP	Antibody-dependent phagocytosis
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
AU	Absorption units
AUC	area under the concentration vs. time curve
BMI	Body mass index
C3a	Complement factor 3a
C5a	Complement factor 5a
CD	Cluster of Differentiation
CDC	Complement-dependent cytotoxicity
CI	Confidence interval
CIP	Cleaning in place
Cmax	Maximum concentration
CoA	Certificate of analysis
CoR	Confirmation of receipt
CPP	Critical process parameter
CR	Complete response
CRF	Case report form
CRS	Cytokine release syndrome
CSR	Clinical study report
CT	Computed tomography
CTCAE	Common terminology criteria for adverse events
DLT	Dose limiting toxicity
DSB	Dose Steering Board

ECOG	Eastern Cooperative Oncology Group
EORTC	European Organization for Research and Treatment of Cancer
EOS	End of study
EpCAM	Epithelial cell adhesion molecule
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30
EU	European Union
FACIT-AI	Functional Assessment of Chronic Illness Therapy-Ascites Index
FAS	Full analysis set
FIGO	International Federation of Gynaecology and Obstetrics
GGT	Gamma-glutamyltransferase
HAMA	Human anti-mouse antibody
HARA	Human anti-rat antibodies
HCP	Host cell proteins
HETP	Height of a theoretical plate
HILIC	Hydrophilic interaction chromatography
HMW	High molecular weight
HPAEC	High-pH anion exchange chromatography
HPAEC-PAD	High-performance anion-exchange chromatography with amperometric detection
HPLC	High performance liquid chromatography
HPW	Highly purified water
HR	Hazard ratio
IgG	Immunoglobulin G
IL	Interleukin
i.p.	Intraperitoneal
i.pl.	Intrapleural
IPC	In-process control
IPM	In-process monitoring
IPP	In-process parameter
IPT	In-process test
ITT	Intention-to-treat

i.v.	Intravenous
KPP	Key process parameter
LLOQ	Lower limit of quantification
MCB	Master cell bank
MTD	Maximum tolerated dose
MVM	Minute virus of mice
NCPP	Non-critical process parameter
NK	Natural killer
NOAEL	No observed adverse effect level
NOR	Normal operating range
NSCLC	Non-small cell lung cancer
ORR	Objective response rate
OS	Overall survival
PAR	Process acceptance range
PBMC	Peripheral blood mononuclear cells
PCR	Polymerase chain reaction
PD	Progressive disease
PFS	Progression-free survival
PK	Pharmacokinetics
PP	Per-protocol
PR	Partial response
PuFS	Puncture free survival
QOL	Quality of life
RECIST	Response evaluation criteria in solid tumours
SAE	Serious adverse event
SAP	Statistical analysis plan
SC	Subcutaneous
SCC	Squamous cell carcinoma
SCID	Severe combined immune deficiency
SD	Standard deviation
TNF-α	Tumour necrosis factor-α

TTPu	Time to therapeutic puncture
ULN	Upper limit of normal
USP	Upstream process
VLP	Virus-like particles
WCB	Working cell bank
ZA	Cell free harvest

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Lindis Biotech GmbH submitted on 1 August 2022 an application for marketing authorisation to the European Medicines Agency (EMA) for Korjuny, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004.

The applicant applied for the following indication:

KORJUNY is indicated for the intraperitoneal treatment of malignant ascites in adults with EpCAM-positive carcinomas where standard therapy is not available or no longer feasible.

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is 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).

1.3. Information on paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0053/2021 on the granting of a (product-specific) waiver.

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

1.5. Scientific advice

The applicant received the following EMA scientific advice on the development relevant for the indication subject to the present application:

Date	Reference	SAWP co-ordinators
18 November 2004	EMEA/H/SA/506/1/2004/II	Prof. Minne Casteels and Dr Bertil Jonsson
28 June 2006	EMEA/H/SA/506/1/FU/2006/II	Dr Bertil Jonsson and Dr Christian Schneider

3 May 2021	IRIS:00814000054	Dr Jens Ersbøll, Dr Walter Janssens and Prof. Rembert Elbers

The scientific advice pertained to the following non-clinical and clinical aspects:

- The appropriateness of the non-clinical data package to support a marketing authorisation;
- The design of the single open-label pivotal phase II/III study in patients with symptomatic malignant ascites and EpCAM positive tumours to support a Marketing Authorisation, in particular, the choice of control, of primary and secondary endpoints (including QoL questionnaires), the selection criteria for the study population, the methodology aspects for the assessment of the primary endpoint interim analysis and censoring rules; the approach to submit data primarily for an indication in ovarian or gastric cancer, the time of follow-up;
- The proposed PK program and the rationale for the choice of dosing regimen.

1.6. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Jan Mueller-Berghaus Co-Rapporteur: Alexandre Moreau

The application was received by the EMA on	1 August 2022
The procedure started on	18 August 2022
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	8 November 2022
The CHMP Co-Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	21 November 2022
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	21 November 2022
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	15 December 2022
The applicant submitted the responses to the CHMP consolidated List of Questions on	8 September 2023
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	16 October 2023
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	26 October 2023
The CHMP agreed on a list of outstanding issues in writing to be sent to the applicant on	9 November 2023

The applicant submitted the responses to the CHMP List of Outstanding Issues on	25 March 2024
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	10 April 2024
The CHMP agreed on a list of outstanding issues in writing to be sent to the applicant on	25 April 2024
The applicant submitted the responses to the CHMP List of Outstanding Issues on	20 August 2024
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	4 September 2024
The outstanding issues were addressed by the applicant during an oral explanation before the CHMP during the meeting on	18 September 2024
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 Korjuny on	17 October 2024

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

The initially applied indication for Korjuny was for the intraperitoneal treatment of malignant ascites in adults with EpCAM-positive carcinomas where standard therapy is not available or no longer feasible.

2.1.2. Epidemiology

Malignant ascites accounts for ~10% of all cases of ascites and occurs in association with a variety of neoplasms. Malignant effusion is the escape of fluid from the blood or vessels into tissues or cavities; it is a common problem in patients with cancer. All types of cancer can metastasise to any of the body's serous cavities, resulting in malignant effusion. In the Western world, the most common cause of malignant ascites is ovarian cancer. Other common primary sites are the pancreas, stomach, and uterus, with breast, lung, and lymphoma representing the most common extra-abdominal sites (Gines 2004). Up to 20% of all patients with malignant ascites have cancer of unknown primary origin (Parsons 1995). Except in breast and ovarian cancer, the presence of malignant ascites in patients with neoplastic disease frequently signals the terminal phase of cancer. The mean survival time for ovarian cancer is 30 to 35 weeks, and for tumours of lymphatic origin 58 to 78 weeks, whereas for cancers of the gastrointestinal tract, mean survival is only 12 to 20 weeks. In patients with carcinoma of unknown primary (CUP), the median survival shows great variability, ranging from 1 week to 3 months in different series.

2.1.3. Biologic features/aetiology and pathogenesis

Malignant ascites, i.e. ascites in cancer patients, is a sign of peritoneal carcinomatosis, i.e. presence of malignant cells in the peritoneal cavity and peritoneum (Sangisetty 2012). These cells may be primary tumours of the peritoneum, but more frequently, they disseminate as peritoneal metastasis from tumours of intraperitoneal origin (digestive and female reproductive tract; sarcoma) or even of extraperitoneal origin (lung, breast, kidney) (Cortés-Guiral 2021). Tumour cells seeding along the peritoneal wall can obstruct lymphatic drainage, resulting in decreased fluid efflux from the peritoneal cavity. Also, cytokines and growth factors produced by tumour cells lead to tumour neovascularisation and increased permeability of the capillaries of tumour and peritoneum, supporting increased fluid influx into the peritoneal cavity (Nagy 1995; Tamsma 2007). Some malignancies can also form ascites due to massive liver metastases (Seeber 2015b), causing ascites by increased portal venous pressure (Tarn 2010).

Epithelial cell adhesion molecule (EpCAM) is a 40-kDa transmembrane glycoprotein that mediates epithelium-specific, calcium-independent, homotypic cell-to-cell adhesion in epithelia (Litvinov 1994). It is expressed at the basolateral cell membrane of simple, pseudo-stratified, and transitional epithelia, but not in differentiated cells of normal squamous stratified epithelia. In healthy adults, EpCAM is expressed in most organs and glands, although expression levels differ between tissues; typically, tissues with high EpCAM expression are high in proliferating and low in differentiated cells (Schnell 2013). EpCAM is expressed in various stem and progenitor cells (Spizzo 2011, Schnell 2013). EpCAM is involved in cell signalling, proliferation, differentiation, and migration, and formation and maintenance of organ morphology (Schnell 2013).

High EpCAM expression correlates with poor prognosis, e.g. in cancer of the breast, ovaries, pancreas, gallbladder, and urothelial cancer (Spizzo 2011, Schnell 2013). Overexpression is associated with enhanced proliferation, tumour cell migration, and tumour invasion (Litvinov 1994; Gastl 2000; Spizzo 2004) and with enhanced transcription and translation of proto-oncogenes c-myc, cyclin A and E (Huang 2018). Proteolytic cleavage of the intracellular domain of EpCAM confers a mitogenic signal. DNA methylation appears to be a potential mechanism for regulation of EpCAM expression (Spizzo 2011). In the peritoneal cavity, EpCAM is not only a tumour-associated but also a tumour-specific antigen, since the mesothelial cells of the peritoneum do not express EpCAM (Bailey 1996; Davidson 1999; Okamoto 2005).

2.1.4. Clinical presentation, diagnosis and stage/prognosis

Malignant ascites is a typical manifestation of end stage cancer disease (Saif 2009). The prognosis of patients is to a certain extent dependent on the underlying cancer type, leading to variability in the outcome of different populations of patients presenting with malignant ascites. Nevertheless, malignant ascites overall has a poor prognosis, with only 11% of patients surviving >6 months (Kipps 2013). A relatively better prognosis is reported for patients with ascites from epithelial ovarian cancer; and patients with stage III/IV ovarian cancer with ascites may still achieve median progression-free survival (PFS) of 16 to 22 months and a 5-year survival rate of 27% after surgery and combination chemotherapy (Kipps 2013). In these patients, outcome may be further improved with advancements in anticancer therapy (Stukan 2017).

2.1.5. Management

Malignant ascites (MA) carries a poor prognosis, often becoming symptomatic in patients with only weeks to months to live. Despite this, the presence of MA can have a significant detrimental impact on quality of life (QoL), with increasing abdominal distention, pain, and dyspnoea. Diuretics and dietary sodium restriction, the traditional first-line therapies for ascites in cirrhosis, do not work well for MA unless it occurs due to hepatic metastases.

Treatment depends on the cause; the severity of symptoms; the cancer type, extent of spread, and suitability of anticancer treatments; and patient preferences (Kipps 2013, Seah 2022).

Methods are listed below:

- Treatment of the cancer itself with systemic therapy - Advantages: possibly life prolonging. Disadvantages: often not possible as ascites is a symptom of relapsed and refractory end-stage metastatic cancer.
- Paracenteses as indicated +/- albumin substitutions – Advantages: providing relief, uncomplicated and relatively safe procedure possible also in out-patient setting. Disadvantages: procedure to be repeated, rarely gastrointestinal (GI) perforation, infection, bleeding.
- Permanent catheters – surgical procedure of insertion of tunnelised catheter required. Surgical tunnelisation is required for infection prophylaxis. Also non-tunnelled catheters exist. Benefits: no additional paracenteses needed; home management. Risks: Infections, Bleeding, GI perforation.
- Other solutions: indwelling peritoneal ports, peritoneovenous shunts (PVSs), or hyperthermic i.p. chemotherapy (HIPEC).

The last three methods do not improve overall survival, although they do improve QoL and decrease hospital visits and interventions in an end-stage disease palliative care (RCOG 2014).

At present there is no available medicinal product specific for the treatment of malignant ascites.

2.2. About the product

Catumaxomab is a trifunctional rat-mouse hybrid monoclonal antibody that is specifically directed against the epithelial cell adhesion molecule (EpCAM) and the CD3 antigen. It has 3 binding sites of which (1) the mouse Fab fragment binds to human EpCAM; (2) the rat Fab fragment binds to human CD3 on T cells; (3) the hybrid Fc-region selectively binds to and activates Fcγ-receptor I, IIa, and III-positive accessory cells. Due to catumaxomab's binding properties, tumour cells, T-cells and accessory immune cells come in close proximity. Thereby, a concerted immunoreaction against tumour cells is induced which includes different mechanisms of action such as T-cell activation, T-cell mediated killing via the granzyme / perforin system, antibody-dependent cell-mediated cytotoxicity (ADCC), complement-dependent cytotoxicity (CDC) and phagocytosis.

The initially applied indication was for the intraperitoneal treatment of malignant ascites in adults with EpCAM-positive carcinomas where standard therapy is not available or no longer feasible.

The finally approved indication was for the intraperitoneal treatment of malignant ascites in adults with epithelial cellular adhesion molecule (EpCAM)-positive carcinomas, who are not eligible for further systemic anticancer therapy.

The dosing schedule comprises the following four intraperitoneal infusions:

1. 10 micrograms on day 0
2. 20 micrograms on day 3
3. 50 micrograms on day 7
4. 150 micrograms on day 10

Patients should remain under close medical supervision for at least 24 hours after the first infusion of Korjuny. For the remaining doses, patients may be hospitalised for at least 6 hours or for a longer time after infusion at the discretion of the treating physician to safeguard patient safety.

The interval between the infusion days can be prolonged at the discretion of the treating physician if needed in order to minimise the risk of adverse reactions. The overall treatment period should not exceed 21 days.

2.3. Type of application and aspects on development

Catumaxomab was granted marketing authorisation (Removab EMEA/H/C/000972) in the EU on 20 Apr 2009 for intraperitoneal (i.p.) treatment of malignant ascites in adults with EpCAM+ carcinomas where standard therapy is not available or no longer feasible. The original marketing authorisation holder was Fresenius Biotech GmbH; later, this changed to Neovii Biotech GmbH. The product has not been marketed in the EU since 2014; it was withdrawn for commercial reasons on 2 June 2017.

Meanwhile, Lindis Biotech GmbH has obtained the rights for catumaxomab and pursued a new marketing authorisation application (MAA).

For the original MAA, the efficacy claim in this indication was based on the results from the following studies:

- Pivotal study IP-REM-AC-01 was performed in patients with malignant ascites due to epithelial cancers, investigating paracentesis + catumaxomab vs. paracentesis alone. This was the only controlled study in which catumaxomab was compared to the standard treatment of paracentesis.
- Supportive studies STP-REM-01 and IP-REM-PK-01-EU performed in the indication of malignant ascites.

Additional studies of catumaxomab were performed with the same route of administration (i.p.) but in different indications, not directly contributing to the claim of efficacy for catumaxomab: AGO-OVAR-2.10 (ovarian cancer), IP-REM-PC-01-DE (peritoneal carcinomatosis) and IPREM- GC-01 (intraabdominal tumours). Despite addressing an indication other than malignant ascites, AGO-OVAR-2.10 was presented as supportive in the original MAA.

Two further studies using different administration routes (intrapleural, i.pl.; intravenous i.v.) and investigating different indications (pleural effusion: IPL-REM-PL-DE; non-small cell lung cancer; IV-REM-01-DE) that had been completed at the time of the original MAA did not contribute to the efficacy claim for catumaxomab.

Studies completed since primary MAA, available as study reports

At the time of the original MAA submission, 5 additional studies of catumaxomab were ongoing; these studies have been completed in the meantime.

- Study IP-REM-AC-02-US of catumaxomab i.p. in patients with recurrent symptomatic malignant ascites due to ovarian cancer; this study was performed in the same indication as the original pivotal study but had only an open-label uncontrolled design and is therefore considered as supportive for this new MAA;
- 4 additional studies of catumaxomab i.p. in indications other than malignant ascites: IPCAT-OC-01 (advanced epithelial ovarian cancer); IP-CAT-OC-02 (epithelial ovarian cancer); IP-REM-GC-02 (gastric adenocarcinoma), and IP-CAT-GC-03 (gastric adenocarcinoma).

Based on the completed studies and their route of administration and investigated indications, one study contributes to this MAA as pivotal (IP-REM-AC-01) while 3 further studies are considered as supportive (STP-REM-01; IP-REM-PK-01-EU; IP-REM-AC-02-US); as shown in the below table.

It is relevant to note that earlier studies, notably studies supporting the efficacy claim in the original MAA, tested catumaxomab as 6-h infusion. This was changed in the course of the clinical development programme to 3-h. Key data supporting the efficacy claim for catumaxomab as 3-h i.p. infusion in the present MAA are mainly derived from study IP-REM-AC-02-US.

The study design of the 4 studies of catumaxomab i.p. in malignant ascites is summarised in the table below.

The other 7 studies shown in the study overview do not directly contribute to the efficacy claim, as they investigated indications other than malignant ascites.

Table 1. Studies in the clinical development programme for catumaxomab

Study ID	Indication	Phase	Study design	Patients, (n)[1]	Infusion duration
Malignant ascites, catumaxomab i.p.					
IP-REM-AC-01	Malignant ascites due to epithelial cancer	II/III	R, C, OL	258	6
STP-REM-01	Malignant ascites due to ovarian cancer	I/II	OL, UC, DE	26	6
IP-REM-PK-01-EU	Malignant ascites due to epithelial cancer	II	OL, UC	13	6
IP-REM-AC-02-US	Malignant ascites due to ovarian cancer	II	OL, UC	32	3
Other indications, catumaxomab i.p.					
AGO-OVAR-2.10	Ovarian cancer	IIa	R, OL, UC	45	6
IP-REM-PC-01-DE	Peritoneal carcinomatosis due to epithelial GI malignancies	I	OL, UC, DE	24	3/6
IP-REM-GC-01	Intraabdominal epithelial tumour	I	OL, UC, DE	12	3
IP-CAT-OC-01	Advanced epithelial ovarian cancer; after complete response to chemotherapy	II	OL, UC	47	3
IP-CAT-OC-02	Epithelial ovarian cancer	II	OL, UC	41	3
IP-REM-GC-02	Gastric adenocarcinoma	II	OL, R, C	55	3
IP-CAT-GC-03	Gastric adenocarcinoma; after neoadjuvant chemotherapy, intended curative resection	II	OL, UC	70	3
IP-CAT-AC-03	Malignant ascites due to epithelial cancer IIIb		R, C, OL	219	3

Abbreviations: C= controlled, DE= dose escalation, i.p.= intraperitoneal; OL= open-label, R= randomised, UC= uncontrolled

[1] Number of patients randomised

Green box : new study supporting indication comparing to Removab MAA

Orange box: Studies used for indication claim of Removab, removed in Korjuny MAA

Red box: Study report submitted with D181 responses

No EMA scientific advice (SA) has been obtained for the current submission. SA was given in 2004 and 2006 as part of the Removab submission.

2.4. Quality aspects

2.4.1. Introduction

The finished product is presented as a concentrate for solution for infusion containing 100 microgram/mL Catumaxomab, with strengths corresponding to 10 µg and 50 µg doses of catumaxomab.

Other ingredients are: trisodium citrate dihydrate, citric acid monohydrate, polysorbate 80 and water for injections.

The product is available in a pre-filled syringe (type I glass, siliconised) with plunger stopper (bromobutyl rubber) and luer lock system (polypropylene siliconised and polycarbonate), with tip cap (bromobutyl rubber).

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2.4.2. Active Substance

2..4.2.1. General Information

Catumaxomab is an intact, trifunctional bispecific monoclonal antibody consisting of a mouse kappa light chain, a rat lambda light chain, a mouse immunoglobulin G (IgG)2a heavy chain, and a rat IgG2b heavy chain. It has 3 binding sites of which (1) the mouse Fab fragment binds to human EpCAM; (2) the rat Fab fragment binds to human CD3 on T cells; (3) the hybrid Fc-region selectively binds to and activates Fcγ-receptor I, IIa, and III-positive accessory cells. Catumaxomab has characteristics that are common for monoclonal antibodies and include amino acid modifications such as disulfide bridging, cysteinylation, N-linked glycosylation, and molecular weight variants.

2..4.2.2. Manufacture, process controls and characterisation

Catumaxomab active substance (AS) is manufactured at, for which proof of GMP compliance is provided. The applicant confirmed that cell banks, reference standards and other relevant materials were stored under GMP conditions the entire period until the transfer of AS manufacturing process.

Catumaxomab is not a recombinant product but manufactured using a hybrid hybridoma (quadroma) cell line. The upstream processing, is comprised of thawing of a working cell bank (WCB) via followed by cells expansion which begins in T-flasks and is continued in cell once a predefined cell amount of viable cells is achieved. The production of catumaxomab is performed in cell factories. Batch fermentation is performed. After production all cell factories are harvested. All harvests are pooled prior cell separation via filtration. Process parameters (PPs) and in-process controls (IPCs) are indicated. The second part of the catumaxomab AS manufacture is the downstream process (DSP) and begins with the Protein A chromatography. The Protein A eluate is kept at low pH to inactivate potential viruses. Subsequently, parental mouse antibodies are removed by Cation exchange chromatography (CEX). After the Cation exchange chromatography step, a Diafiltration step is used for buffer exchange and adjustment of the protein concentration for Nanofiltration. Subsequently, a Nanofiltration step is performed, which is the main virus depletion step. In order to stabilise the active substance, Polysorbate 80 is added to the active ingredient in the last step of the DSP. PP and IPCs are well defined and indicated. The applicant has given a sufficiently detailed overview of the manufacturing process and its control.

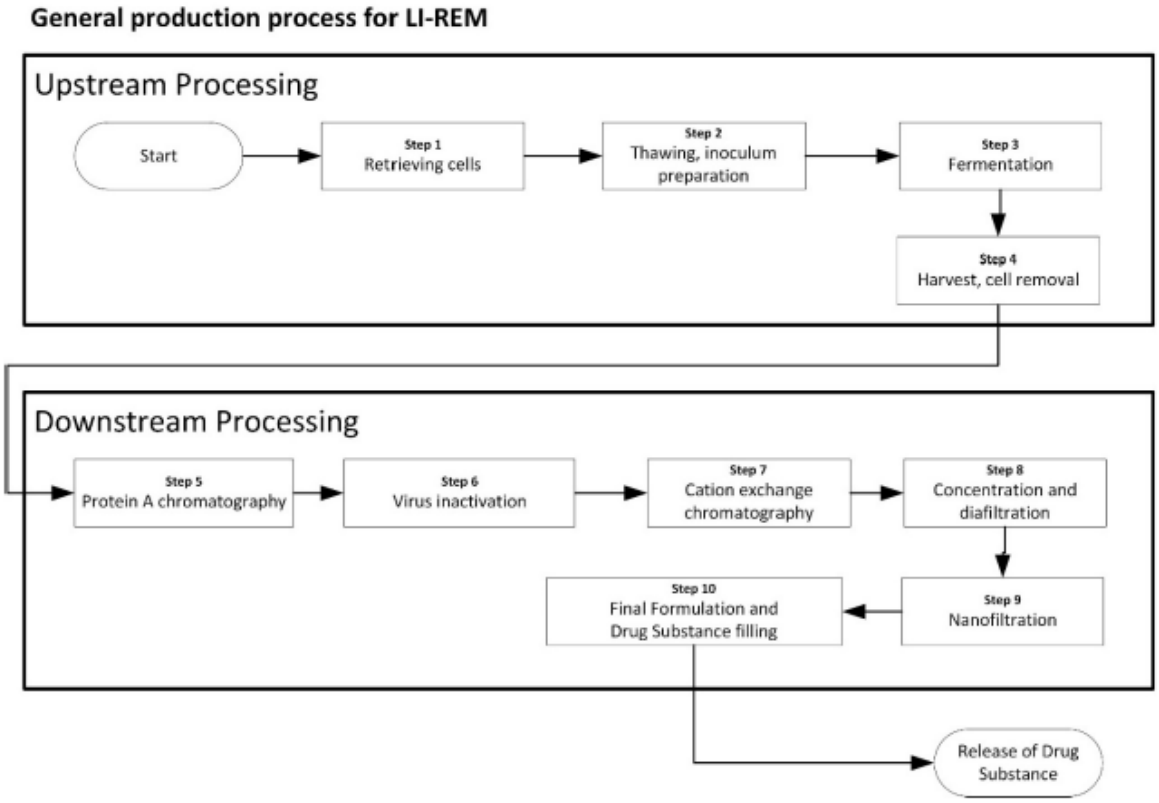


Figure 1. Active substance manufacturing flow chart

Control of materials

Raw materials used in the preparation of cell banks and in the manufacture of catumaxomab AS are listed. They are purchased from qualified vendors. The Raw materials are of pharmacopoeial grade when possible. Non-compendial raw materials are controlled by internal specifications which are provided and seem suitable to assure that materials are controlled. Foetal bovine serum (FBS) was used until lay-down of the Master Cell Bank (MCB) as an additive to the cell culture medium. Two different FBS batches, one of Argentinian and one of US origin were used. Both FBS batches were heat inactivated prior to use. A TSE certificate for FBS is presented. No raw materials of animal origin are used during the manufacture of catumaxomab active substance, with the exception of Medium including a component for which a secondary material of animal origin is used in its manufacture. The respective certificate of origin is provided. Test methods with acceptance criteria are provided for the non-compendial materials.

Catumaxomab is produced by cell culture fermentation using a hybrid hybridoma cell line. Its bispecific binding to human EpCAM and human CD3-positive Jurkat cells was confirmed by ELISA and FACS analysis. A two-tiered cell banking system was implemented. Identity of the MCB cells was confirmed by DNA fingerprinting and the absence of fungi, bacteria, mycoplasma, rat rotavirus, bovine viruses and adventitious viruses was confirmed using standard *in vitro* and in-vivo assays in accordance with ICHQ5A. Since the MCB was produced with FBS, absence of bovine polyoma virus by Q-PCR was demonstrated. A reduced test panel was applied to characterise the WCB in accordance with ICHQ5A. Virus safety characterisation of the WCB was performed on the level of post production cells for which no adventitious viruses were detected. The PPCB was generated after 64 population doubling levels (PDLs). Cell viability found to be in the range of 86 -

89%, indicating that the WCB is stable and suitable for production of catumaxomab. Future WCBs will be qualified according to same principles as established for the current WCB (PF).

Control of critical steps and intermediates

Controls for critical manufacturing process steps have been established for the manufacture of catumaxomab active substance. Definitions for the control strategy of the process follows the principles outlined in ICHQ8. For critical process parameters (CPPs) which may affect the quality and safety of the final product relevant controls have been established. Proven acceptable ranges (PARs), process limits (action limits) and acceptance criteria (AC) have been established. AC set for vial thaw, inoculum preparation, expansion, and final fermentation are considered adequate. No CPP is defined for the harvest and cell separation step, which is acceptable. IPCs are defined and controlled via AC. Hold time conditions e.g. as CPP during Protein A chromatography have been defined.. For viral inactivation at low pH, pH after adjustment and inactivation time are classified as CPPs. During CEX hold time of educt is defined as CPP.

Process validation

Information on analytical methods used for in-process testing is provided. Process validation was performed with three consecutive batches at a 32 L scale according to approved batch records in a qualified facility with qualified staff, using qualified equipment and utilities, as well as validated methods and procedures. All acceptance criteria for the active substance were met and all three batches of the active substance were released. Three PPQ runs have been successfully completed as each of the three consecutive active substance batches met the requirements. A sufficient clearance of impurities (HCP, DNA, ProtA, and parental rat and mouse antibodies) was demonstrated. Control of HCP is also part of the active substance specification panel. Results of the homogenisation study during filling and cleaning validation study for chromatography columns and ÄKTA Pilot chromatography system are provided. The results of homogenisation study performed

The catumaxomab purification process contains five defined hold times. In addition, an extended hold time study was performed during the first PPQ run. The data (microbial and biophysical/biochemical data) in principle support the proposed hold times when the material is stored at 2-8°C.n A normal hold time study was performed for PPQ2 and PPQ3. The results support the hold times from a microbial perspective.

In case of failure of the filter integrity testing for the 0.22 nm and 15 nm filters, re-filtration may be performed and the filtration step will be repeated. In section 3.2.S.2.5 Process Validation and/or Evaluation it is concluded that the validation showed that the reprocessing/refiltration of catumaxomab has no influence on the product quality and can be a transferred. Since the same filters and similar flow rates are used as the ones used, applicant concluded that the filtration process between is comparable and the validation data can be transferred to the purification process.

A risk analysis was performed to identify the risk of leachables in intermediates and final catumaxomab AS. The production steps 1 to 8 bear no risk with regard to leachables as the potential small molecule impurities will be removed during step 8. For the following two purification steps, all materials are from risk group A or B and meet the corresponding requirements except for the used product storage bags, which are classified as risk group C. A toxicological evaluation of leachables/extractables for the bag film was performed and concluded that there is no indication of an toxicological risk due to the leachables or extractables identified and quantified in Stedim 71 film material if used according to product description. Additionally, performed a toxicological evaluation of the filter. Overall, the manufacturing of catumaxomab poses no risk with regard to leachables.

A brief overview about the transport validation is provided. The transport was carried out by. The consignee was the finished product manufacturer. Transport validation was carried out three times (3 PPQ runs) covering three seasons. The shipment distance between to is rather short and the transport via refrigerated trucks is suitable. The manufacturing process could be considered as validated.

Manufacturing process development

The active substance manufacturing process was developed at I. Comparability of AS manufactured with the different processes was considered demonstrated previously. The manufacturing process of catumaxomab has been transferred. Comparability assessment of process is based on comparability of release data for the active substances, side-by-side analysis and forced degradation study Deficiencies in the comparability data were determined and raised as a Major Objection, these issues were resolved in the responses provided. No correlation was found between the oxidation levels and biological activity in an early forced degradation study conducted during the initial development. The limitation regarding the availability of samples is noted and understood. Nevertheless, the applicant commits to determine methionine oxidation of the next commercial batch due to the limited measurements of methionine oxidation available so far and the lack of representative material (REC). The comparison of historical release data and results of extended side-by-side comparability study should be included in section 3.2.S.2.6 (closing sequence).

The applicant provided the approach to develop a control strategy based on principles defined in ICH Q8 to Q11. Critical Quality Attributes (CQAs) were identified and brief justifications for their classification as CQA are provided. Definition of the process control strategy of the active substance manufacturing process was based on assignment of criticality to process control elements (PCE). According to the applicant this is a process in which each process input (parameter) and output (attribute) was assessed in relation to the CQAs. Definition of limits for PCEs was based on historical batch data. The Normal operating range (NOR) was established as the result of the statistical evaluation of the historical data and the data. It was deduced using a statistical ± 2 SD approach. The proven acceptable range (PAR) limit was established as the result of the statistical evaluation of all representative at scale manufacturing batches of. It was deduced using a statistical ± 3 SD approach. The applicant correctly states that the commercial manufacturing process will be operated within the NOR for all CPPs, and all IPCs are expected to be within their predefined acceptance criteria. Nevertheless, if during commercial manufacturing the NOR for a CPP is not met, a deviation will be initiated. The impact of the deviation on product quality (CQAs), process performance and consistency will then be evaluated. PAR data will be taken into account during the investigation in order to help classify the deviation.

Characterisation

Material from batches, which were produced according to the was used for characterisation of catumaxomab. A Broad and mostly adequate panel of analytical techniques and methodologies in line with the recommendations given in ICH Q6B was applied to the characterisation of catumaxomab to evaluate primary structure, posttranslational modifications, charge heterogeneity, higher order structure, and biological activity. With regard biophysical and biochemical parameters catumaxomab can be considered sufficiently characterised. With regard to "potency" the applicant provides binding to the FcgRI receptor. In addition FACS binding analysis data towards EpCAM and CD3 are provided. Proof that all characterisation methods are appropriately qualified (at least summaries of qualification reports) is provided and deemed acceptable. Process- and product related impurities have been identified. Product-related impurities and variants are controlled by release specifications. Clearance of residual mouse DNA, HCP, and residual potentially leached Protein A by the manufacturing process is demonstrated. Similarly, clearance of parental mouse and rat antibodies during purification of catumaxomab AS is shown. The parental antibody content is included in the

release specifications. The applicant provided a risk evaluation concerning the presence of nitrosamine impurities in the catumaxomab AS, applying the principles outlined in Questions and answers on "Information on nitrosamines for marketing authorisation holders" (EMA/409815/2020 or current version) and Nitrosamine Impurities - Final Outcome of Article 5(3) (EMA/369136/2020 or current version).

2..4.2.3. Specification.

Specifications are set in accordance with ICH Q6B and cover the relevant characteristics of catumaxomab AS. The specification for release and shelf-life testing include general tests, identity, purity, potency, protein content and microbiological aspects.

Analytical methods

The specifications and acceptance criteria are sufficient to ensure the overall quality of catumaxomab AS. For carbohydrate structures and isoform distribution the acceptance criteria presented in section S.4.5 are recalculated and for carbohydrate structures only data from HILIC method, for 3 batches, are now presented within section S.4.5. However, since active substance specification is not revised in that sense the updated specification including revised acceptance criteria for carbohydrate structures should be included in the section S.4.1 with the closing sequence.

HCP as a relevant safety parameter is part of AS specification with an appropriate limit set and data on the method provided in relevant sections. Additional information regarding the HCP assay is provided (the coverage of the antiserum and system to ensure consistency and quality of the reagents of generic kit). Compendial analytical methods used for release and stability testing of catumaxomab active substance are mostly listed with the respective references to the Ph. Eur. The non-compendial tests are mostly described in sufficient detail, Overall, the methods are considered well established for testing of monoclonal antibodies.

One catumaxomab specific cell proliferation assay is the commercial assay used for potency determination. This assay is used to analyse the cytotoxic effect displayed by catumaxomab titrated by *in vitro* cultivation of cells and PBMCs where cytotoxic effect is visible in the presence of increasing catumaxomab concentrations. For assay the applicant was asked to include more detailed description as well as an example of titration curve into the section analytical methods of the dossier (the example provided in the validation report are noted).

The verification of the analytical method bioburden (membrane filtration) according to Ph. Eur. 2.6.12. is provided. Since discrepancies of *Pseudomonas aeruginosa* occurred during the first verifications a second study, where the rinsing procedure is optimised and another lot of *P. aeruginosa* was used which showed recovery rates. The recovery rates of all tested reference microorganisms were in the range of 50 to 200% of the expected values. The detection limit of this method is 1 CFU/10 ml. No microbiological growth was detected in the negative controls. The Bioburden method can be considered verified. For the Endotoxin test using the determination of the specificity consists of estimate of the valid test dilution which may be used for routine analysis. The spike recovery rates of every dilution met the acceptance criterion.

Batch analysis

Batch release data for six batches, including 3 PPQ batches manufactured are provided and the data confirm that all pre-defined acceptance criteria were met at the time when implemented. The proposed acceptance criteria are based on test results obtained from a representative set of active substance batches manufactured . Data of all batches used during development are presented in section S.4.4. According to the ICH Q6B Guideline the specification should be linked to lots used to demonstrate suitability of the

manufacturing process, with lots used in preclinical and clinical studies and to analytical procedures. A HILIC method will be used for testing of future batches. This method gave different readout to the additionally employed HPAEC-PAD method, impacting the acceptance criteria. The applicant performed recalculation of the proposed acceptance criteria taking into account only the results obtained by HILIC method as requested during assessment to ensure that future batches will be comparable to PPQ batches.

The release testing panel comprises test items with quantifiable parameters, e.g. protein content, which are specified with numerical values or ranges, and complex test items, e.g. electrophoretic profile by SDS-PAGE, which are specified with descriptive definitions. For a subset of the quantifiable parameters the proposed acceptance criteria were established based on calculation of the statistical mean value and the standard deviation and calculation of the Tolerance intervals with a 95% probability that 99% of the future batches will meet the specification.

Reference materials

A two-tiered approach for reference standard management will be established whereby a secondary reference standard is used in routine tests, while a primary reference standard is used to assess the stability of the secondary standard and to bridge from one to the next reference standard. reference standard is used for release, in-process and stability testing of active substance and finished product. This reference standard was qualified against the primary reference standard. Material from the active substance batch has been extensively characterised to be used as in-house primary reference material. Methods used for characterisation were adequate to test for identity, quantity, purity and potency of the reference material. The finally approved release certificate for the primary reference material is provided. The approach for determination of the potency is clearly indicated. A qualification program for future secondary reference standards is presented. The acceptance criteria have been updated to correspond to the acceptance criteria of the revised release parameters. In addition, a strategy to define the potency of a new reference standard is proposed which is considered acceptable for Steps 1 and 2. Setting the potency of the new reference standard to 100% in routine assays if mean $\bar{x}$ is located in the range of % is appropriate. The current secondary reference standard: is derived from AS batch manufactured with process. Qualification results and the certificate of analysis of the secondary reference standard: are provided. Future secondary reference standards will be derived from representative active substance batches and must be qualified before use. The establishment report and certificate of analysis have been provided.

The formulated catumaxomab active substance is stored in bags as primary container closure system. The applicant indicated bags from exclusively. The bags are sterile, gamma-irradiated, tested for bacterial endotoxins and pyrogen-free. The fluid contact layer and connector tube comply with European Pharmacopeia. The bags used have a capacity of 5 L or 10 L and are equipped with tubing with medical pharma coupling (MPC) quick connectors to facilitate easy filling and sampling under aseptic conditions. The bags are closed with clamps (no product contact) and female MPC end caps. The fluid contact layer consists of ethylene vinyl acetate mono-material (EVAM) which is in compliance with Ph. Eur. requirements. Specification for each component and drawings of the bags are provided. Bioburden and Physicochemical tests are in accordance with Ph. Eur. 3.1.7 for contact layer The applicant indicated the critical dimensions of the AS container closure system components for both bag sizes. The container closure manufacturer conducted an extensive and comprehensive testing program on biocompatibility, mechanical and physico-chemical properties which included studies on chemical resistance, leachables/extractables, protein adsorption and the stability of stored water for injections. The primary container closure components are extensively tested in accordance with USP and Ph. Eur. For extractables/leachables a set of eight solvents has been used: The quantification of volatile and semi-volatile extractables in aqueous solutions shows very low

concentration in the range of parts per million (ppm) or micrograms per millilitre (µg/mL). Compounds released from EVA materials and detected in this study are and which are not detected at levels to be considered to have an impact on safety.

2..4.2.4. Stability

For active substance manufactured at a shelf-life of 9 months is proposed at the storage conditions 2 - 8°C. Stability data (real time) are provided for 5 representative AS batches manufactured, of which 3 PPQ batches and 2 additional batches – one GMP and one pilot batch. The applicant confirmed the container closure system used in the stability studies is equivalent/representative of the one described in section S.6. The trend in isoform distribution determined by cIEF is noted but could be accepted considering that all catumaxomab isoforms exhibit similar activity in the assay, which is also reflected by the results obtained during the stability study.

Overall, stability data are provided for a sufficient number of batches at long-term and accelerated conditions. The batches are tested for stability indicating parameters according to the proposed specification in section S.4.1 (except the different IEF method for two out of five batches). The testing frequency is in accordance with the ICH Q1A (R2) guideline.

2.4.3. Finished Medicinal Product

2..4.3.1. Description of the product and Pharmaceutical Development

Catumaxomab 100 microgram/mL is supplied as a concentrate for solution for infusion. There are two presentations of the finished product (FP), corresponding to 10 µg and 50 µg doses of catumaxomab. The 10 µg and 50 µg presentations are supplied in pre-filled 1 mL glass syringes containing a nominal volume of 100 µL and 500 µL. The composition of the finished product presentations is detailed in the Table below.

Table 2. Composition of the finished product

Name of component	Unit formula per 1 mL	Unit formula per 100 µL	Unit formula per 500 µL	Function	Reference to quality standards
Active component					
Catumaxomab	100 µg	10 µg	50 µg	Active substance	in-house
Excipients					
Tri-sodium citrate dihydrate	24.4 mg[a]	2.44 mg[a]	12.2 mg[a]	Formulation buffer/ isotonicity	Ph. Eur., USP
Citric acid monohydrate	0.1 M q.s. ad pH 5.6	0.1 M q.s. ad pH 5.6	0.1 M q.s. ad pH 5.6		Ph. Eur., USP
Water for injections	q.s. ad 1 mL	q.s. ad 100 µL	q.s. ad 500 µL		Ph. Eur.
Polysorbate 80	216 µg	21.6 µg	108 µg	Protein stabilization/ inhibition of aggregation	Ph. Eur., USP-NF

q.s. = quantum satis (as much as necessary)

a. Within the limitations of the gravimetric determination, the stated value may not correspond exactly to the actual amount used to manufacture the final dosage form since a 0.1 M sodium citrate solution is titrated with 0.1 M citric acid solution until the solution has reached a pH-value of 5.6.

Catumaxomab is an intact trifunctional antibody. Catumaxomab active substance (AS) is an aqueous solution of 100 µg/mL catumaxomab in 0.1 M sodium citrate buffer with 0.02 % polysorbate 80. The excipients for catumaxomab FP, their selection, concentration as well as their characteristics and their respective functions are based mainly on previous knowledge. All excipients comply with corresponding monographs in the current European Pharmacopoeia.

No formulation studies that evaluated the product quality attributes as a function of process parameters (for example pH, buffer type, buffer concentration, excipient, excipient concentration, and protein concentration) has been mentioned in dossier or provided. Simulated stress studies during handling and storage and formulation robustness studies were not performed either. In comparison to previous dossier (available in common repository), no such studies were provided for the first time either and no issues had been raised back then. Although this is not completely in line with current guidelines, taking into account that (1) product was marketed for a couple of years, (2) withdrawal was not connected with Q, S or E issues, (3) all pivotal non-clinical and clinical studies were conducted with the proposed formulation, (4) stability studies confirm compatibility of the AS and excipients and (4) formulation is based on well-known and commonly used substances, including known active substance, formulation development information can be in general accepted. This is based mainly on previous authorisation and life cycle of the previously authorised product. Selection of Polysorbate 80 concentration study has been performed. A protein concentration of 100 µg/mL is adequate because catumaxomab has been shown to be efficacious in very low doses. Since the product contains a combination of the polysorbate 80 surfactant and citrate as a chelator, which is known as potential contributor to LER (low endotoxin recovery) effect, studies investigating LER (spike / hold studies) were requested to be submitted. The applicant performed requested study and concluded that the product does exhibit LER effect. The applicant commits to evaluate and to propose an adequate mitigation strategy since catumaxomab is determined to be LER exhibiting product. Additionally, the applicant committed not to

release any batch before the implementation and approval of the adequate method or method supplement for bacterial endotoxin content. (REC).

Whereas the AS production of the was transferred, the manufacturer of the finished product was not changed, and only minor changes were introduced into the manufacturing process of the FP during the course of development, in parallel to the four major stages in the development of the AS manufacturing process. Considering the nature of the changes introduced, that product was already authorised and on the market and haven't been withdrawn for quality, safety or efficacy reasons, no issues are raised to the limited comparability exercises performed between the FP processes up to commercial FP process with batches. Taking into account that FP is formulated at the AS level and manufacturing process for FP thus consists of only simple steps (sterile in-line filtration of the formulated AS followed by filling and stoppering of the syringes), this approach is in general supported.

Catumaxomab 100 microgram/mL is filled into single dose containers. The established primary container closure system is a syringe consisting of the three following components: a glass barrel, a rubber plunger stopper and a closure system. The glass syringe barrel meets Ph. Eur. requirements for type I borosilicate glass containers. The rubber material of the plunger stopper and tip cap was evaluated for compatibility by analysis of material characteristics including extractable and leachable studies. The overall toxicological evaluation revealed that there is no indication of a toxicological risk associated with the identified and quantified leachables/extractables. The break loose and glide force necessary to move the plunger stopper is a measure to test the functional performance of the container closure system. This parameter was monitored during process validation and is part of the IPC testing panel during routine production. The integrity of the container closure system was demonstrated by). From a microbiological point of view the catumaxomab infusion solutions are stable for up to 8 h at ambient temperature and up to 24 h at 2 - 8°C after dilution of catumaxomab concentrate for infusion with NaCl 0.9 % solution per infusion (see SmPC). Two different commercially available catheters which were used as part of the infusion system during the clinical studies with catumaxomab, were investigated in regard to their compatibility with catumaxomab solution for infusion. The application of catumaxomab is mainly influenced by adsorption of the antibody to the inner surface of the application system. It was shown that with 10µg at least 50% of the study dose are applied, whereas with doses of 50µg and higher more than 90% of the intended dose are applied to the patient.

Although detected loss in activity in mentioned studies is significant in comparison to labelled dose and therefore compatibility from the aspect of the quality cannot be considered demonstrated, in the context of the demonstrated efficacy in the pivotal clinical study IP-REM-AC-01-DE, where product was administered over a period of 6h, and taking into account proposed indication, this finding could be considered as not critical since it doesn't impact safety and efficacy.

2..4.3.2. Manufacture of the product and process controls

is the manufacturer of the bulk finished product. The information on manufacturing sites and their responsibilities presented are detailed in the Table below.

The manufacturers and testing sites, EU MIA and GMP documents are submitted in the M1. It is acknowledged that term "bulk finished product" is explained in Module 2 as filled and fitted with the closure system and rubber stopper syringes constitute the bulk medicinal product, which is subsequently shipped to for release testing.

Visual inspection, release testing, and stability testing can be performed at different sites of the company. Secondary packaging is also performed by. The volume of a typical batch size of formulated active substance can range from 5 to 10 L.

The manufacturing process for the finished product is detailed in the flow chart below.

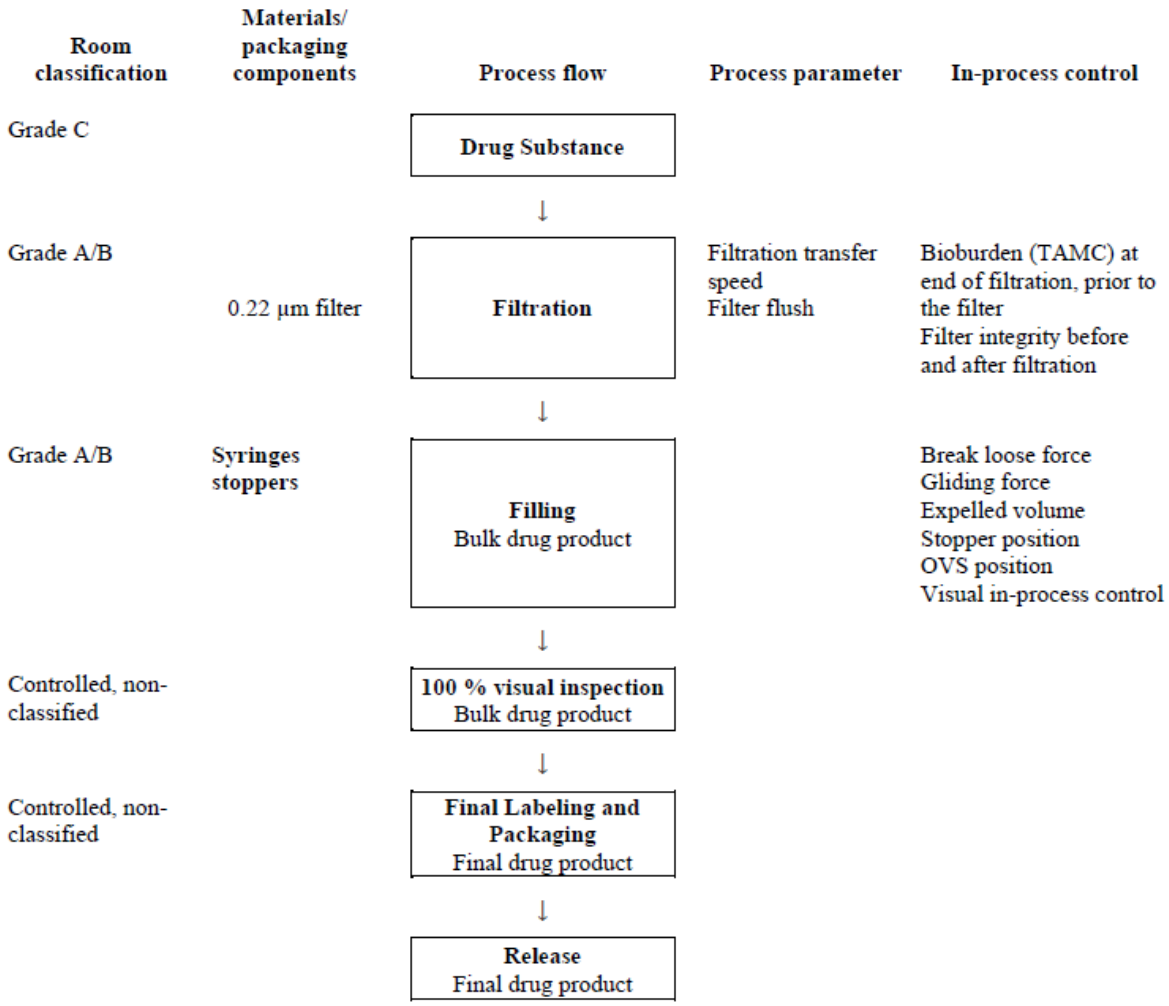


Figure 2. Finished product manufacturing flow chart

Final formulation including freezing, thawing, splitting and/or pooling is completed as part of AS manufacture. Catumaxomab FP manufacturing includes sterile filtration, filling and visual inspection. After receipt of AS by the FP manufacturer, an identification test is performed on a representative satellite sample of each bag of the AS prior to manufacturing activities. Just before filling, the solution is subjected to an in-line sterile filtration through a 0.22 µm filter into a break tank in Grade A environment using a peristaltic pump. Following the in-line filtration, aliquots of the sterile active substance solution are automatically filled into sterile syringes under nitrogen protection and are fitted automatically with plunger stoppers by the filling machine. Filling and stoppering operations are carried out under aseptic conditions in a Grade A environment. The target volumes for filling are µL and µL, respectively. The IPCs are checked at regular intervals during filling. After filling the syringes are stored at 2 - 8°C. The filled syringes are 100% visually inspected according to SOP in line with Ph. Eur. and USP requirements. Non-compliant syringes are rejected. The bulk

syringes are shipped in qualified shipment containers under controlled conditions at 2 - 8°C. The syringes are labelled with a product code, and then packed into trays. These trays are stacked and then wrapped and labelled. Critical steps are controlled by the performance of IPC and IPT tests. For analytical methods for IPC testing, which are not referred to sections S.4.2. and P.5.2., (filter integrity, brake loose and gliding forces, bioburden and expelled volume) short summary for methods concerned is provided. All operational parameters, i.e. flow rate of peristaltic pump and filter flush volume, have been assessed as being non-key operational parameters (NKOPs), i.e. they have been demonstrated to be easily controlled or have a wide acceptable limit. The process limits and acceptance criteria for IPCs/IPTs were established through process development and in consideration of the FP specification.

PPs for sterile filtration are stated as NORs and PARs and they are assigned the same value. Sufficient information is provided on PPQ batches (batch number, manufacturing date, compounding size, number of filled final containers). PPQ batches results are included in section P.5.4. The filled units underwent 100% visual inspection. The cumulative limit for critical defects (≤ 0.5%) was exceeded for the third PPQ batch. After implementing CAPAS a second visual inspection for PPQ batch no units with the identical defect were detected indicating the procedure in place is adequate. Container closure integrity was evaluated by blue dye ingress tests for one PPQ batch including both volumes of filling. Results provided confirm integrity of the container closure.

The hold times were verified on PPQ batches. Validation of filters used for sterile filtration (in addition to PPQ) encompassed bacteriostatic and antibacterial properties of catumaxomab, retention capability of the filter, compatibility of the filter and extractables and leachables. Design of the studies is considered adequate and results confirm that filters used are suitable, compatible and don't pose risk of contamination from filter material. FP batches containing AS manufactured were used, where product needed to be involved in the studies. Filter pressure study (investigating pressure correlation with the pump speed) is also summarised in the dossier, and design as presented is endorsed. Overall, the validation data in general demonstrate that the catumaxomab FP manufacturing process is consistent and reproducible. The aseptic process in the clean room (CR) site was validated by three successful consecutive media fill runs. The aseptic filling process in is re-validated at least after 6 months (+ 1 month) by media fills, which is acceptable.

2..4.3.3. Product specification, analytical procedures, batch analysis

Catumaxomab FP release and stability specifications are set according to the requirements of the ICHQ6B guideline and the Ph. Eur. monograph 2031 on "monoclonal antibodies for human use". They cover the relevant characteristics of catumaxomab FP: general tests, identity, purity, potency, protein content and sterility.

Analytical methods

The break loose and glide force necessary to move the plunger stopper is a measure to test the functional performance of the container closure system. This parameter was monitored during process validation and is part of the IPC testing panel during routine production. Compendial methods are listed. The majority of non-compendial methods is used for testing of catumaxomab AS and FP and are already described in the AS section. The only additional non-compendial method is testing for PS80 which is quantified by release of oleic acid by basic hydrolysis and subsequent determination of oleic acid by RP-HPLC and calibration standard. For bacterial endotoxin turbidimetric kinetic method (method C) is stated in the specification (section P.5.1). Validation of non-compendial methods used for testing of catumaxomab AS is discussed In the AS section.

The compendial methods are verified to demonstrate that the methods can be used under the actual conditions of use. Catumaxomab specific pre-tests are performed for Sterility and Endotoxin testing in order to exclude an inhibitory effect on the sterility-test procedure by catumaxomab and to show that there is no inhibition or enhancement of the endotoxin test method caused by interfering factors of the FP. Also, the validation of the PS80 determination indicated that the method is suitable.

Batch analysis

Batch release data for six FP batches for each strength are provided and the results show that the acceptance criteria in place were met. The applicant provided an overview on the methods used during development within section P.5.4. as requested.

Catumaxomab is formulated at the stage of active substance to obtain the final formulated bulk solution (definition: active substance) which is subject to sterile filtration and aseptic filling into syringes to manufacture the finished product. Impurities resulting from the active substance manufacturing process are classified according to ICH Q6B as process- and product-related and are discussed in detail in the AS section. Three batches of finished product () were analysed for their content of elemental impurities and evaluated according to ICH Q3D. The analytical results are reported with a reporting threshold which represents the lowest ICH Q3D threshold for the chosen doses. All three tested batches comply to the ICH Q3D limitations. evaluated potential sources within the manufacturing process which might result in potential impurities of nitrosamines and their potential chemically related substances entering the final finished product manufactured. Due the design of the manufacturing processes as well as the quality systems applied, the overall risk of a potential release of nitrosamines into the products at during production is evaluated as low. The proposed acceptance criteria are based on test results obtained from a representative set of finished product batches. The release testing panel comprises test items with quantifiable parameters, e.g. protein content, which are specified with numerical values or ranges, and complex test items, e.g. electrophoretic profile by SDS-PAGE, which are specified with descriptive definitions. The applicant committed to report appearance testing for future stability studies as now stated in finished product specification.

For equivalency of analytical methods for isoform distribution data has not been presented as such, however, results of testing by both methods for one AS batch and some of the FP batches on stability are presented in the relevant sections of the dossier. For FP as well as AS for isoform distribution only PPQ batches manufactured with AS and measured with method were taken into consideration.

Reference materials

reference standard is used for release, in-process and stability testing of active substance and finished product. This reference standard was qualified against the primary reference standard.

Container closure system

The established primary container closure system is a syringe consisting of the three following components: a glass barrel, a rubber plunger stopper and a closure system. Two different materials have contact with the product: silicone coated borosilicate glass type I and bromobutyl rubber (rubber plunger stopper and tip cap). The glass syringe barrel meets Ph. Eur. requirements for type I borosilicate glass containers. The rubber material of the plunger stopper and tip cap was evaluated for compatibility by analysis of material characteristics including extractable and leachable studies. The overall toxicological evaluation revealed that there is no indication of a toxicological risk associated with the identified and quantified leachables/extractables. Regarding the single-use pre-filled syringe, a Notified Body Opinion Request Outcome was provided but it is noted that it was concluded that neither the individual nor the assembled components of the catumaxomab PFS fall under the second subparagraphs of Article 1(8) or 1(9) of the MDR and that a Notified Body Opinion in accordance with article 117 MDR is not required. It was emphasised that the intended purpose of the device part of catumaxomab PFS is to transfer the active substance concentrate to another syringe for the preparation of a solution for intraperitoneal infusion (by a health care professional) Thus, it is used exclusively and solely for the transferring the concentrate to another syringe, it does not fall under second subparagraph of Articles 1(8) or 1(9) of the MDR.

2..4.3.4. Stability of the product

For the finished product, comprised of active substance manufactured at, stored at 5 ± 3°C, a shelf-life of 24 months is accepted based on stability profiles obtained from 24 months stability data for 6 representative batches (3 of each fill volume). Additionally, both 10 and 50 mcg product presentations were subject to accelerated (25°C) and stress testing (37°C). The applicant will continue to monitor stability of the finished product in accordance with the post-approval stability protocol.

The prepared solution for infusion is physically and chemically stable for 48 hours at 2°C to 8°C and for 24 hours at a temperature not above 25°C. From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C to 8°C, unless dilution has taken place in controlled and validated aseptic conditions.

2..4.3.5. Adventitious agents

Compliance with the TSE Guideline (EMEA/410/01 – rev.3) has been sufficiently demonstrated. The active substance of catumaxomab is produced in a serum- and protein-free culture medium. No direct animal derived material is added during fermentation of catumaxomab. The MCB which has been established is free from TSE-risk substances. The fermentation process of catumaxomab is in a serum- and protein-free medium and no animal derived material is added during fermentation minimising possible contamination by adventitious viruses. The cells used for production of catumaxomab have been sufficiently screened for viruses. These tests failed to demonstrate the presence of any viral contaminant in the MCB and PPCB of catumaxomab, with the exception of intracellular A-type and C-type retroviral particles and detection of infectious retroviruses after extended passage, which is not unexpected in murine cells. However, this is

acceptable since there is sufficient capacity within the manufacturing procedure of catumaxomab for reduction of this type of viral particles. A summary of the virus validation studies is included.

The purification process of catumaxomab includes several steps for inactivation/removal of enveloped viruses i.e. treatment at low pH, virus filtration and detergent treatment; the effectiveness of these steps has been sufficiently demonstrated. In addition, the protein A affinity chromatography step of catumaxomab also contributes to the virus safety. The removal capacity of small non-enveloped viruses is mainly based on the filtration using virus filter. Removal of the chromatography steps is virus specific and has only some effectiveness for small non-enveloped viruses such as minute virus of mice (MVM). However, this can be accepted since a screening for viruses including MVM is routinely performed at the end of the fermentation runs. The applicant`s overall approach to achieve viral safety of catumaxomab is adequate and consists of complementary approaches to control potential viral contamination:

- selecting and testing cell lines and raw materials, for the absence of undesirable viruses,
- testing the product adequate step (unprocessed bulk) of manufacturing process for absence of contaminating viruses,
- assessing the capability of manufacturing process to clear viruses.

The approach as presented in dossier is in general in line with:

- ICH Q5A (R1) Note for guidance on quality of biotechnological products: Viral safety evaluation of biotechnology products derived from cell lines of human or animal origin and
- EMA Note for guidance on virus validation studies: the design, contribution and interpretation of studies validating the inactivation and removal of viruses, (CPMP/BWP/268/95).

In summary, the virus safety of catumaxomab has been sufficiently demonstrated.

2.4.4. Discussion and conclusions on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use. During the assessment a major objection was raised on the comparability of product from sites used during the development programme, this objection was resolved during the procedure.

From the quality point of view, the application for Korjuny (catumaxomab) of Lindis Biotech GmbH is considered approvable with 2 recommendations and submission of up-dated module 3 sections with the closing sequence, as follows.

The applicant commits to determine methionine oxidation of the next commercial batch due to the limited measurements of methionine oxidation available so far and the lack of representative material. The data should be submitted for review as soon as available but no later than 12 months post approval. (REC)

The applicant commits to evaluate and to propose an adequate mitigation strategy since catumaxomab is determined to be LER exhibiting product as well as not to release any batch before the implementation and approval of the adequate method or method supplement for bacterial endotoxin content. The applicant should

provide the LER risk mitigation strategy as soon as available but no later than 12 months post approval. (REC)

In addition, the applicant will up-date with the closing sequence, the following module 3 sections as agreed during the assessment:

- The comparison of historical release data and results of extended side-by-side comparability study should be included in section 3.2.S.2.6.
- The results of homogenisation study performed at should be included in section 3.2.S.2.5.
- The results of the cleaning validation of chromatography system at should be included in section 3.2.S.2.5.
- The validation data for SE-HPLC pH 5.6 analytical method should be included in section 3.2.S.2.6.
- In section S.4.5 for isoelectric focusing the old text describing the pictures of the gel which is not presented any more still remained. This should be corrected and revised section S.4.5 submitted
- Active substance specification in section S.4.1 has been revised in accordance to the acceptance criteria for carbohydrate structures by HILIC stated in section S.4.5. and explained within response document: core F1GN1G0S0: %, core F1GN1G1S0: ≤ %, core F1GN2G0S0: %, core F1GN2G1S0: % and core F1GN2G2S0: %.
- Active substance specification in section S.4.1 has been revised in accordance to the acceptance criteria for isoform distribution by Maurice stated in section S.4.5. and within response document: AB1 isoform: %, AB2 isoform: %, AB3-5 isoforms: %.

2.4.5. Conclusions on the chemical, pharmaceutical and biological aspects

The overall quality of Korjuny is considered acceptable when used in accordance with the conditions defined in the SmPC. The different aspects of the chemical, pharmaceutical and biological documentation comply with existing guidelines.

Two Recommendations for future quality development have been made.

In conclusion, based on the review of the quality data provided, it is considered that the marketing authorisation application for Korjuny is approvable from the quality point of view.

2.4.6. Recommendation(s) for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

The applicant commits to determine methionine oxidation of the next commercial batch due to the limited measurements of methionine oxidation available so far and the lack of representative material. The data should be submitted for review as soon as available but no later than 12 months post approval. (REC)

The applicant commits to evaluate and to propose an adequate mitigation strategy since catumaxomab is determined to be LER exhibiting product as well as not to release any batch before the implementation and approval of the adequate method or method supplement for bacterial endotoxin content. The applicant should provide the LER risk mitigation strategy as soon as available but no later than 12 months post approval. (REC)

2.5. Non-clinical aspects

2.5.1. Introduction

Catumaxomab is a bi-specific mAb produced from rat/mouse hybrid hybridoma cells. The rat Fab fragment targets human CD3, the signalling component of the T cell receptor, and the mouse Fab targets human epithelial cell adhesion molecule (EpCAM), an antigen that is over-expressed on most adenocarcinomas. The Fc region composed of rat IgG2b and mouse IgG2a is able to bind and activate Fcγ RI, RIIa and RIII-positive cells; and thereby provides a 3rd functional binding site.

Information on the catumaxomab batches used in non-clinical studies are provided in the below table.

Table 3. Summary of catumaxomab batches used in non-clinical studies

Drug substance batch no.	Nonclinical studies			Clinical studies
	Pharmacology	PK	Toxicology	
process I				
101A02-P	X			
101A03-P			X	
101A04-P[a]		X	X	
101B01[b]	X			X
101C03[c]	X	X		X
process II				
101D02-P	X	X	X	
101E01			X	
101E03-1	X		X	X
101E03-2	X	X	X	X
process III				
101G02	X		X	X
advanced process III				
101H09	X		X	X

[a] Note, this batch is also known as ABT-001

[b] Note, this batch is also known as 010004

[c] Note, this batch is also known as 020005

Since the non-clinical studies had been performed to support the initial MAA of catumaxomab for Removab, the batches are derived from the initial manufacturing process (process I through to "advanced process III", the initial commercial material).

Pharmacology studies were performed with catumaxomab and the variant antibodies BiUII and BiLu (see table below).

Table 4. Characteristics of antibody variants used in the non-clinical pharmacology studies

		Anti-EpCAM (mouse IgG2a)	Anti-CD3 (rat IgG2b)	Studies
Catumaxomab	Species-specificity Parental antibody	Anti-human HO-3	Anti-human 26/II/6	*In vitro* and *in vivo* studies
BiUII	Species-specificity Parental antibody	Anti-human C215*	Anti-human 26/II/6	Early proof of concept studies
BiLu	Species-specificity Parental antibody	Anti-human C215*	Anti-mouse 17A2	*In vivo* studies in mice

** HO-3 and C215 bind to the same epitope region on human EpCAM (overlapping epitopes)*

2.5.2. Pharmacology

2..5.2.1. Primary pharmacodynamic studies

The anti-CD3 moiety of catumaxomab binds to a linear epitope in the C-terminal region of human CD3ε, while the anti-EpCAM moiety of catumaxomab (HO-3) binds to discontinuous epitopes of the EpCAM N-terminus region.

Catumaxomab was shown to bind to EpCAM-positive tumour cell lines derived from different tissues and to T cells from peripheral blood mononuclear cells as characterised by fluorescence-activated cell sorting (FACS) analysis. Catumaxomab showed a concentration-dependent binding to monocytes (CD14+), T cells (CD4+ or CD8+), NK cells (CD56+) and granulocytes; there was only minimal binding to B-cells (CD19+). When cells were pre-incubated with a different anti-CD3 antibody, the binding of catumaxomab to CD4+ and CD8+ cells was reduced (data not shown). This confirmed that binding of catumaxomab to T-cells is dependent on CD3. In addition, the ability of catumaxomab to bind to Fcγ receptors was shown. The binding via FcγR was verified by blocking catumaxomab binding by the addition of autologous serum. This is a pre-requisite for bridging EpCAM-positive tumour cells and CD3-positive T effector cells as well as accessory cells such as monocytes or NK cells.

In vitro, catumaxomab mediated concentration-dependent cytotoxicity towards EpCAM-expressing tumour cell lines from different tissue origin in the presence of human peripheral blood cells at *in vitro* concentrations ranging from 1-10 ng/mL. This lies within the same range as the concentration observed in ascites of human patients (0.2-40 ng/mL). Importantly, catumaxomab also mediated killing of patient-derived, human HNSCC in the presence of autologous PBMC.

Several Fc-dependent effector functions contribute to the catumaxomab mode of action: catumaxomab mediated dose-dependent phagocytosis of EpCAM-expressing tumour cells by macrophages. Complement dependent cytotoxicity, perforin-mediated lysis and granzyme B release also contributed to the catumaxomab-induced elimination of tumour cells. Catumaxomab caused proliferation of PBMC accompanied by a shift in the lymphocyte subpopulation to a near pure T-cell population (primarily due to an increase in cytotoxic T-cells). B-cells and NK-cells seemed to decrease.

Due to the lack of catumaxomab reactivity with murine CD3, the variant antibody BiLu (anti-human EpCAM & anti-mouse CD3) was used to demonstrate proof of concept in syngeneic mouse tumour models expressing human EpCAM. C57BL/6 mice (6 per group) were inoculated i.p. with murine B16 melanoma tumour cells (5 x 10^3 cells) transfected with human EpCAM, and then treated i.p. with BiLu or the parental antibodies or

without antibodies (controls). Treatment was initiated on Day 2 after tumour cell inoculation. A total BiLu antibody dose of 4.5 µg per animal (2.5 µg on Day 2, plus 1 µg on Days 4 and 7) resulted in 100% survival; whilst all control mice died within 28 days. The therapeutic outcome of the group that received 4.5 µg of each parental antibody was significantly worse compared to the BiLu group. The growth of untransfected B16 wild-type tumour cells (no human EpCAM expression) was not inhibited by BiLu.

In a subsequent experiment, 14 out of 18 mice treated with BiLu (10 µg on Day 2, plus 5 µg on Days 4 and 7) survived the primary B16-EpCAM tumour challenge. These mice were rechallenged i.p. with a minimal lethal dose of 750 B16-EpCAM tumour cells without the addition of BiLu on Day 144 after the first tumour inoculation. All animals survived the rechallenge, and were able to reject the tumour and were still alive on Day 300. Tumour eradication and subsequent protection of the mice after rechallenge was only observed after treatment with BiLu antibody.

Analogous experimental results were obtained with an EpCAM-transfected murine B-cell lymphoma model in BALB/c mice (groups of 7-12 mice). The A20-EpCAM tumour cells were injected i.v.; animals were treated i.p. with BiLu or F(ab')2 or the parental antibodies. A single i.p. dose of 4 µg BiLu per animal was sufficient to inhibit tumour growth, with 100% survivors. Treatment with a combination of an equimolar amount of both parental antibodies per animal led to a significantly worse outcome with 29% survivors. After administration of the bispecific F(ab')2 fragment of BiLu, no survivors were observed.

Immunisation of BALB/c mice with irradiated (5×10^4) A20-EpCAM cells and BiLu resulted in the formation of tumour-reactive antibodies only if the intact bispecific antibody (BiLu) was used. No tumour-reactive antibody formation was observed if a bispecific F(ab')2 fragment or no antibody was used for immunisation. Mice developed a humoral response against wild-type A20 cells, although A20-EpCAM cells were used for immunisation. As a consequence, an anti-tumour response against antigens other than the target antigen EpCAM had been induced. There was a strong correlation between induction of a humoral immune response with tumour-reactive antibodies and survival of mice.

This study also confirmed the trifunctional mechanism of action. Depletion of CD4-positive T-cells resulted in a reduced anti-tumour efficacy. The therapeutic outcome of the group that received the bispecific F(ab')2 fragment of BiLu was significantly worse compared to the BiLu group, which demonstrates the essential function of the intact Fc region.

In vivo pharmacology of catumaxomab was investigated in a xenograft model of malignant ascites in immuno-deficient SCID mice. Mice received a human ovarian carcinoma xenograft i.p. and were treated one day later with human PBMCs (i.p.) together with a single i.p. injection of catumaxomab. Visible tumours developed in all mice inoculated with tumour cells alone on Day 55. Injection of PBMC delayed tumour formation to Day 65. Treatment with catumaxomab or parental antibodies in the presence of PBMC further delayed tumour appearance to Day 71.

2..5.2.2. Secondary pharmacodynamic studies

Cytokine release *in vitro* [18G01018, GLP]

Whole blood samples from three healthy human donors were incubated with catumaxomab (2.5, 25 or 250 ng/mL) in the presence or absence of HCT-8 human colon tumour cells at 37°C for 2 h or 24 h. Additional samples of blood were incubated with mitogens (LPS or PHA) as positive controls. Cytokine release (IL-1β, IL-2, IL-6, IL-12 and TNF-α) was evaluated in the supernatants by ELISA. *In vitro* stimulation with catumaxomab resulted in the production of pro-inflammatory cytokines. The stimulatory effect of

catumaxomab was most prominent when catumaxomab was incubated with blood cells in the presence of HCT-8 tumour cells compared to incubation with blood cells alone. 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.

Effect of human ADA on binding of catumaxomab to tumour cells [18G01018, GLP] and cytotoxic *in vitro* [RPRE-B111006-4]

Human anti-mouse antibody (HAMA)-containing patient sera and catumaxomab were pre-incubated for 20 min before addition of EpCAM-positive HCT-8 cells or CD3-positive Jurkat cells and incubated for a further 30 min. Binding of catumaxomab was detected by FACS. HAMA-positive sera from patients (n=2) treated with catumaxomab or a combination of catumaxomab and ertumaxomab inhibited binding of catumaxomab to EpCAM-positive cells (HCT-8) and CD3-positive cells (Jurkat). The inhibitory effect of HAMA was concentration-dependent [18G01018, GLP].

A total of 18 patients were monitored for HAMA and human anti-rat antibody (HARA) during treatment and follow-up in the context of the clinical trial IP-REM-AC-01. In addition, 99 serum samples from stockmen (healthy donors with history of close contact to rats or mice) were tested. HAMA/HARA status was determined by ELISA. The effect of HAMA/HARA on the anti-tumour activity of catumaxomab was analysed by an *in vitro* neutralisation assay using EpCAM-positive HCT-8 tumour target cells and human mononuclear cells (effector cells). Serum samples were pre-incubated with catumaxomab (0.72, 0.29 or 0.12 ng/mL) for 30 min. Effector cells (human PBMC) and target cells (HCT-8) were added in an E:T ratio of 10:1 in order to detect catumaxomab-mediated cytotoxic activity. After 4 days incubation at 37°C, the residual tumour cells were quantified using an XTT assay. All of the 18 patients analysed according to the clinical trial protocol were tested negative for HAMA and HARA during the treatment phase. However, during follow-up, HAMA/HARA responses were detected in all 18 patients. Stockmen were considered to be highly exposed to murine antigens; however, the HAMA and HARA prevalence was low: 2.02% of samples were tested positive for HAMA and 17.17% were tested positive for HARA. Evaluation of the neutralising capacity of HAMA/HARA antibodies revealed that pre-existing HAMA/HARA (unrelated to catumaxomab) did not influence catumaxomab-mediated cytotoxicity *in vitro*. None of the tested samples derived from stockmen showed an effect on the cytotoxic activity of catumaxomab *in vitro* (10 positive serum samples tested). In contrast to this finding, catumaxomab-induced HAMA/HARA were able to neutralise catumaxomab-mediated cytotoxicity *in vitro* (serum samples from 9 out of 10 patients tested showed neutralising activity) [RPRE-B111006-4].

Effect of CD3 binding on lymphocytes in mice [074.429.789]

Groups of female BALB/c mice received i.v. doses of BiLu (a surrogate anti-human EpCAM x anti-mouse CD3 antibody) as in a bolus application of 10 mL/kg. The study was divided into 2 parts: Part 1 was a pilot study (15 animals/group) to determine the optimal doses and time points for use in Part 2 (48 animals/group). In Part 1, the animals in Group 1 received a single dose of 300 µg/kg and the animals in Group 2 were treated on 4 subsequent days with an increasing daily dose (20, 40, 100 and 300 µg/kg). In Part 2, all animals received single doses (30, 100 or 300 µg/kg). A total of 2 blood samples (each of 0.2 mL) were taken from each mouse. In Part 1, blood samples were taken from all mice before administration of BiLu and a single sample was taken from each mouse at 3, 6 or 72 h after the last application. In Part 2, blood samples were taken from all mice before administration of BiLu and a single sample was taken from each mouse at 4, 8, 16, 24, 48, 72, 96 or 120 h after the last application. CD3, CD4, CD8 and CD45 positive leukocytes were measured by FACS analysis. The treatment of BALB/c mice with BiLu resulted in dose-dependent transient decreases in T cell counts. There was a dose-dependent transient decrease in total CD3+ T-cells that was

apparent 4 h after application of BiLu and persisted up to 24 h post-application, after which CD3+ cell levels returned to baseline values (after 48 h). A similar effect was seen with CD4+CD3+ T helper cells (data not shown). There was also a similar transient decrease in CD8+CD3+ cytotoxic T cells that persisted for 24 h, after which the levels of these cells rebounded to values greater than baseline before recovering to baseline values by 120 h.

2..5.2.3. Safety pharmacology programme

Due to the restricted specificity of catumaxomab for human target antigens, safety aspects were assessed *in vivo* using the surrogate antibody BiLu in a secondary PD study and as part of a toxicology study (see Toxicology section). In addition, safety aspects were deduced from tissue cross-reactivity studies with normal human tissues *in vitro* and from experiments with human hepatocytes *in vitro*.

Cross-reactivity with normal human tissue [38426-991114, 075.854.662, GLP; 2654-003-D6149, GLP]

Two GLP studies have investigated the potential cross-reactivity of catumaxomab and HO-3 (the parental anti-EpCAM antibody) with normal human tissues. The tissues were from 3 unrelated donors for each study. In both studies, the assessment of human tissue integrity indicated that the panel of human tissues was viable. In addition, sections from all tissues empirically stained with H&E indicated that there were no marked nuclear or cytoplasmic indicators of autolysis. Positive staining by catumaxomab and HO-3 was achieved in positive control tissue and cells (human lymphoid tissue, blood cells and HCT-8 cells). With catumaxomab, there was specific staining of T-lymphocytes demonstrating granular membranous staining in human tonsil tissue and in the blood cell preparation. In addition, there was specific granular membranous staining of HCT-8 cells. With HO-3, there was specific granular cytoplasmic to membranous staining of HCT-8 cells. The negative controls showed no staining in any tissues. In both studies, catumaxomab demonstrated granular membranous staining of the epithelium, and, in addition, granular membranous staining of T-lymphocytes present in many of the human tissues examined; no other cell types or tissue structures in any of the tissues examined showed cross-reactivity with catumaxomab. HO-3 demonstrated granular membranous staining of the epithelium only in many of the human tissues examined; no other cell types or tissue structures in any of the tissues examined demonstrated cross- reactivity with HO-3. Binding to epithelium, via the EpCAM binding arm, with both antibodies was comparable and was found with tissues for which EpCAM expression has been described in the literature (Balzar 1999, Went 2004).

2..5.2.4. Pharmacodynamic drug interactions

Effect of steroids on antibody activity [TR-KF-0002-05, LMU-HN-0001-05]

PBMC were incubated with catumaxomab (1 - 50 ng/mL) and HCT-8 tumour cells (ratio of 5% tumour cells: PBMC) for 11 days in the presence of various concentrations (0.01 - 100 µg/mL) of dexamethasone or hydrocortisone. There was no or little effect of dexamethasone on catumaxomab-induced up-regulation of T-cell activation markers (CD25, CD69 and HLA DR). Dexamethasone (≥ 0.1 µg/mL) inhibited catumaxomab-induced release of IFN-γ, TNF-α, IL-6, IL-10, IL-2 and granzyme B. Dexamethasone (≥ 0.01 µg/mL) significantly inhibited killing of EpCAM-expressing tumour cells (HCT 8) only at a low catumaxomab concentration of 1 ng/mL. At higher catumaxomab concentration (10 and 50 µg/mL), dexamethasone (0.1 and 1 µg/mL) had only limited inhibitory effect on tumour cell killing. Hydrocortisone (≥ 1 µg/mL) showed

weaker inhibition of cytokine and granzyme B release and had no or only a weak effect on catumaxomab-induced tumour cell killing [TR-KF-0002-05].

PBMC were incubated with BiUII (10 ng/mL) and EpCAM-positive multicellular tumour spheroids (hypopharyngeal cell lines: FaDu and 22A) for 24 h in the presence of prednisolone (5 µg/mL) (LMU-HN-0001-05). Addition of prednisolone (5 µg/mL) significantly reduced BiUII-induced release of TNF-α: 82% inhibition of release from FaDu cells and 76% inhibition of release from 22A cells. Prednisolone (5 µg/mL) had no effect on BiUII-induced tumour cell killing of FaDu or 22A cells [LMU-HN-0001-05].

Effect of chemotherapeutic drugs on catumaxomab activity [RP-180405, RP-210405, RP-050906]

MKN-45 cells were incubated with 5 FU (0.0125 to 0.8 µg/mL) or cisplatin (0.0625 to 1 µg/mL) for 24 h, and then incubated with catumaxomab (0.078 to 5 ng/mL) for 48 h in the presence of PBMC (RP-180405 & RP-210405). SKOV-3 or MKN-45 cells were incubated with chemotherapeutic drugs (cisplatin plus 5-FU plus 1 µg/mL leukovorin [MKN-45], cisplatin plus paclitaxel [SKOV-3], carboplatin plus paclitaxel [SKOV-3] or cisplatin plus epirubicin [MKN-45]) for 48 h and then incubated with catumaxomab (0.156 ng/mL – 20 ng/mL) plus human PBMC for 3 days; or with catumaxomab plus PBMC for 3 days first, followed by 48 h incubation with chemotherapeutic drug (RP-050906). In all cases, catumaxomab and chemotherapeutic drug were added at an equipotent ratio (based on ED50 of each single agent) over a broad range of concentrations. The cytotoxic effect was quantified by analysis of residual surviving tumour cells (MTT assay or XTT assay), and a potential synergistic effect was determined by the method of Chou & Talalay (1984). Using the median-effect analysis by Chou & Talalay, a combination index (CI) was calculated that classifies synergy, antagonism or additive effects of catumaxomab and chemotherapeutic drugs. A CI of >1 was considered to be antagonistic and <1 was considered to be synergistic.

In MKN-45 cells, the *in vitro* cytotoxicity of catumaxomab in consecutive combination with 5-FU ($0.1<CI<0.5$) or cisplatin ($0.06<CI<0.2$) was synergistic (RP-180405 & RP-210405). This was partly confirmed in study RP-050906 as various degrees of synergy and slight antagonism ($0.03<CI<1.4$) were observed when catumaxomab was applied first (in case of 5-FU) and last (in case of epirubicin plus cisplatin). The combination of cisplatin plus paclitaxel and catumaxomab on SKOV-3 cells showed strong synergistic results for both sequences of incubation ($0.01<CI<0.07$). The results of the combination of carboplatin plus paclitaxel and catumaxomab on SKOV-3 cells were inconclusive as various degrees of synergy and antagonism ($0.2<CI<3.9$) were observed without any consistencies with regards to the concentration.

2.5.3. Pharmacokinetics

Two validated ELISA methods were developed and validated for detection of catumaxomab in mouse plasma. Both methods use the same capture and detection mAbs which target mouse IgG2a and rat IgG2b. Thus, the methods not only detect catumaxomab but also other bispecific mAbs with a mouse/rat Fc portion, such as mAb BiLu.

The assay for detection of anti-drug antibodies was developed and validated for use with human samples, but is not species-specific and was also used for detection of anti-mouse Ig and anti-rat Ig in cynomolgus samples.

Absorption

PK studies were performed in wildtype mice using catumaxomab and the variant bi-specific mAb BiLu, which detects mouse CD3. Single doses of catumaxomab or BiLu were administered either i.v. or i.p., the clinical route of administration. More specifically, comparison of PK profile was made both for i.p. and i.v. administration of BiLu and i.v. administration of BiLu and catumaxomab. Given that catumaxomab does not recognise target antigens in mice, the effect of target-mediated disposition on PK cannot be assessed. BiLu recognises only one of two human target antigens.

Upon i.v. administration into non-tumour-bearing mice, both BiLu and catumaxomab showed plasma concentration-time curves with a two-compartmental pattern. The terminal half-life (t1/2) of catumaxomab (128 hrs) was longer than the half-life of BiLu (26-84 h); overall recovery was lower for BiLu than for catumaxomab. This may be indicative of target-mediated disposition of BiLu (based on binding to murine CD3).

Upon i.p. administration, bioavailability of the antibodies was high (for BiLu in BALB/c mice, F ≥ 100%; for catumaxomab in SCID mice without human target cells, F = 82%).

The effect of human EpCAM-positive tumour cells and human PBMC on PK of catumaxomab was evaluated in a SCID mouse xenograft model, in which catumaxomab and target-positive cells were administered i.p.. Bioavailability of catumaxomab after i.p. administration (without human cells) was 82%. As may be expected, in the presence of human cells, the catumaxomab bioavailability decreased. Systemic exposure and plasma Cmax of catumaxomab correlated inversely with target cell number: the higher the number of target-expressing cells, the lower the systemic concentration of catumaxomab.

Distribution

The distribution and localisation of radio-labelled catumaxomab was evaluated following i.v. administration into SCID mice bearing EpCAM-positive tumour xenografts subcutaneously. The biodistribution of [123I]catumaxomab (anti-EpCAM x anti-CD3) was compared with a co-injected control antibody, [131I]BiZ (anti-HER-2 x anti-CD3). To determine the time course of catumaxomab localisation, mice bearing 140-320 mg tumours were injected i.v. with both labelled antibodies, and blood-perfused tissue levels of each isotope were analysed at 1 and 8 h, and on Day 1 to Day 4. Tumour uptake of catumaxomab was 12.3% ID/g (% injected dose per gram tissue) at 24 h post-injection. Tumour uptake of catumaxomab increased over the first 48 h and peaked at 15.7% ID/g; it then declined to 6.6% ID/g on Day 4. The maximum tumour uptake of control Ab BiZ was 10.5% ID/g 8 hours post-injection, which rapidly decreased to 1.7% ID/g on Day 4. There was a high uptake of both antibodies in spleen, kidney, liver and lung due to the high perfusion and blood pool of these organs. In these organs, the time-activity course of [123I]catumaxomab was similar to the control antibody (BiZ) irrespective of tumour specificity. Specific binding to tumour cells was demonstrated by the tumour localisation index.

The potential of [123I]catumaxomab for radio-imaging human tumours in SCID mice was also assessed in GHD subcutaneous xenografts (600-900 mg). Radio-imaging was conducted using a gamma camera; images were obtained daily up to 3 days after administration of radio-labelled catumaxomab. Use of gamma camera imaging demonstrated that catumaxomab effectively localises to the tumour. Maximum tumour uptake was reached 48 h post-injection and resulted in good tumour/non-tumour ratios.

Metabolism and excretion studies were not conducted.

2.5.4. Toxicology

Species cross-reactivity studies

A series of cross-reactivity studies were performed to evaluate the suitability of animal models for pharmacology and toxicology studies. Tissue cross-reactivity by immunohistochemistry was determined using selected tissues from rabbit, dog, marmoset, cynomolgus and rhesus monkeys. By flow cytometry, the binding of catumaxomab to cells from various animal species was tested. Binding to mouse EpCAM and mouse CD3 was evaluated using murine cell lines. In addition, binding of catumaxomab to peripheral blood lymphocytes from rat, rabbit, dog and several NHP species was assessed in comparison to human peripheral blood T cells. None of the studies demonstrated binding of catumaxomab to cells from non-clinical species. None of the animal species analysed is suitable for assessing the safety of catumaxomab. Any *in vivo* study with catumaxomab provides results on safety of catumaxomab with limited information for humans. Therefore, a limited toxicology programme was performed, i.e. single dose toxicity studies with catumaxomab in mice, rats and cynomolgus. Furthermore, local tolerance to catumaxomab was assessed in rabbits and abnormal toxicity was evaluated in guinea pigs and mice. In addition, a single escalating dose study was performed with the surrogate mAb BiLu in mice. Since BiLu recognises only murine CD3 but not murine EpCAM, the surrogate mAb only partially reflects the functionality of catumaxomab.

The intraperitoneal (i.p.) route of administration corresponds to the intended therapeutic use in humans. The intravenous (i.v.) route of administration is assumed to represent a maximal systemic exposure scenario for other routes of administration.

2..5.4.1. Single dose toxicity

NMRI mice (5/sex/group) were administered a single i.v. dose of catumaxomab at 0, 1.5 and 5.2 mg/kg. Animals were assessed for mortality, clinical signs, and body weight. Individual animals in the control and high-dose group were apathetic 3-5 minutes after dosing. One high-dose F had convulsions and died within minutes after dosing (without macroscopic findings). No further clinical signs were detected in any of the groups during the observation period. Body weight gain was not affected, and no macroscopic findings were observed during necropsy. The acute toxicity level (LD50) of catumaxomab in NMRI mice is > 5.2 mg/kg body weight. One of 10 mice (a female animal) died under convulsions shortly after injection. The transient apathy of animals observed shortly after injection, is considered to be vehicle-induced since this symptom was also observed in the vehicle treated animals. The single i.v. dose of 1.5 mg/kg body weight was well tolerated; all animals survived the 14-day observation period without any clinical signs [075.002.315, GLP].

Wistar rats (5/sex/group) were administered a single i.v. dose of catumaxomab at 0, 0.5 and 5 mg/kg. Animals were assessed for mortality, clinical signs, and body weight. Animals in the control group were slightly stunned within the first 5 minutes after dosing. One high-dose animal showed convulsions for about 1 minute after administration. No clinical signs were observed in the low-dose group. All animals survived the 14-day observation period without any clinical signs. Body weight gain was not affected, and no macroscopic findings were observed during necropsy. The acute toxicity level (LD50) of catumaxomab in Wistar rats is > 5 mg/kg body weight. The transient convulsions observed in one animal shortly after dosing might indicate borderline toxicity. The transient apathy of animals observed shortly after injection is considered to be vehicle-induced since this symptom was also observed in the vehicle treated animals. The single i.v. dose of 0.5 mg/kg body weight was well tolerated [075.002.314, GLP].

In a GLP escalating dose study, a single male cynomolgus was treated with i.v. infusions of catumaxomab from 1 to 300 µg/kg. No test article-related changes were observed in the parameters evaluated. TK was not evaluated as part of the study, although the development of ADA was assessed. One week after the last dose, antibodies against mouse Ig and rat Ig were detected.

The toxicity of escalating doses of BiLu (anti-human EpCAM x anti-mouse CD3) was assessed in mice [075.121.848, GLP]. Animals received vehicle or BiLu on Day 0, 3, 7 and 10, by i.v. or i.p. injection.

Noteworthy findings were observed for liver, mammary gland, spleen, bone marrow, reticulocytes and lymphocytes. The reduction in lymphocyte number can be ascribed to the pharmacology of BiLu and has been shown to be reversible in the pharmacology study 074.429.789.

In this study, the no observed adverse effect level (NOAEL) for BiLu is considered to be the low dose (0.2 to 3.0 µg/kg). This mouse dose is equivalent to the catumaxomab dose used in the clinical regimen; the maximum human dose is 100 µg (i.e. 1.43 µg/kg in a 70 kg person).

2..5.4.2. Repeat dose toxicity

Repeat-dose toxicity studies have not been performed with catumaxomab due to the lack of an appropriate animal species.

2..5.4.3. Genotoxicity

Genotoxicity studies have not been performed according to ICH S6(R1).

2..5.4.4. Carcinogenicity

Standard carcinogenicity studies are generally inappropriate for biotechnology-derived pharmaceuticals according to ICH S6. Catumaxomab does not have the potential to induce proliferation of EpCAM-positive or CD3-positive tumour cells (as demonstrated in 2° PD studies *in vitro*).

2..5.4.5. Reproductive and developmental toxicity

Studies to investigate reproductive and developmental toxicity have not been performed due to the lack of an appropriate animal species, the intended patient population with late-stage malignant disease.

2..5.4.6. Toxicokinetic data

Toxicokinetics have not been evaluated as part of the single dose toxicity studies with catumaxomab or BiLu due to the limited relevance of the non-clinical species for catumaxomab and BiLu.

2..5.4.7. Local Tolerance

Local tolerance was evaluated in two dedicated GLP studies in NZW rabbits. Both studies evaluated local tolerance to catumaxomab administered via the intended clinical route of administration (0.15 mg/animal i.p.) and to other, accidental routes of administration (0.05 mg/animal i.v., p.v., i.a., s.c., i.m.). No catumaxomab-related local intolerance reactions were observed.

In addition, local tolerance at the i.v. injection sites was assessed as part of the escalating dose studies with catumaxomab in one cynomolgus and with BiLu in mice. In both studies, no test-article related local intolerance at the i.v. injection sites was observed.

2..5.4.8. Other toxicity studies

The final purified bulk solution of catumaxomab was subjected to abnormal toxicity testing according to the Ph.Eur. [European Pharmacopoeia (1997), 3rd edition, General Chapter 2.6.9]. Mice (5/group) received a single i.p. dose of 100 or 200 µg in 1 ml i.p.; guinea pigs received a single dose of 0.5 mg or 1 mg i.p.. Animals were observed for a period of 7 days for signs of disease and body weight was determined. All animals survived and did not show any symptoms of disease. Since 2017, testing for abnormal toxicity is no longer a Ph.Eur. requirement.

2.5.5. Ecotoxicity/environmental risk assessment

Catumaxomab is a monoclonal antibody and is consequently classified as a protein. According to the Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use (EMEA/CHMP/SWP/4447/00 corr 2), amino acids, peptides and proteins are exempted from submitting an ERA because they are unlikely to result in significant risk to the environment.

2.5.6. Discussion on non-clinical aspects

Catumaxomab is a trifunctional rat-mouse hybrid monoclonal antibody that is specifically directed against the epithelial cell adhesion molecule (EpCAM) and the CD3 antigen.

The submitted non-clinical studies had been performed to support the initial MAA of catumaxomab (Removab). The catumaxomab batches used are derived from the initial manufacturing process (process I through to "advanced process III", the initial commercial material). Based on the analytical data provided with the present submission there is sufficient evidence that the materials manufactured previously (TRION process) and catumaxomab from the current manufacturing process can be considered comparable (refer to Quality section). Therefore, the non-clinical data generated with material from the TRION processes are valid for the current application.

Pharmacodynamic studies have adequately demonstrated binding of catumaxomab to its target antigens human CD3, EpCAM and human Fcγ receptors while. At the same time, absence of cross-reactivity with CD3 and EpCAM from routinely used non-clinical species (including NHPs) was established. Therefore, the non-clinical programme is based on *in vitro* studies and a tailored *in vivo* programme with catumaxomab and a surrogate mAb BiLu, that is cross-reactive with CD3 and therefore partially active in mice. This is accepted.

In vitro data show that catumaxomab can induce the production of pro-inflammatory cytokines (e.g. TNF-α, IL-6 and IL-2) in the presence of EpCAM-expressing tumour cells. This is expected given that T cell activation is part of the catumaxomab mode of action. Therefore, it is likely that catumaxomab induces a similar response in the presence of native EpCAM-expressing cells.

Catumaxomab contains a mouse and a rat IgG Fc part; thus, it is a non-human protein which can be expected to induce the development of ADA in treated patients

Indeed, in clinical trial IP-RE-AC01 almost all patients developed a HAMA/HARA response after i.p. treatment with catumaxomab. *In vitro*, anti-catumaxomab antibodies from catumaxomab-treated patients inhibited the binding of catumaxomab to its target antigens and neutralised catumaxomab-mediated cytotoxicity. Such neutralising activity of ADA may also occur *in vivo*.

The effect of antibody binding to CD3 on lymphocytes was investigated in a non-clinical *in vivo* study in BALB/c mice (without tumours) using surrogate mAb BiLu (anti-human EpCAM x anti-mouse CD3). Single administrations of BiLu at doses up to 300 µg/kg i.v. caused a transient decrease in CD3-positive T-cells (both CD4 and CD8 positive), with T cell numbers returning to normal levels by 48 hrs post-dose. Such response is a known effect of mAbs targeting CD3 administered intravenously and is likely due to T cell margination rather than T cell depletion. This non-clinical finding is consistent with clinical findings of a transient decrease in peripheral blood lymphocyte counts after administration of catumaxomab.

Catumaxomab cytotoxicity against EpCAM-positive tumour cells and the underlying mode of action was sufficiently demonstrated *in vitro* and in a xenograft model of malignant ascites in immuno-deficient mice. *In vivo* studies with the surrogate mAb in models of syngeneic tumours established the requirement of CD4 T cells and Fc-mediated effector function for an effective anti-tumour response. Potential risks associated with the use of catumaxomab were identified in secondary PD studies, i.e. cytokine release that is enhanced in the presence of EpCAM-positive tumour cells and transient lymphopenia. These risks are adequately addressed in the SmPC and the risk management plan (see Clinical safety discussion).

Due to the restricted specificity of catumaxomab to human target antigens, safety aspects were assessed *in vivo* with the surrogate antibody BiLu in a secondary PD study and as part of a toxicology study. Dedicated safety pharmacology endpoints were not included in these studies. However, catumaxomab is unlikely to affect the central nervous system as it is not expected to cross the blood-brain-barrier. Cardiovascular effects are not expected considering the lack of catumaxomab to human heart tissue in the tissue cross-reactivity study. Effects on the respiratory system would only be expected due to catumaxomab-mediated toxicity towards lung epithelium cells; this would need to be monitored in the clinic.

In tissue cross-reactivity studies with human tissues, catumaxomab demonstrated granular membranous staining of the epithelium and granular membranous staining of lymphocytes present in many of the human tissues examined; no other cell types or tissue structures in any of the tissues examined showed cross-reactivity with catumaxomab. Binding to epithelium by catumaxomab and its parental antibody HO-3 was comparable, and was found in tissues for which EpCAM expression has been described in the literature. Thus, it is likely that catumaxomab will bind to native human EpCAM-expressing tissues if accessible from the vascular bed or peritoneum.

Using *in vitro* cultures of human PBMC and EpCAM-positive tumour cells, the effect of steroids on cytokine production and cytotoxicity by catumaxomab was investigated. The studies showed that glucocorticoids not only reduce cytokine secretion, but may also reduce the anti-tumour activity of catumaxomab.

The anti-tumour activity of catumaxomab in combination with several chemotherapeutic agents was investigated in the presence of human PBMC and EpCAM-positive tumour cells. In general, catumaxomab showed synergism *in vitro* when administered in consecutive combination with several other cytotoxic drugs. However, catumaxomab is strongly dependent on a functional immune system. Thus, drugs that compromise the patient's immune system may affect the anti-tumour effect of catumaxomab.

Pharmacokinetics were derived from studies in mice using catumaxomab and the surrogate mAb, after single i.v. or i.p. administration. Due to the lack of target recognition in mice, the effect of target-mediated disposition on PK cannot be assessed. Hence, catumaxomab half-life in mice has to be interpreted with

caution as it may overestimate the half-life in humans. Nevertheless, the studies established high bioavailability after i.p. administration, which was decreased in the presence of intraperitoneal EpCAM tumour cells. A distribution study with radio-labelled catumaxomab confirmed that EpCAM does locate to tumour *in vivo*; however, given that human CD3 is not present and that mouse normal tissue is lacking human EpCAM,

Accumulation of catumaxomab in tumour tissue was demonstrated with [123I]catumaxomab in tumour xenografts; maximum uptake was observed at 48 hrs post-injection. For other organs (liver, lung, spleen, kidney, heart, intestine) the time-radioactivity courses of radio-labelled catumaxomab were comparable to that of a control antibody not binding to EpCAM. With this study, proof-of-concept was provided that catumaxomab binds to EpCAM-positive tumour cells *in vivo*, although localisation of tumour (SC) and route of administration do not correspond to the clinical setting. Furthermore, considering that human CD3 is not present in these mice and, that mouse normal tissue is lacking human EpCAM, the distribution data have limited value for the situation in patients' malignant ascites.

Metabolism and excretion studies were not conducted, since monoclonal antibodies are expected to be catabolised into peptides and amino acids.

The applied dosing schedule in the GLP study 075.121.848 resembles the clinical dosing schedule and is in line with "step-up-dosing" employed for other T cell-engaging bi-specific antibodies. The present study indicates that liver may be a target organ of toxicity, although liver findings were only observed in animals treated i.p. and not i.v.. Given that BiLu does not bind to murine EpCAM, the mechanism underlying the liver findings is unclear. However, given that increases in liver parameters have also been observed clinically, a warning statement and a recommendation for monitoring of liver parameters is included in the SmPC (section 4.4).

Catumaxomab was well tolerated at the lower dose levels (1.5 mg/kg in mice, 0.5 mg/kg in rats). However, mortality of a single high-dose female mouse was observed shortly after dosing at 5.2 mg/kg and convulsions in a single high-dose rat (5.0 mg/kg) immediately after administration. Extrapolation of these non-clinical findings to humans is limited, given that catumaxomab is not pharmacologically active in rodents.

Overall, the safety assessment for catumaxomab is hampered by the lack of a relevant animal species. By using the surrogate mAb BiLu the applicant tried to overcome this problem. However, also BiLu is only partially active in mice (anti-mouse CD3). Thus, an important issue, reactivity of catumaxomab against non-tumour cells expressing EpCAM cannot be addressed. Therefore, the results from the toxicity studies performed with both catumaxomab and BiLu have only limited relevance and predictive value for the clinical situation. However, taking into account the available clinical experience with catumaxomab at the current stage of development, additional studies with a surrogate mAb that recognises both CD3 and EpCAM in a non-clinical species are not warranted.

Based on the available information from the non-clinical part the below text is reflected in the SmPC.

Women of childbearing potential: Korjuny is not recommended during pregnancy and in women of childbearing potential not using contraception.

Pregnancy: There are no or limited amount of data from the use of catumaxomab in pregnant women. Animal studies are insufficient with respect to reproductive toxicity.

Breast-feeding: It is unknown whether catumaxomab/metabolites are excreted in human milk. A risk to the newborns/infants cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Korjuny therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility: No data on the effect of catumaxomab on fertility are available.

The active substance is a natural substance, the use of which will not alter the concentration or distribution of the substance in the environment. Therefore, catumaxomab is not expected to pose a risk to the environment.

2.5.7. Conclusion on the non-clinical aspects

Overall, the non-clinical studies provided are adequate to support the MAA of catumaxomab in the applied indication.

2.6. Clinical aspects

2.6.1. Introduction

GCP aspects

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

The applicant has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Table 5. Tabular overview of clinical studies

Study ID	Indication	Phase	Study design	Catumaxomab doses	Infusion	Route	Patients	Premedication
Studies in malignant ascites								
IP-REM-AC-01 (06 Sep 2004-3 Nov 2006)[3]	MAs due to epithelial cancers	II/III	R, C, OL	10-20-50-150 µg	6-h	i.p.	Total: 245 Cat: 157 CatCr: 46	Paracetamol 1000 mg 30 min before each IMP admin., +500 mL 0.9% NaCl i.p.[2]
STP-REM-01 (12 Nov 2001-8 May 2003)	MAs due to OCa	I/II	OL, UC, DE	5-10-10-10 µg 10-50-50-50 µg 10-20-50-50 µg 10-20-50-100 µg 10-20-50-200 µg 10-20-50-200-200 µg	6-h	i.p.	23	At 30 min before infusion start: paracetamol 1000 mg in the first 4 pts; additionally 500 mL Ringer solution in the next 2 pts. Per AM2, addition of dexamethasone 20 mg i.v. in case of liver enzyme increase ≥G3 or persistent fever >39°C on D1 after infusion without signs of infection. Per AM3, DSB to decide use of dexamethasone or antihistamines.
IP-REM-PK-01-EU (11 Nov 2005-7 Nov 2006)	MAs due to epithelial tumours	II	OL, UC	10-20-50-150 µg	6-h	i.p.	13	Paracetamol 1000 mg +500 mL 0.9% NaCl i.p. 30 min before IMP admin.[2]
IP-REM-AC-02-US (25 Jul 2006-13 Nov 2009)	MAs due to OCa	II	OL, UC	10-20-50-150 µg	3-h	i.p.	32	Ibuprofen 400 mg + 500 mL 0.9% NaCl 30 min before IPM admin., +single dose of a 5-HT3 antagonist 2 h after each infusion[2]
Studies in other indications								
AGO-OVAR-2.10 (17 May 2004-11 Aug 2005)	OCa	IIa	R, OL, UC	10-10-10-10 µg 10-20-50-100 µg	6-h	i.p.	41	Paracetamol 1000 mg p.o. +500 mL 0.9% NaCl i.p. 30 min before IMP admin.
IP-REM-PC-01-DE (18 Aug 2003-1 Aug 2005)	Peritoneal carcinomatosis due to epithelial GI malignancies	I	OL, UC, DE	10-10-30-50 µg; 6-h 10-20-50-100 µg; 6-h 10-20-50-200 µg; 6-h 10-20-100-200 µg; 6-h 10-20-50-200 µg; 3-h 20-50-100-400 µg; 3-h +dexamethasone 40-100-200-800 µg; 3-h +dexamethasone	3/6-h	i.p.	24	Paracetamol 1000 mg p.o. +1000 mL NaCl i.p. 30 min before IMP admin., + dexamethasone 10 µg in 2 cohorts
IP-REM-GC-01 (13 Sep 2005-23 Apr 2007)	Intraabdominal epithelial tumours	I	OL, UC, DE	5-20-50-150 µg 10-20-50-150 µg 20-10-20-50-150 µg 20-10-20-50-150 µg	3-h	i.p.	12	Paracetamol 1000 mg i.v. (intraoperative)/p.o. (postoperative) or other (NSAIDs), 30 min before IMP admin.
IP-CAT-OC-01 (21 Sep 2006-15 Feb 2008)	OCa; CR to chemotherapy	II	OL, UC	10-20-50-150 µg	3-h	i.p.	47	Ibuprofen 400 mg + 500 mL 0.9% NaCl 30 min before IPM admin., +single dose of a 5-HT3 antagonist 2 h after each infusion
IP-CAT-OC-02 (23 Nov 2007-8 Aug 2008)	OCa	II	OL, UC	10-10-20-50-150 µg	3-h	i.p.	41	Paracetamol 1000 mg i.v. (intraoperative)/p.o. (postoperative) 30 min before IMP admin. (alternative NSAIDs allowed) + 500 mL 0.9% NaCl i.p.
IP-REM-GC-02 (14 Jun 2006-22 Jun 2009)	GCa; curative resection	II	OL, R, C	10-10-20-50-150 µg	3-h	i.p.	Total: 55 C: 28	Paracetamol 1000 mg i.v. 30 min before intra-operative admin.; 500 mL 0.9% NaCl i.p., followed by IMP admin. At IMP Infusions 2-5, 1000 mg paracetamol (or other NSAID) p.o. 30 min before IMP admin.+ 500 mL 0.9% NaCl i.p.[2]
IP-CAT-GC-03 (14 Jul 2007-27 Apr 2009)	GCa; curative resection	II	OL, UC	10-10-20-50-150 µg	3-h	i.p.	54	Paracetamol 1000 mg i.v. 30 min before intra-operative admin.; 500 mL 0.9% NaCl i.p., followed by IMP admin. At IMP Infusions 2-5, 1000 mg paracetamol (or other NSAID) p.o. 30 min before IMP admin.+ 500 mL 0.9% NaCl i.p.

Study ID	Indication	Phase	Study design	Catumaxomab doses	Infusion	Route	Patients	Premedication
IPL-REM-PL-01-DE (6 Oct 2004-21 Nov 2005)	Pleural effusion	II	OL, R, U	5-10-20 µg 10-20-50 µg 20-50-100 µg	3-h	i.pl.	24	Paracetamol 1000 mg p.o. or as suppository 30 min before IMP admin.; optional: antihistamines; followed by 100 mL 0.9% NaCl intrapleurally
IV-REM-01-DE (3 Dec 2001-18 Dec 2003)	NSCLC	II	OL, UC	Single doses of 2, 5, 10, 15, 20 µg[1]	8-h	i.v.	24	MTD to be determined separately without and with premedication (paracetamol 500 mg suppository; clemastine 2 mg i.v., cimetidine 5 mg/kg i.v., dexamethasone 40 or 10 mg, given 30 min before IMP admin.)

Abbreviations: admin.= administration; AM= amendment, C= controlled; Cat= catumaxomab; CatCr= catumaxomab crossover; CR= complete response; D= Day, DE= dose escalation; DSB= Dose Steering Board; G= CTC(AE) grade, GCa= gastric cancer; GI= gastrointestinal; IMP= investigational medicinal product; i.p.= intraperitoneal; i.pl.= intrapleural; i.v.= intravenous; MAs= malignant ascites; MTD= maximum tolerated dose; NSAID= non-steroidal antiinflammatory drug; NSCLC= non-small cell lung cancer; OCa= ovarian cancer; p.o.= oral; OL= open-label; R= randomised, UC= uncontrolled

[1] Additional dose levels were planned to be tested. The study was prematurely discontinued after the first patient treated in the 10 µg cohort died of drug-related acute liver failure (see Section 6.3), so that higher dose levels were omitted from testing.

[2] Premedication with corticoids or antihistamines was prohibited

[3] Including main study period and crossover period

2.6.2. Clinical pharmacology

2..6.2.1. Pharmacokinetics

Catumaxomab is intended for local treatment of the peritoneal cavity. The efficacy is assumed to be mediated primarily via local cell reactions. Thus, pharmacokinetic data on systemic exposure to the active substance are mainly used for the safety evaluation.

The proposed dosing regimen consists of a single treatment cycle of four i.p. infusions at doses of 10 µg on Day 0, 20 µg on Day 3, 50 µg on Day 7 and 150 µg on Day 10. The recommended infusion time is 3-hr.

Results on the characterisation of catumaxomab concentrations in ascites fluid and plasma following i.p. administration were mainly obtained from study IP-REM-PK-01-EU in patients with malignant ascites due to epithelial cancer. Limited PK information was also retrieved from studies IP-REM-PC-01-DE and AGO-OVAR-2.10. There are no data on catumaxomab from healthy volunteers. Analysis of free catumaxomab in plasma and ascites was made using a validated ELISA method.

In all clinical studies, patients were monitored for the development of anti-drug antibodies against the chimeric rat/mouse catumaxomab (HAMA, HARA). Systemic cytokine levels were also assessed in all clinical studies as safety-related pharmacodynamics. Immunogenicity data were collected from all catumaxomab studies as tabulated above.

Three different ELISA tests were developed and validated for detection of HAMA/HARA antibodies against catumaxomab:

- the Gallati test for detection of antibodies against rat and mouse immunoglobulins
- the Medac test for detection of antibodies against mouse immunoglobulin (a commercially available test validated by the manufacturer)
- the more sensitive double antigen binding assay (DABA) for detection of the catumaxomab-specific subset of HAMA/HARA

After demonstrating a correlation of Gallati and Medac, the Medac test was used alone for the routine monitoring of patients (data on correlation not shown).

Pharmacokinetic data analysis applied standard non-compartmental analysis. Dataset distributions were described by mean and SD as well as median and minimum-maximum values. No inference tests have been applied.

Absorption

Study IP-REM-PK-01-EU was a phase II, open-label study in patients with malignant ascites due to epithelial tumours. Patients received catumaxomab as 6-hr constant-rate i.p. infusion at ascending doses of 10, 20, 50, and 150 µg. Study drug was administered on Days 0, 3, 6, and 10, always after a preceding removal of ascites fluid via an indwelling catheter that was placed prior to the first study drug administration. PK parameters of free catumaxomab in plasma and ascites fluid were assessed after the 3rd and 4th intraperitoneal infusions. Initial plasma PK analyses showed implausibly high catumaxomab concentrations at timepoints after the termination of treatment in some patients, which were due to an interference of anti-drug antibodies (ADA) (i.e., Human anti-mouse antibodies, HAMAs and Human anti-rat Antibodies, HARAs) with the catumaxomab assay. Therefore, all ADA-positive samples were re-analysed by a modified and validated method, using a specific HAMA/HARA blocking agent. Despite the use of the HAMA/HARA blocking agent, however, some re-analysed samples still showed pharmacokinetically and analytically implausible increases in systemic catumaxomab concentration after termination of treatment. To account for these technical and analytical difficulties, the following PK data sets were defined:

- Data set I ("maximum possible exposure set") includes the *implausible* data from the re-analysed ADA-positive samples as well as *all* data from ADA-negative samples.
- Data set II ("pharmacokinetically plausible set") includes only the *plausible* data from the re-analysed ADA-positive samples starting at the third catumaxomab infusion, as well as *all* data from ADA-negative samples.

Catumaxomab in ascites fluid

A total of 13 patients were enrolled in the study: 2 male and 11 female patients. The mean age was 58.2 years and the mean weight was 68.2kg. Nine patients had a diagnosis of ovarian cancer, three of pancreatic cancer, and one had gastric carcinoma. Eleven patients received four i.p. infusions of catumaxomab and two patients received three i.p. infusions of catumaxomab. Catumaxomab was detected in the ascitic fluid of all but one evaluable patient following the first infusion (10 mg). Predose (C_{trough}) concentrations of free catumaxomab were measured only until before the fourth infusion. Predose catumaxomab concentrations in ascites varied from 0.27 to 39.9 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. Concentrations after the fourth infusion are likely much higher. However, there was no analysis of presence of anti-catumaxomab antibodies in ascites.

Catumaxomab in plasma

Catumaxomab was detectable in plasma in 10 of 11 patients after the 3rd and 4th peritoneal infusions. The variability between subjects was high. In patients included in Data set II, the geometric mean plasma AUC was 1.7 day*ng/mL, ranging from indeterminate to 13.4 ng/mL. The corresponding geometric mean plasma

C_{max} was 0.5 ng/mL (range 0 to 2.3 ng/mL). The geometric mean apparent terminal plasma elimination half-life ($t_{1/2}$) was 2.5 days (range 0.7 to 17.5 days). These parameters were determined after a 6-hr infusion. Additional PK data from a dose finding study (IP-REM-PC-01-DE, n=5) in a very limited number of patients receiving the 3-hr infusion confirm the expectation that a shorter infusion time will lead to higher plasma C_{max} and thus might be lead to higher cytokine response and higher anti-catumaxomab antibodies.

There are no studies on distribution, elimination mechanisms or pharmacokinetics in patients with organ impairment and no pharmacokinetic interaction studies.

There was no obvious relationship between catumaxomab plasma concentrations and cytokine release in the pharmacokinetic study, but PK data are limited (data not shown).

The overall plasma PK parameters for data set II is tabulated below:

Table 6. PK of catumaxomab in plasma, study IP-REM-PK-01-EU, Data set II

	$AUC_{0\text{-tlast}}$ [day pg/mL]	C_{max} [pg/mL]	$C_{max,3}$ [pg/mL]	$C_{max,4}$ [pg/mL]	λ [day^{-1}]	$t_{1/2}$ [days]
n	11	11	11	11	8	8
Mean	3512	692	207	682	0.36584	4.05
SD	4341	756	343	759	0.26976	5.51
Minimum	0	0	0	0	0.03961	0.73
Median	2270	431	0	420	0.31713	2.19
Maximum	13448	2290	1108	2290	0.94406	17.50
gMean	-	-	-	-	0.27453	2.52
gMean >0	1700	489	353	478	-	-
%CV% >0	392.05	134.51	90.08	134.63	-	-
%CV	-	-	-	-	115.75	115.75

Abbreviations: $AUC_{0\text{-tlast}}$= area under the concentration-time curve from the time of Infusion 3 to the last measurement time point (i.e. concentration >LLOQ) of Data set II; $C_{max,3}$= C_{max} after Infusion 3 ($C_{max,4}$ was calculated accordingly for Infusion 4); C_{max}= maximum of $C_{max,3}$ to $C_{max,4}$; CV= coefficient of variation; λ= apparent terminal elimination rate constant; SD= standard deviation; $t_{1/2}$= apparent terminal elimination half-life

For one patient (no. 805/101), quantifiable catumaxomab concentrations could not be determined in plasma; therefore, gMean PK values were in the CSR partially displayed as gMean >0.

Source data: IP-REM-PK-01-EU CSR Corrigendum 12 Sep 2007, Appendix A1 Table 35.4

Based on Data set I (i.e. including all data), gMean $AUC_{0\text{-tlast}}$ was 3728 day pg/mL (patients with gMean >0), C_{max} was 760 pg/mL, and median $t_{1/2}$ was 3.33 days. Thus, in terms of exposure, the values for the PK parameters calculated using all data (i.e. including the implausible values of Data set I) resulted in higher means.

Infusion time

The infusion time in the pharmacokinetic study was 6-hr instead of the proposed therapeutic use with a 3-hr infusion time. Limited data using a 3-hr infusion are available from study IP-REM-PC-01-DE in patients with peritoneal carcinomas due to gastrointestinal (stomach, colon, pancreas) malignancies (non-malignant ascites). PK data were available from 5 of the 6 patients from Groups V and VI who received all four 3-hr infusions. In this study, catumaxomab was determined without ADA blocking agent. The mean and median plasma concentration of catumaxomab was 705.9 and 187.4 pg/mL, respectively, before Infusion 4, and 697.2 and 1742.9 pg/mL, respectively, at 24-h after Infusion 4. Median C_{max} in IP-REM-PK-01 was 489 pg/mL, C_{max} values after Infusions 3 and 4 were 353 and 478 pg/mL, respectively. Maximum plasma

concentrations in study IP-REM-PC-01-DE were 16880 pg/mL which is approximately 7-times higher compared to the maximum plasma concentration measured in study IP-REM-PK-01.

Distribution

Plasma and ascites data from 11 patients receiving the proposed 4 doses of catumaxomab but as 6-hr i.p. infusion (instead of 3-hr) were submitted.

Catumaxomab was detectable in plasma in 10 of 11 patients after the 3rd and 4th peritoneal infusions (50 µg and 150 µg). Total systemic exposure (in terms of median area under the concentration-time curve from dosing of the third dosing interval to the last measurement timepoint; $AUC_{0\text{-}tlast}$) was 1700 day pg/mL (for patients with gMean >0) (Table 6, based on Data set II). Median C_{max} overall (for patients with gMean >0) was 489 pg/mL, C_{max} values after Infusions 3 and 4 for patients with gMean >0 were 353 and 478 pg/mL, respectively. Median $t_{1/2}$ was 2.19 days.

In ascites, only predose (C_{trough}) concentration of free catumaxomab were measured, and only until before the 4th infusion. Predose catumaxomab concentration (C_{max}) in ascites varied considerably from 272 to 39912 pg/mL (no blocking agent was used).

Elimination

No specific studies on metabolism or excretion have been performed. The metabolism and elimination of catumaxomab is similar to endogenous IgG i.e. primarily via proteolytic catabolism throughout the body without relying primarily on elimination through the kidneys and liver.

Dose proportionality and time dependencies

Dose proportionality in plasma could not be determined. In study IP-REM-PK-01-EU there was a trend of increasing plasma concentrations with the higher i.p. doses in period 3 and 4.

Development of anti-catumaxomab antibodies

In several studies, ADAs were detected at screening, but in individual patients only. Some studies implemented ADA sampling already during the catumaxomab infusion period. In studies IP-REM-PK-01-EU and IP-REM-AC-02, 30-40% of patients were ADA positive at Day 10 or 11 (around Infusion 4). However, in pivotal study IP-REM-AC-01, <10% of patients were ADA positive before Infusions 3 or 4. In AGO-OVAR-2.10, around 30% of patients were ADA positive 24 h after Infusion 4 in the high dose group (10-20-50-100 µg i.p.), vs only 6% of patients in the low dose group (10-10-10-10 µg).

At Day 8 after Infusion 4, as many as 70-80% of patients were ADA positive (studies IP-REMAC-01, IP-REM-AC-02), or even >90% in study IP-CAT-OC-01. At 28 to 30 days after the last infusion, 90-100% of patients were ADA positive across the studies. Few studies had also late ADA sampling time points. In IP-REM-AC-01, 80-90% of patients were still ADA positive at therapeutic puncture, which happened after a median duration of 71 days in ovarian cancer patients and 80 days in nonovarian cancer patients. In IP-REM-AC-02 and IP-CAT-OC-01, up to 100% of patients were ADA positive 180 days after the last infusion.

Additional information is available from literature, including ADA data in ascites. Study IPCAT-AC-03 was a Phase IIIb open-label, randomised (catumaxomab vs catumaxomab + prednisolone) study in >200 patients with malignant ascites of catumaxomab 10-20-50-150 µg i.p. as 3-hr infusion. All patients were ADA negative at screening. During the catumaxomab infusion period, plasma samples were ADA positive in up to 15% of patients, and ascites samples were ADA positive in up to 2%. At Days 8 as well as 28 after treatment, 100% of plasma samples were ADA positive. At therapeutic puncture, ascites samples were ADA

positive in 67% of patients (Pietzner 2014); median time to puncture was 102 days for catumaxomab and 78 days for catumaxomab+ prednisolone (hazard ratio [HR] 0.901) (Sehouli 2014). Patients from IP-CAT-AC-03 could roll over into IP-CAT-AC-04 to receive a second cycle of catumaxomab (10-20-50-150 µg i.p. as 3-hr infusion). All evaluated patients (n=6) were ADA positive in ascites and plasma at screening (i.e. after a first course of catumaxomab in study IPCAT-AC-03) and remained ADA positive until the end of study IP-CAT-AC-04. ADA levels were consistently higher in plasma than in ascites, although this is not further quantified in the article (Pietzner 2014).

The neutralising potential of ADAs from catumaxomab treated patients from the pivotal study was assessed *in vitro*. Samples were taken from 18 patients and analysed by *in vitro* neutralisation assay using EpCAM+ HCT-8 tumour cells (target cells) and human PBMCs (effector cells). All 18 patients were ADA negative during the treatment phase, but thereafter became ADA positive. Catumaxomab-induced ADAs from 9/10 patients with results were shown to neutralise catumaxomab-mediated cytotoxicity *in vitro*.

Formal subgroup analyses of safety by ADA status have not been performed. The majority of patients developed ADAs in response to catumaxomab treatment. Thus, the safety of catumaxomab as described in this MAA is for a generally ADA positive patient population. There were no safety signals detected regarding infusion reactions, anaphylaxis, immune complex-mediated diseases, or more serious AEs with catumaxomab that might potentially be a consequence of ADAs.

Special populations

There were no studies investigating intrinsic factors and special populations. From the 11 subjects in the PK part there were 9 below the age of 65 and 2 in the age range of 65-74.

Pharmacokinetic interaction studies

No *in vitro* or *in vivo* pharmacokinetic drug-drug interaction studies have been performed.

Pharmacokinetics using human biomaterials

No dedicated studies have been performed.

Exposure relevant for safety evaluation

For an estimate of "maximum possible plasma exposure" Data set I (including implausibly high values), was used. The geometric mean total exposure according to Data set I ($AUC_{0\text{-}tlastI}$) was considerably higher than for Data set II. The geometric mean of values above zero was 3.7 ng*day/mL for Data set I vs. 1.7 ng*day/mL for Data set II. However, the maximum value was the same for Data set I and II (from below LLOQ up to 13.4 ng*day/mL). Similarly, mean above zero C_{max} values for Data set I were higher than for Data set II but maximum values were identical (0.76 ng/mL Data set I compared to 0.49 ng/mL for Data set II, maximum value Data set I and II: 2.3 ng/mL). The mean $t_{1/2}$ for Data set I was 5.36 days and 4.05 days for Data set II. Again, maximum values were identical (17.5 days).

2..6.2.2. Pharmacodynamics

The pharmacodynamics of catumaxomab has been subject to investigation in 4 different trials is patient suffering from various primary cancers and malignant ascites. Additional PD results are available from 9 studies with non-malignant ascites. Additional 2 studies (CASIMAS, SECIMAS) have been submitted with published results.

The most important *in vivo* pharmacodynamics parameters have been:

- Number of EpCAM+ tumour cells in malignant ascites
- Ratio between EpCAM+ tumour cells and CD45+ leukocytes
- Expression of T cell activation markers CD69 and IFN-γ
- Systemic cytokine levels (+ Post-hoc cytokine levels in ascites – Jaeger et al. 2012)
- Also *in vitro* pharmacodynamics activity as well as ADA evaluation has been performed.

Sufficient number of immune cells for the effect of catumaxomab are present in ascites in patients, provided they have not had cytostatic therapy very recently. An interval of 4 weeks from last chemotherapy to catumaxomab treatment seems to be quite sufficient for the claimed effect of catumaxomab.

Mechanism of action

Catumaxomab is a non-humanised hybrid rodent antibody (mouse heavy chain IgG2a and rat IgG2b) directed against human CD3 on T lymphocytes (rat Fab) and human EpCAM (mouse Fab) and contains a hybrid Fc portion targeting Fc receptor I and III positive accessory cells. Its host specificity (human) makes the use of animal models to further explore primary and secondary pharmacodynamics, other than in xenograft models, less informative.

Destruction of malignant cells as causal treatment of this symptom has been considered a mechanism to reduce ascites.

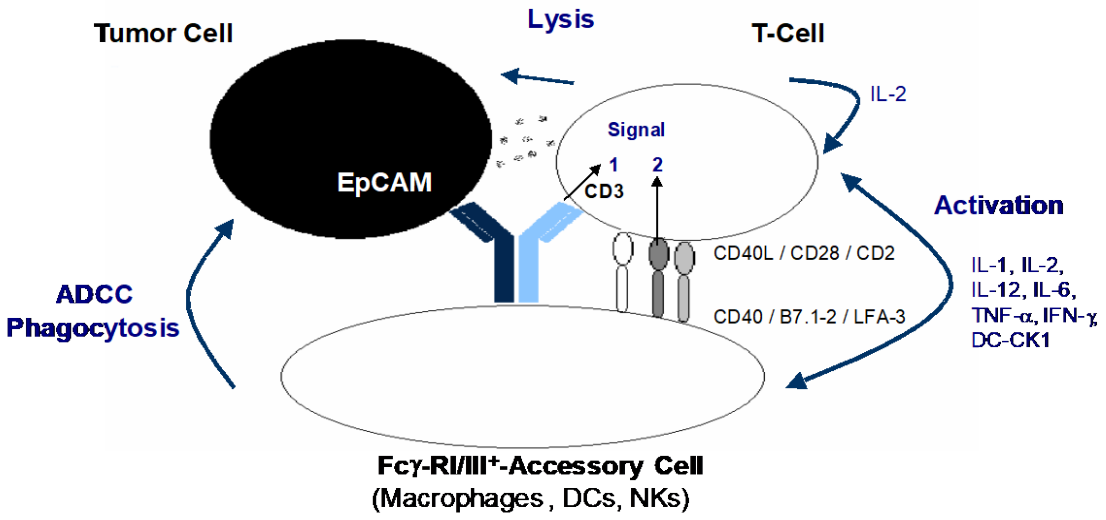


Figure 3. The postulated tricell-complex: Catumaxomab mediates the recognition and elimination of tumour cells by different immune cells

Primary and Secondary pharmacology

Primary pharmacology

In vitro PD

Catumaxomab appeared potent and active in *in vitro* systems at concentrations <10 ng/mL. In summary, the antitumor activity of catumaxomab appears to be dependent on the presence of PBMC. It includes

immunostimulatory effects such as activation of T cells in the presence of tumour cells, stimulation of cytokine release from blood cells, granzyme B release (T cells) and perforin-mediated lysis which promotes lysis of tumour cells. Binding of catumaxomab at the FcγR (I and III) can possibly contribute to activation of FcγR positive accessory cells and tumour cell killing, by direct phagocytosis (ADCP). Catumaxomab-induced ADCP by macrophages is dependent of EpCAM expression on tumour target cells. Catumaxomab also activates antigen-presenting dendritic cells and NK cells. In addition, complement-dependent cytotoxicity may also contribute to the antitumor activity of catumaxomab at high local antibody titre.

In vivo clinical PD

In vivo pharmacodynamics in humans was investigated in samples of human ascites from clinical trials by:

1) determination of EpCAM+ tumor cell/CD45+ leukocyte ratios in ascites and expression of EpCAM RNA by RT- PCR

Table 7. Results of the cross study analysis of EpCAM/CD+45 ratios

Timepoint	**Statistic**	**EpCAM+ tumor 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 EpCAM+ tumor cell / CD45+ leukocyte ratio decreased between screening and the second and fourth infusions of catumaxomab, reaching a median of 0 before the fourth infusion.

Table 8. In vitro incubation of malignant ascites fluid with and without catumaxomab

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.

In Study IP-REM-AC-01, the median EpCAM+ tumour cell count decreased in samples with catumaxomab compared to the samples without catumaxomab in both cancer strata.

In Study IP-REM-PK-01-EU, the results are limited due to the small number of patients included.

The median CD45+ leukocyte count increased in samples with catumaxomab compared to samples without catumaxomab in Study IP-REM-PK-01-EU and in the ovarian cancer patients in Study IP-REM-AC-01.

In the non-ovarian-cancer patients, there was no relevant increase in CD45+ leukocytes in samples incubated with catumaxomab.

2) measurement of activation markers on T-cells

Table 9. Results of the cross-study analysis of activation markers

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.

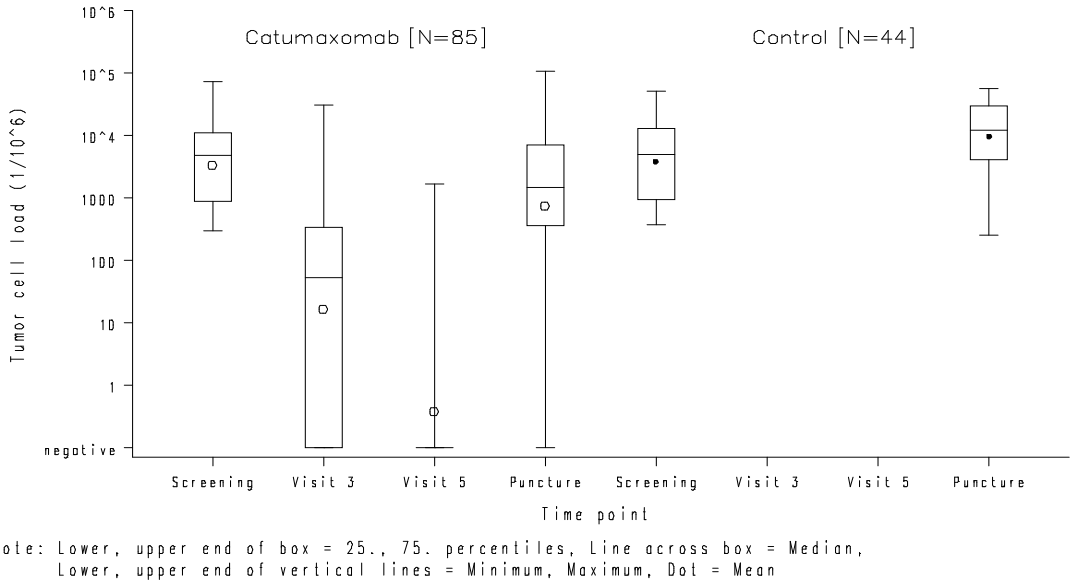
The median percentages of CD45+ CD4+ T cells and CD45+ CD11c+ monocytes/macrophages expressing CD25 did not indicate a relevant change compared to screening before either the second or fourth infusions, or at therapeutic puncture. In Study IP-REM-AC-01, there were no relevant differences between the treatment groups (paracentesis plus catumaxomab vs. paracentesis alone) at screening and at the puncture visit for either cell type. The median percentage of HLADR-expressing CD45+ CD8+ T cells increased between screening and the fourth infusion in patients receiving catumaxomab. In Study IP-REM-AC-01, there were no relevant differences between the treatment groups (paracentesis plus catumaxomab vs. paracentesis alone) at screening and at the puncture visit.

The median percentages of CD45+ CD4+ and CD45+CD8+ T cells showing T cell activation marker CD69 increased steadily during the treatment period in patients receiving catumaxomab. At therapeutic puncture, the median percentages of both T cell types with CD69 expression returned to baseline (IP-REM-AC-01: CD45+ CD4+ and CD45+ CD8+ T cells in ovarian cancer patients and CD45+ CD4+ T cells in non-ovarian cancer patients) or decreased to elevated levels (IP-REM-PK-01-EU: CD45+ CD4+ and CD45+ CD8+ T cells; IP-REM-AC-01: CD45+ CD8+ cells in non-ovarian cancer patients).

Systemic cytokine production in all studies

Across studies, increases in IL-6 were observed between baseline and after infusion of catumaxomab, with no clear dose relationship. Increases, or clear trends towards increases, after infusion of catumaxomab were also observed in TNF-α, IL-10, and IFN-γ, despite a high inter-individual variability. IL-2 and IL-4 remained relatively unchanged or were only slightly increased after infusion of catumaxomab.

3) Tumour load was determined in ascites samples in catumaxomab-treated patients and controls (in study IP-REM-AC-01). Ovarian cancer patients (full analysis set)



Note: Lower, upper end of box = 25., 75. percentiles, Line across box = Median,
Lower, upper end of vertical lines = Minimum, Maximum, Dot = Mean

Figure 4. Tumour load in ascites samples in catumaxomab-treated patients (study IP-REM-AC-01). Ovarian cancer patients (full analysis set)

Literature references were provided in support of the above results, by analysis of ascites samples from the pivotal study (Jaeger et al., 2012). Study CASIMAS (Fosatti 2015) has shown similar results in activated T-cells in samples as have been shown in the pivotal study (data not shown).

Secondary pharmacology

Safety pharmacology

Immunogenicity

Table 10. The numbers of patients developing HARA/HAMA in the various studies are tabulated below

Study **Time point**	**N** [a]	**Number (%) of patients with positive test result**
Study IP-REM-PK-01-EU [b]		
Screening	13	1 (7.7)
28±4 days after 4th infusion (EoS)	12	9 (75.0)
Study IP-REM-PK-01-EU (DABA results)		
Screening	13	1 (7.7)
1 day before 4th infusion (Day 9)	11	2 (18.2)
2 days after 4th infusion (Day 12)	13	7 (53.9)
9 days after 4th infusion (Day 19)	13	10 (76.9)
Study IP-REM-AC-01 (patients with ovarian cancer) [b, c]		
Screening	85	1 (1.2)
Before 3rd infusion	74	1 (1.4)
Before 4th infusion	69	6 (8.7)
8±4 days after 4th infusion	67	49 (73.1)
28 ±4 days after 4th infusion	42	36 (85.7)
Puncture visit [d]	36	21 (58.3)
Study IP-REM-AC-01 (patients with non-ovarian cancer) [b, c]		
Screening	85	2 (2.4)
Before 3rd infusion	72	2 (2.8)
Before 4th infusion	63	1 (1.6)
8±4 days after 4th infusion	55	35 (63.6)
28±4 days after 4th infusion	34	30 (88.2)
Puncture visit [d]	28	17 (60.7)
Study STP-REM-01 [c]		
Screening	22	0 (0)
28±4 days after last infusion [e] (EoS)	15	14 (93.3)
Study IP-REM-PC-01-DE (Groups I to i.v.) [c]		
Screening	14	0 (0)
14±4 days after 4th infusion (EoS)	14	4 (28.6)
Study IP-REM-PC-01-DE (Groups III and V) [c]		
Screening	12	0 (0)
14±4 days after 4th infusion (EoS)	12	5 (41.7)
Study IP-REM-PC-01-DE (Group VI) [c]		
Screening	1	0 (0)
14±4 days after 4th infusion (EoS)	1	0 (0)
Study AGO-OVAR-2.10 (high-dose group) [b]		
Screening	16	1 (6.3)
24 hours after 4th infusion	16	4 (25.0)
18±4 days after first infusion (follow-up 1)	16	15 (93.8)
30±4 days after first infusion (follow-up 2)	16	16 (100.0)
(table continued overleaf)		
Study AGO-OVAR-2.10 (low-dose group) [b]		
Screening	18	0 (0)
24 hours after 4th infusion	18	1 (5.6)
18±4 days after first infusion (follow-up 1)	18	10 (55.6)
30±4 days after first infusion (follow-up 2)	18	11 (61.1)

Study Time point	N [a]	Number (%) of patients with positive test result
Study IP-REM-GC-01 [b] (HAMA results)		
Screening	12	0
Before 5th infusion [f]	6	4 (66.7)
14±4 days after 4th or 5th infusion (EoS)	12	9 (75.0)
Study IP-REM-GC-01 [b] (HARA results)		
Screening	12	2 (16.7)
Before 5th infusion [f]	6	3 (50.0)
14±4 days after 4th or 5th infusion (EoS)	12	8 (66.6)

[a] Including patients with missing data.
[b] Gallati test (HAMA and HARA).
[c] Medac test (HAMA).
[d] The puncture visit occurred at a median of 71 days (**ovarian** cancer patients) / 80 days (**non-ovarian** cancer patients) after Day 0
[e] Patients received up to 5 catumaxomab infusions.
[f] For the patients with a first catumaxomab dose of 20 µg, a further measurement was scheduled before the fifth catumaxomab infusion.
N: number of patients; EoS: end of study.

Pharmacodynamic interactions with other medicinal products or substances

Available information is in relation to rescue medication given to patients in the pivotal study.

According to the Clinical Study Protocol for study IP-REM-AC-01, rescue medication could be given as follows: "In the event of relevant AEs to the application of the antibodies, treatment shall be given to alleviate symptoms and/or avoid their further aggravation".

There was a total of 119 patients with cytokine release syndrome (CRS) causally related to catumaxomab treatment in the randomised part of the pivotal study IP-REM-AC-01. 101 of these patients received concomitant symptomatic treatment. In only 6 of these patients the concomitant treatment was steroids, in particular dexamethasone (4 patients) or hydrocortisone (2 patients). The symptoms were nausea / vomiting (dexamethasone) in 3 and pyrexia / chills (hydrocortisone / dexamethasone) in 2 patients. 1 patient with patient number 90201 had both, vomiting and pyrexia (hydrocortisone). In 5 of the 6 patients, all symptoms resolved completely. Only one patient (vomiting, treated with dexamethasone) still had ongoing symptoms at time of death.

Other drugs were not tested in conjunction with catumaxomab in the pivotal clinical study.

2.6.3. Discussion on clinical pharmacology

The proposed dosing regimen consists of a single treatment cycle of four i.p. infusions at doses of 10 µg on Day 0, 20 µg on Day 3, 50 µg on Day 7 and 150 µg on Day 10. The recommended infusion time is 3-hr.

Results on the characterisation of catumaxomab concentrations in ascites fluid and plasma following i.p. administration were mainly obtained from study IP-REM-PK-01-EU in 11 patients with malignant ascites due to epithelial cancer receiving the proposed 4 doses of catumaxomab. 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, which could be partly overcome by using an anti-blocking agent in the analysis method. This is acceptable as the development of antibodies is expected and do not cause major concern if only developed late after treatment. The anti-blocking agent was not used during analysis of ascites samples, as there was no ascites sampling after Day 10 (4th dose). Catumaxomab was

detected in the ascitic fluid following the first infusion (10 mg) and there was a trend of increasing concentrations with increasing doses. Interindividual variability was very high; the detected free concentrations varied more than 100-fold: the ascites catumaxomab concentration ranged from 0.2 to 39.9 ng/mL, however, are not subject to meaningful analysis as, in contrast to plasma PK (with an approximately constant blood volume), ascites volumes vary, affecting the measured catumaxomab concentration in ascites fluid. Mean and median C_{max} for ascites fluid were 7.12 and 3.27 ng/mL, respectively. The geometric mean plasma C_{max} was 0.5 ng/ml (range 0 to 2.3), and the geometric mean plasma AUC was 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 2.5 days (range 0.7 to 17.5). Of note, the infusion time in this pharmacokinetic study was 6-hr instead of the proposed therapeutic use with a 3-hr infusion time. Additional PK data from a dose finding study in a limited number of patients receiving the 3-hr infusion (study IP-REM-PC-01-DE, n=5) confirm the expectation that a shorter infusion time will lead to higher plasma C_{max}. However, data should be interpreted with caution considering that no blocking agent was used in this study and the high intraindividual variability.

In most patients there was an increase in plasma concentration after application of catumaxomab and, after reaching a maximum, a decrease was observed. This indicates that elimination from plasma is greater than invasion from the application compartment (peritoneal cavity).

The high pharmacokinetic variability in plasma is suggested to be due to disease factors such as different degree of tumour burden, different number of immune effector cells in the ascites fluid, and differently diseased peritoneum. The variability introduced by these factors is likely largely overweighing any variability due to intrinsic factors such as age, gender or race.

In general, though, pharmacokinetic evaluations are not considered of important relevance for this i.p. applied monoclonal antibody.

Most of the patients developed anti-drug antibodies against the mouse and rat sequence of catumaxomab, but usually not before the last infusion, and as catumaxomab is intended for a single treatment cycle, the applicant suggests that antibodies are not expected to affect efficacy or safety of catumaxomab. However, in a small proportion of patients anti-catumaxomab antibodies were detectable in plasma before the 4th infusion. The effect of the presence of ADA on safety and efficacy of catumaxomab was assessed in study IP-CAT-AC-04 (Pietzner 2014). This study showed that a second cycle of catumaxomab treatment is feasible and provides clinical benefit to highly selected patients, with tolerability and safety of catumaxomab comparable to that after one cycle. Presence of ADAs did not seem to affect the safety or efficacy of catumaxomab. However of note, patients in this study were highly selected, as they needed to have a puncture free interval of ≥ 60 days after Cycle 1 of catumaxomab and still had to be in a good general health condition despite their already advanced stage of disease; this was confirmed by the fact that only 8 patients could be included in this study.

No specific studies on metabolism or excretion have been performed. This is in accordance with current guidelines for antibodies.

Overall, virtually all patients will develop ADA upon catumaxomab treatment. The data suggest differences between studies in ADA dynamics, in particular the time point when ADAs first occur in patients. This may be due to different factors, such as the patient population included in each study as well as the assay used (Gallati, Medac, double antigen binding assay [DABA]). It also needs to be considered that all study protocols defined time windows for both catumaxomab infusion time points and ADA sampling time points. Hence, ADA data given in relation to a specific nominal infusion time point, e.g. Infusion 4, could have been collected in

different studies earlier or later relative to the infusion (due to inter-patient variation in sampling time), and the actual infusion might have happened earlier or later (due to inter-patient variation in infusion time).

In most patients, anti-catumaxomab antibodies were not detectable in plasma until sometime after the last infusion, and as catumaxomab is intended for a single treatment cycle, ADA are not expected to affect efficacy or safety of catumaxomab. In addition, catumaxomab repeated treatment was assessed in study IP-CAT-AC-04 (SECIMAS, Pietzner 2014). This study showed that a second cycle of catumaxomab treatment is feasible and provides clinical benefit to patients, with tolerability and safety of catumaxomab comparable to that after one cycle. Presence of ADAs did not seem to affect the safety or efficacy of catumaxomab. However, of note, patients in this study were highly selected, as they needed to have a puncture free interval of ≥60 days after Cycle 1 of catumaxomab and still had to be in a good general health condition despite their already advanced stage of disease; this was confirmed by the fact that only 8 patients could be included in this study.

There were no studies investigating intrinsic factors and special populations. The variability in plasma concentrations introduced by disease factors is large, overweighing any variability due to intrinsic factors such as age, gender or race.

No *in vitro* or *in vivo* pharmacokinetic drug-drug interaction studies have been performed. This is acceptable given the nature of the substance and the route of administration, as clinically relevant drug-drug interactions are unlikely.

The primary pharmacodynamics of catumaxomab have been reasonably well studied using relevant biomarkers for elimination of tumour cells, immunoactivation and cytokine production. Results from the pivotal clinical efficacy study and the PK study demonstrate decrease of EpCAM+/CD45+ ratio. This may be achieved by decrease of EpCAM positive cells and/or increase of CD45+ cells. Supporting *in vitro* data confirmed EpCAM+ cell decrease but were inconclusive on numbers of CD45+ cells. One contradictory finding has been identified; in study IP-REM-PK-01-EU there was no decrease, but an increase in median value of EpCAM-positive (tumour cells), after incubation with catumaxomab (N=6). This was rather due to low patient numbers and does not raise a concern.

The experimental strategies to show proof of principle of primary pharmacodynamics *in vivo* in cancer patients are convincing. One of the challenges 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.

In ascites samples from catumaxomab treated patients an increased number of leucocytes containing increased numbers of activated effector cells (CD 25, HLADR and CD 69) were found. This was more obvious in the PK study and less, but still prominent in the pivotal study for CD69+ cells but not for CD25+ cells.

Systemic cytokine response was documented as elevated levels of IL-6. Also, TNF-α, IL 10, and IFN–γ, were noted albeit with high between-patient variability.

Results were supported by analysis of ascites samples from pivotal study (Jaeger et al., 2012). Study CASIMAS (Fosatti 2015) has shown similar results in activated T-cells in ascites samples as seen in the pivotal study.

The in *vitro/in vivo* data presented in the non-clinical/pharmacology dossier provide support to some of the manifested adverse events reported in the clinical trials (symptoms of cytokine release, hepatotoxicity, cholangitis). Cytokines as well as EpCAM-binding to bile ducts may cause hepatotoxicity (see also non-clinical part and clinical safety).

Catumaxomab is a rodent hybrid monoclonal antibody which leads to the development of neutralising HAMA/HARA antibodies. This is confirmed in several studies by identification of neutralising antibodies in plasma, in some patients already before the last dose. The production of neutralising antibodies also has been shown to occur in the peritoneal cavity. The HAMA/HARA levels in serum may underestimate their levels in ascites. Results were supported by post-hoc analysis of ascites punctures from the pivotal study (Jaeger et al., 2012), another supportive study and by published data from CASIMAS (Sehouli et al. 2014) where ADA production in ascites was confirmed and seems to correlate with systemic ADA production established in the pivotal study. ADA production was also analysed in SECIMAS (Pietzner et al. 2014), which was a study of second catumaxomab cycle in subjects previously treated in CASIMAS study. Presence of such neutralising antibodies was shown to inhibit binding of EpCAM positive tumour cells *in vitro* as well as CD3 positive target cells in a concentration dependent manner. Study SECIMAS however investigated second course of catumaxomab, where it was shown that presence of ADA probably did not affect catumaxomab´s safety and efficacy (data not shown).

The shown cytokine release stimulation of catumaxomab on effector cells constitutes a safety concern. Systemic exposure and interaction with EpCAM positive tissue constitutes another concern. Only very little data is at hand regarding the magnitude of systemic exposure following intraperitoneal administration (see Clinical safety). As additional data don’t exist, no additional information is requested.

The *in vitro* pharmacodynamic interaction studies between catumaxomab and corticosteroids, where cytokine release but not tumour killing is dampened, are important for the clinical scenario. As to pharmacodynamic effects of rescue medication, the exact time relationship between administration of corticosteroid rescue and alleviation of symptoms is unclear, but in general, steroids were administered only for one day and the event ended the day of administration. Guidance on steroid rescue medication in the SmPC sections 4.2 and 4.4 reflects this scenario.

The plasma concentrations of catumaxomab are not of relevance for efficacy since the administration mode is intraperitoneal. However, for safety assessment they may be of relevance. The scarce PK data show an unpredictable leakage of catumaxomab to the plasma compartment after intraperitoneal administration. This is most probably due to individual permeability and binding in peritoneal compartment. A trend of increase after subsequent administrations is noted. The concentrations of free catumaxomab in ascites show a high degree of variability, although lower than for plasma concentration. The difference in ascites production over time in individual patients will influence concentrations measured at a certain time point.

Based on the provided information on special populations the following text is reflected in the SmPC:

Hepatic impairment: No dose adjustment is needed for patients with mild to moderate hepatic impairment. Patients with severe hepatic impairment and/or with more than 70% of the liver metastasised and/or portal vein thrombosis/obstruction have not been investigated. Treatment of these patients with Korjuny should only be considered after a thorough evaluation of benefit/risk.

Renal impairment: No dose adjustment is needed for patients with mild renal impairment. Patients with moderate to severe renal impairment have not been studied. Treatment of these patients with Korjuny should only be considered after a thorough evaluation of benefit/risk.

Transient elevations of liver parameters after catumaxomab infusions were observed in clinical studies which subsequently improved in the majority of patients shortly after completion of the last catumaxomab infusion. In rare cases, catumaxomab -drug induced liver injury (DILI) or hepatitis may occur, potentially leading to hepatic failure including fatal outcome. Patients treated with Korjuny should be closely monitored for signs of clinically significant elevated liver parameters.

2.6.4. Conclusions on clinical pharmacology

Catumaxomab is systemically available after peritoneal administration, with measurable plasma concentrations after the third and fourth infusion (50 and 150 µg). The variability between subjects in ascites and plasma catumaxomab levels was high, due to varying ascites volume and malignant cell burden in the peritoneal cavity, with an inter-subject coefficient of variation for AUC of 400% (see SmPC 5.2). From pharmacodynamics point of view, catumaxomab possesses immunologically mediated antitumoral activity supported by preclinical data. Primary pharmacodynamics on tumour elimination *in vivo* are reasonably well studied. Secondary pharmacodynamic properties (also part of primary pharmacodynamics) such as cytokine release and T-cell activation are well established.

Despite the limited PK data, the 3-hr infusion rate is further supported by additional clinical studies (see Clinical Efficacy and Clinical Safety) and can be agreed.

In conclusion, the clinical pharmacology part is acceptable to support the i.p. administration of catumaxomab in the intended indication.

2.6.5. Clinical efficacy

2..6.5.1. Dose response study(ies)

No dedicated dose-response study has been conducted. The proposed dosing is based on results from study STP-REM-01. This Phase I/II, multi-centre, 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.

The dosing schedule is based on the following considerations:

1) First i.p. dose of 10 µg catumaxomab in malignant ascites:

- Antitumor activity of catumaxomab against epithelial human tumor cell lines from different tissue origins that express high to low levels of EpCAM was already seen at catumaxomab concentrations of <10 ng/mL *in vitro*.
- In the Phase I/II dose-finding Studies STP-REM-01 and IP-REM-PC-01-DE, the starting dose of 10 µg catumaxomab was well tolerated, with only moderate and fully reversible symptoms attributed to systemic cytokine release.

2) Second i.p. dose of 20 µg catumaxomab in malignant ascites:

- A dose of 50 µg was tested in 3 patients (Study STP-REM-01: dose level IIa). However, due to a reversible bilirubin elevation of CTC Grade 3 in 1 of 3 patients, the dose steering board decided to reduce the second dose to 20 µg as a precaution.

- The data indicate that low doses should be applied at the first and second infusion to minimise the risk for strong initial reactions, especially those associated with systemic cytokine release.

3) Third i.p. dose of 50 µg catumaxomab in malignant ascites:

- In Study STP-REM-01, the third dose was set at 50 µg. This dose was well tolerated and no safety concerns were raised. Therefore the dose was maintained in subsequent dose groups.
- In Study IP-REM-PC-01-DE, the third dose was escalated to 100 µg. However, at this dose level, 2 DLTs (both cytokine release-related symptoms) in 2 out of 3 patients were observed indicating that the patients do not tolerate a dose escalation above 50 µg as the third dose.

4) Fourth i.p. dose of 150 µg catumaxomab in malignant ascites:

- In Study STP-REM-01, an SAE occurred at the fourth dose with 200 µg on day 10 (bowel obstruction). Subsequently, the sponsor decided to reduce the 4th dose to 150 µg for subsequent ascites studies.

2..6.5.2. Main study(ies)

Study IP-REM-AC-01, two-arm, randomised, open-label phase II/III study in EPCAM-positive cancer patients with symptomatic malignant ascites using paracentesis plus the trifunctional antibody Removab (anti-EPCAM x anti-CD3) versus paracentesis alone

Methods

This was a multi-centre, multi-national 2 arm, randomised (2:1), open label Phase II/III study. Patients in the control group were allowed to cross over to catumaxomab after two therapeutic ascites punctures.

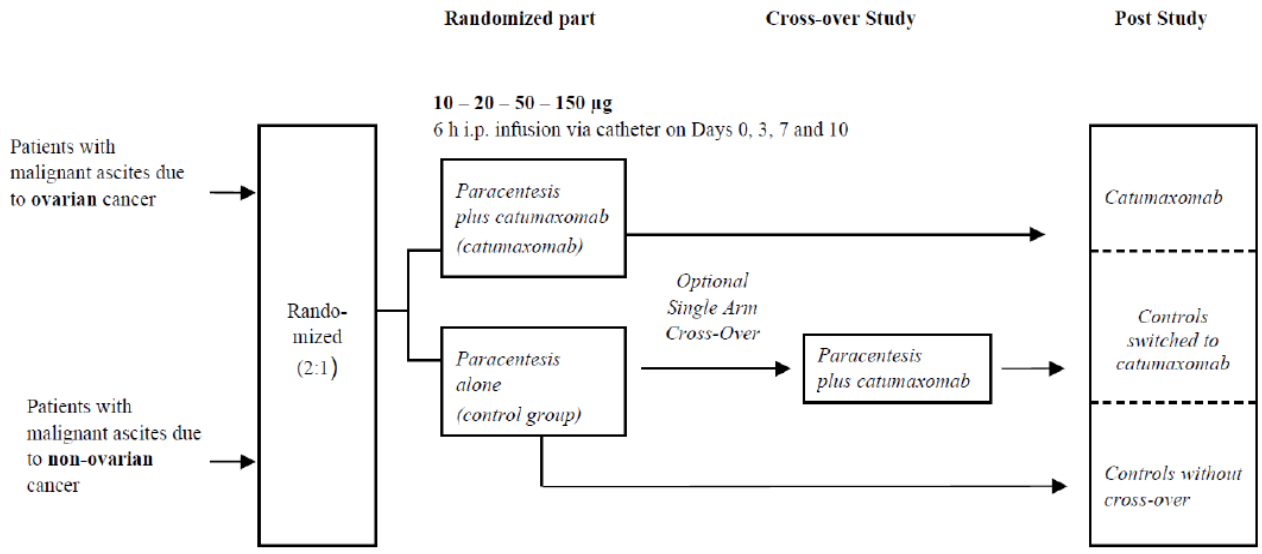


Figure 5. Study IP-REM-AC-01, schematic presentation of the study design

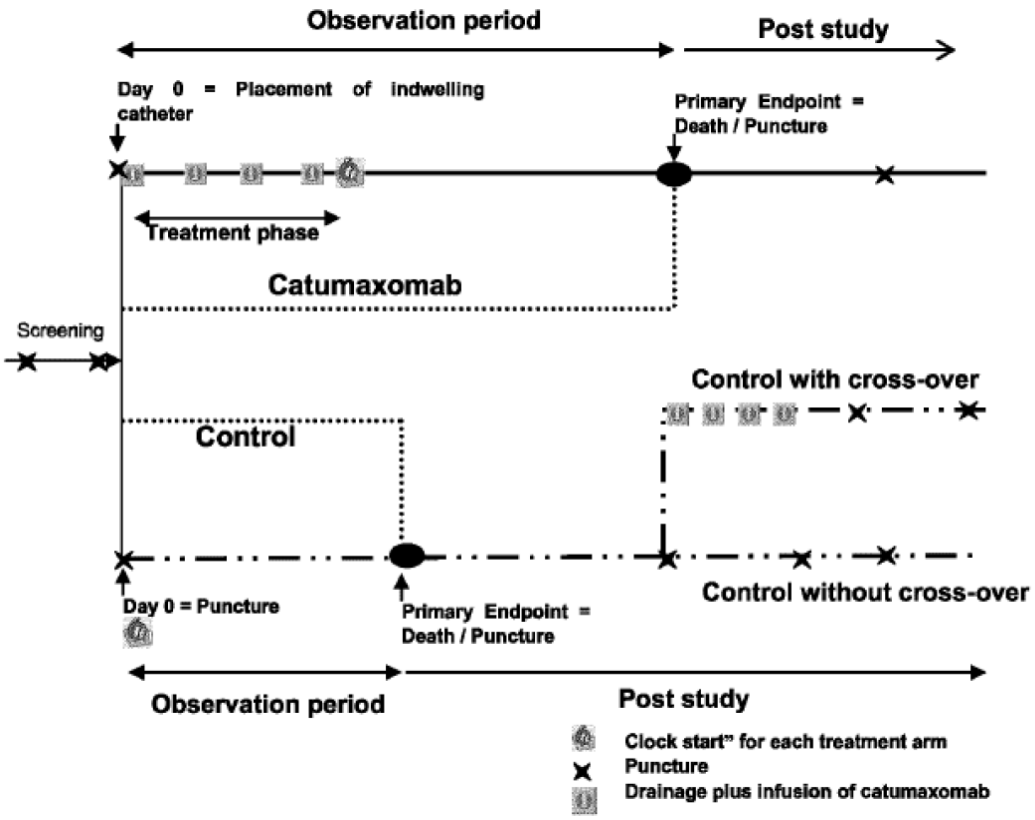


Figure 6. Study IP-REM-AC-01, schematic presentation of punctures relative to study periods and endpoint assessment

- **Study Participants**

The main inclusion criteria were as follows:

1. Histologically confirmed diagnosis of cancer.
2. EpCAM+ tumor cells in the ascites fluid (ascites fluid contained ⩾400 EpCAM+ cells/10^6 analysed ascites cells determined using an immunohistochemistry (IHC) assay).
3. Symptomatic malignant ascites requiring therapeutic ascites puncture.
4. Refractory/resistant to chemotherapy or where the standard chemotherapy was no longer feasible.
5. Karnofsky Index ≥60.
6. Life expectancy >8 weeks.
7. At least 1 therapeutic ascites puncture within 5 weeks before screening puncture.

The main 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/mm3; absolute neutrophil count (ANC) < 1500 cells/mm3
8. BMI <17
9. Patients with a reduced nutritional 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 catumaxomab group, patients received 4 catumaxomab infusions i.p. of 6 h duration each at doses of 10 µg on Day 0, 20 µg on Day 3, 50 µg on Day 7, and 150 µg on Day 10 via an indwelling catheter. Prior to each of the 4 catumaxomab infusion as well as after the last infusion, fluid was discharged from the peritoneal cavity ('draining to dryness'). This was the treatment established in the dose finding study. For catumaxomab administration, patients were infused 500 mL 0.9% NaCl solution i.p. to ensure enough fluid volume in the peritoneal cavity for drug distribution, followed by a 250 mL 0.9% NaCl solution infused at 41.6 mL/h in parallel with the catumaxomab solution, which was infused via a perfusion syringe connected in parallel to the infusion pump. The 4 doses of catumaxomab were administered diluted in fluid volume of 10, 20, 50, and 50 mL. As a consequence, the fluid volume administered at each of the 4 catumaxomab infusions was 760, 770, 800, and 800 mL. It was permitted to prolong the interval between infusion days in case of AEs, but the entire treatment period was not to exceed 21 days.

The control group was treated by paracentesis only (drainage to dryness).

- **Objectives**

The primary objective of the trial was to demonstrate the superiority of a treatment with paracentesis plus catumaxomab over a treatment with paracentesis alone in terms of puncture-free survival.

The secondary objectives were to assess quality of life, patient's health state, timing of the first post-baseline therapeutic ascites puncture, and compare efficacy and assess safety.

- **Outcomes/endpoints**

The primary efficacy endpoint was puncture-free survival (PuFS) defined as time to first need for therapeutic ascites puncture or death, whichever occurred first.

- 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.

The need for therapeutic ascites puncture in an individual patient was determined locally, based on the presence of ascites signs and symptoms and ascites volume >1 L in this patient, estimated by the local radiologist based on computed tomography (CT) scans. Ascites signs and symptoms were assessed in a standardised manner, using a 4-point Likert scale. This assessment included an interview, abdominal examination, and overall assessment. The investigator stated in the overall assessment if the patient had symptomatic ascites or not. If this was the case, a CT scan had to be performed locally to determine the ascites volume, and a therapeutic ascites puncture was performed if the ascites volume was >1 L.

Secondary and additional endpoints supporting the primary endpoint were:

- Time to first need for therapeutic ascites puncture; TTPu was the first component of the primary endpoint. The need for therapeutic ascites puncture was based on the assessment of ascites signs and symptoms and ascites volume (as per CT) ≥1 L.
- Additional variables to objectify the need for therapeutic ascites puncture:
    - Ascites volume (collected and calculated). Daily collected ascites volume was calculated as ascites volume collected at puncture visit divided by the number of days between 1 day after the last infusion (catumaxomab group) or Day 0 (control group) and puncture.
    - Body weight and abdominal girth.
    - Total protein concentration in ascites collected during therapeutic ascites punctures.
- Time to death without therapeutic ascites puncture
    - Time to death without therapeutic ascites puncture was the second component of the primary variable. It differed from OS by using the same starting point as the primary endpoint
- Ascites signs and symptoms
- Overall survival (OS)
    - OS was defined as time from randomisation to death due to any cause. Individual patient data

were only collected up to the time of withdrawal for patients who withdrew consent. Vital status/survival data were not collected for patients who withdrew consent. For the predefined OS analysis, control patients who did not enter the crossover period, as well as all catumaxomab patients were censored at the date of the last post-study (or safety-follow-up) visit when they were still alive or (if no post-study/ safety follow-up data available) at the date of the last documented visit. An additional OS analysis was done including crossover patients receiving catumaxomab as a third treatment group. For this analysis, control patients who did not enter the crossover period and all catumaxomab patients were censored as described above. Control patients receiving catumaxomab during the crossover period were censored at the date of the last post-study visit in or after the crossover period on which they were still alive or (if no post-study data after crossover available) at the last documented visit of the crossover period.

- Time to progression
- Progression-free survival
- Tumour response according to response evaluation criteria in solid tumours (RECIST) for patients with measurable disease.
    - Response was evaluated locally, using CT images. In addition, CT images were read by 2 independent, blinded reviewers (and a blinded third party adjudication, in case of a discrepancy between the first 2 readers, according to the study's imaging review charter).
- Tumour cell load in ascites fluid
- Tumour markers
- Quality of life (QoL)
- Subgroup analysis; subgroup analyses were performed for time-to-event endpoints by:
    - cancer type (ovarian vs nonovarian cancer, as part of all predefined analyses of the study; and additionally for other cancer types, including gastric cancer as the largest subpopulation within the nonovarian cancer stratum);
    - presence of distant metastases (yes/no) and presence of liver metastases (yes/no) at baseline;
    - ADA status at Visit 6 (i.e. 8 days after the last catumaxomab infusion).

- **Sample size**

Based on the original assumptions, a total of 108 patients (catumaxomab: 72, control: 36) had to be randomised in each of the ovarian and non-ovarian cancer subgroups to achieve a power of 90% in detecting at least a doubling of median time puncture free survival between catumaxomab and control, after rounding up to allow an appropriate block size, i.e. 216 overall (108+108) based on the following considerations:

- Primary efficacy variable: puncture free survival
- Duration of patient observation: 7 months (30 weeks),
- 10% of patients lost to follow-up (censored before Month 7) for this variable,
- Alpha level: 0.05, 2-sided, no adjustment for 2 tests (ovarian and non-ovarian subgroup)
- Randomisation ratio: 2:1 (catumaxomab versus control).

According to the procedures in the protocol, when a total of 148 patients (ovarian and non-ovarian) were randomised, 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. A sample size re-assessment using the observed censoring rate across treatment groups was performed. This led to a slight increase in sample size to 126 ovarian cancer patients and 120 non-ovarian cancer patients, respectively.

- **Randomisation and Blinding (masking)**

The patients were to be allocated to the treatment groups in a 2:1 ratio (catumaxomab: control) stratified by cancer entity (ovarian versus non-ovarian) and country using a central interactive voice response system (IVRS). Block-randomisation with a block length of 6 was used. The initial randomisation list was amended 3 times during the study as new countries were included. An additional modification for the non-ovarian cancer stratum was implemented after 120 subjects were randomised to ensure a study-wide 2:1 randomisation. 9 patients were enrolled based on the modified list. The same number of patients were initially planned to be randomised in the 2 cancer entity group. Randomisation was to take place as soon as the EpCAM results were available, but no later than on Day 0. No blinding was implemented as it was considered unethical to expose the control group to the risk of an infusion with a non-active agent. Access to the study data base was limited to the CRO and not possible during the study for the sponsor. Likewise, no access to the randomisation list was granted to the sponsor until the end of study. However, the local investigator, the sponsor and the CRO were informed about each enrolled subject at the time of randomisation.

- **Statistical methods**

Analysis sets

The statistical analyses were to be based on separate analysis sets as defined below:

- Full analysis set: All patients randomised
- Safety analysis set: The safety analysis set consists of all patients who received catumaxomab in the catumaxomab group and all randomised patients in the control group.
- Per-protocol (PP) set: All patients of the full analysis set for whom no major protocol deviations occurred.
- Single-arm cross-over period set: All patients who entered the single-arm cross-over period.

Demographic and background characteristics were to be analysed for all 4 analysis sets. Efficacy data was to be evaluated using the full analysis set and the PP set. Safety data was to be evaluated using the safety analysis set. A sensitivity analysis was to be performed for the primary endpoint using the patients who were enrolled according to amendment 2. The data from the single-arm cross-over period set were to be analysed separately with descriptive statistics.

Statistical analyses for primary endpoint (PuFS)

The analysis of puncture free survival within the 2 cancer groups (ovarian and non-ovarian) was to be considered as the only confirmatory analysis. A log-rank test comparing the 2 treatment groups was to be used for the confirmatory analysis. Since these patient groups are independent groups, no alpha-adjustment was deemed necessary for the confirmatory analysis. Also, no alpha adjustment or other approaches dealing with multiple testing was to be applied to secondary analyses, i.e., all other p-values were to be considered as supportive and descriptive rather than confirmatory results.

Kaplan-Meier estimates were to be provided and 95% confidence intervals were to be calculated within both treatment groups and for the difference between the treatment groups for the median time to end of puncture free survival. Additional supportive analyses were to be performed using Cox regression.

The primary statistical analyses was to be performed using the full analysis set. The same analyses as specified above was to be performed using the PP set. The following censoring algorithm was to be applied for the analysis of the primary variable:

- Patients who complete the study up to Visit 10 (Month 7) without a therapeutic ascites puncture after Day 0/treatment period were to be censored at the date of Visit 10 (Month 7).
- Deaths occurring in the catumaxomab group before completion of 4 catumaxomab infusions and, in the control group, before Day 0 were to be handled by using the same date for the starting point and the *censoring point* in order to provide a zero time to event.
- Patients lost to follow-up before the planned end of study in Month 7 (lost to follow-up, consent withdrawn etc) were to be censored at the date of their premature study end using the same algorithm as for deaths, if necessary.

The primary variable also was to be analysed for the pooled cancer groups using the same methods as specified above for the confirmatory analysis. The 2 components of the primary efficacy variable also was to be analysed using the same methods as for the primary variable as specified before. This was to be done separately for the 2 cancer groups, and for time to first therapeutic ascites puncture also for the pooled cancer groups.

Definition of observation period for PuFS

The clock for the primary variable was to be started after the therapeutic ascites puncture (drainage to dryness) on Day 0 in the control group, but not until 1 day after the last infusion in the catumaxomab group. Based on the assumption of a continuous deterioration of the patients' cancer, it was considered a conservative approach because more of the remaining short life expectancy had passed in the catumaxomab group than in the control group when the clock started. This implied that the condition in a catumaxomab patient had had a longer time to worsen and the propensity to produce ascites or to die had increased when the clock started to tick. Therefore, the time to the end of puncture-free survival was not deemed to be artificially prolonged in the catumaxomab patients.

Methods for selected secondary endpoints

Overall survival and PFS were to be defined as the time from randomisation until death; patients lost to follow-up were to be censored at the date of their last visit as documented on the termination record. Analyses were to be conducted analogously to the primary endpoint but without sensitivity analyses.

Time to first need for therapeutic ascites puncture (TTPu) was to be analyses as the primary endpoint (excluding sensitivity analyses). Censoring was to be done analogous to censoring for the primary efficacy variable but including death prior to first therapeutic puncture as censoring time point. The analyses were to be performed separately for the ovarian and the non-ovarian stratum plus for the pooled group (ovarian plus non-ovarian).

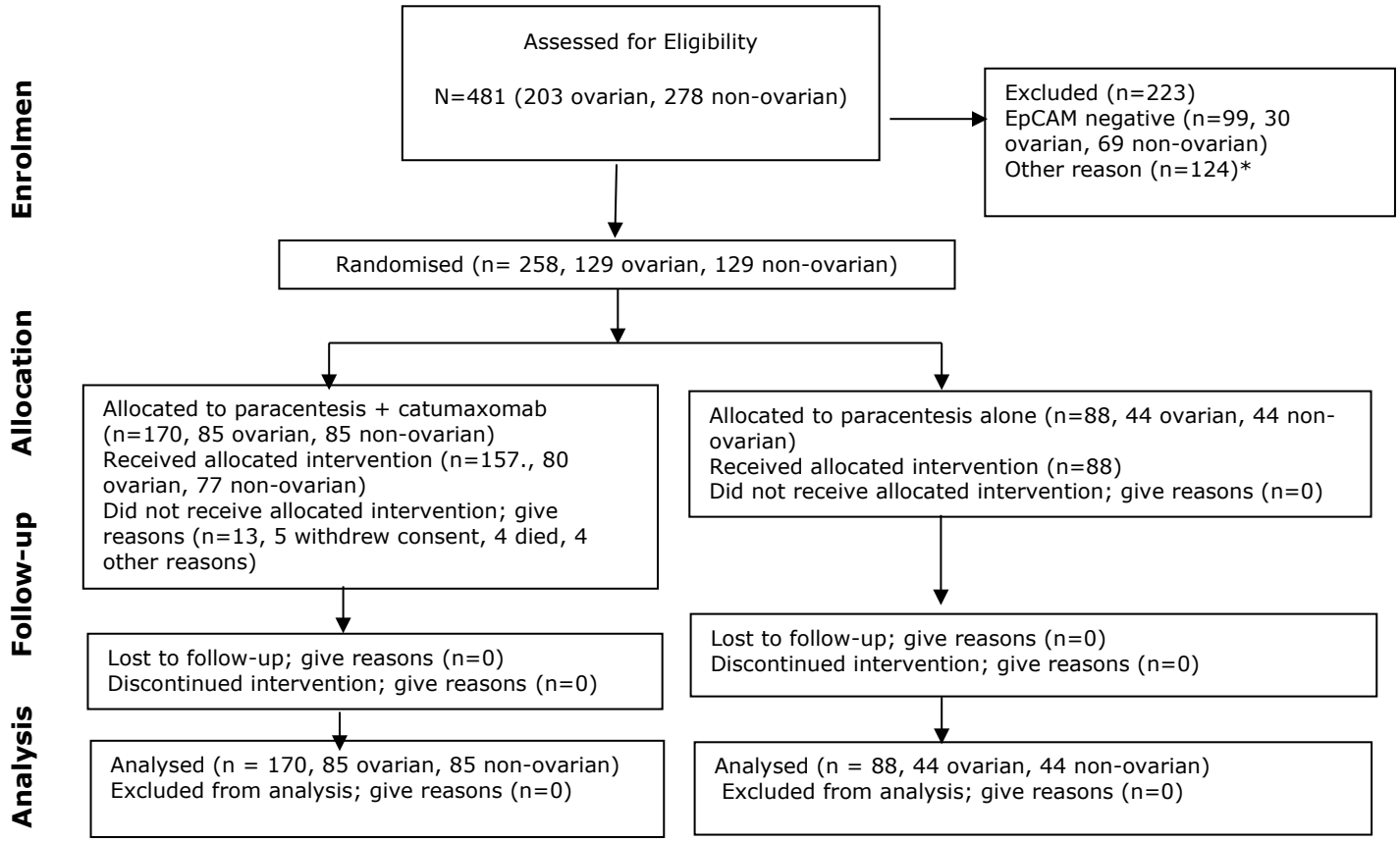
Crossing over

The patients in the control group needing therapeutic ascites punctures were required to have 2 protocol-conforming therapeutic ascites punctures after Day 0 before they were permitted to continue to the single-arm cross-over period. This requirement was introduced to reduce the bias that could have been caused by

premature ascites punctures. However, the time to first therapeutic ascites puncture was used for the analysis of puncture-free survival, the primary efficacy variable.

Results

- **Participant flow**



**Other reasons of screen failures (N=124) – sorted by frequency*

Reason for exclusion	Number of patients (N)	Percentage of patients (%)
Ascites not evaluable*	51	41.1
Others**	13	10.5
Ascites < 1 L	12	9.7
No tumor cells detectable in ascites	11	8.9
Adverse events	11	8.9
Informed consent withdrawn	9	7.3
Portal vein thrombosis	9	7.3
Deaths	8	6.5
Total	**124**	**100**

* Ascites not evaluable e.g. due to frozen or leaking samples during transport or due to technical reasons during sample preparation

** Others were as follows: medical history of myocardial infarction, investigator decision, hepatitis, increased liver enzymes, increased risk for hepatic adverse events, > 70 % liver metastasis, > 1.5 ULN creatinine, BMI < 17, Karnofsky of 50, start of anti-cancer treatment, tumor progression

- **Recruitment**

Most patients were recruited from Poland (23%), followed by Germany (18%), Ukraine (14%), and the Russian Federation (11%); each of the other countries contributed <10% of patients overall. The number of patients from the EU was 195 (76%), i.e. including the UK at that time, and without Ukraine and the Russian Federation.

The pivotal study included the first patients in both ovarian and non-ovarian cohorts on 6 September 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 29 September 2006 and the non-ovarian study on 3 November 2006.

- **Conduct of the study**

This was a phase II/III, randomised, open-label study performed at 53 centres in 13 countries in the EU as well as Ukraine and the Russian Federation. The study is stated to have been conducted compliance with current GCP requirements.

Study IP-REM-AC-01 had a total of 5 global protocol amendments issued.

Per Amendment 1 (11 May 2004) required calculated ascites volume to perform a therapeutic ascites punction was reduced from 2 L to 1 L. The same situation applied for the replacement of ascites questionnaire by assessment of ascites symptoms by the investigator, and for the number of assessments being reduced. Per Amendment 1 also the time for removal of the catheter was shortened to 1 day after last catumaxomab infusion. Per Amendment 2 the primary endpoint PuFS was defined. Also, decision for therapeutic puncture was to be based on ascites signs and symptoms in addition to the assessment of ascites volume per CT. Also, drainage to dryness before removal of catheter has been implemented per amendment 2. Positive EpCAM test was no longer required for gastric cancer patients per Amendment 4 (10 May 2006). According to screening methods, all recruited subjects have been screened for EpCAM. Also, per Amendment 4, it was planned to first recruit 126 ovarian and 120 non-ovarian cancer patients. Thereafter, an interim analysis was to be performed for patients with gastric cancer (within the stratum of non-ovarian cancer patients). Depending on the results of the interim analysis, additional gastric cancer patients were to be enrolled for a possible total of up to 140 gastric cancer patients in the study. However, per Amendment 5 (11 Aug 2006) which superseded Amendment 4, no further patients were enrolled, and an interim analysis was not performed.

Protocol deviations

Major protocol deviations occurred in more catumaxomab patients than control patients. Overall, across strata, numbers were 39 in the catumaxomab arm (23%) and 3 in the control arm (3%). The reason was that the most frequent major protocol deviation, i.e. receipt of <3 catumaxomab infusions only applied to the catumaxomab group (30 patients, 18%, 13 patients in the ovarian cancer stratum and 17 patients in the non-ovarian cancer stratum) that were reflected in the sensitivity analyses. There was no difference seen between groups for the other protocol deviations.

- **Baseline data**

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.

Among patients randomised (n=258), 79% of patients were female (100% in the ovarian cancer stratum, 59% in the non-ovarian cancer stratum). Mean age was 58.5 years in the ovarian cancer stratum and 58.8 years in the non-ovarian cancer stratum. Caucasians accounted for 99% of patients overall. The most frequent cancer types in the non-ovarian cancer stratum was gastric cancer (51%), followed by breast cancer (10%); other cancer types (colon, pancreas, lung, endometrium, others) were individually present in < 10% of patients in the non-ovarian cancer stratum.

For the **ovarian** cancer group all patients were females of Caucasian origin. Median (range) time since first cancer diagnosis was 19.0 (0 to 188) months in the catumaxomab group and 23.5 (0 to 102) months in the control group. FIGO staging was IIIc or i.v. in more than 80% of the patients. Most patients had undergone 1 or 2 surgeries. The 2 treatment groups were comparable regarding number of previous anti neoplastic medication regimens with 3.0 (0-8) in the catumaxomab group and 3.0 (1-10) in the control group. The treatment groups were comparable in terms of time since diagnosis of ascites with 7.0 (0 to 62) months in the catumaxomab group and 6.5 (0 to 82) months in the control group. The treatment groups were comparable in terms of time since last therapeutic ascites puncture with 17.0 (1 to 46) days in the catumaxomab group and 19.5 (3 to 36) days in the control group. The number of previous therapeutic ascites punctures ranged from 1 to 10 and was similar between the 2 treatment groups. Most of the patient had undergone 1 or 2 previous therapeutic ascites punctures (overall: 56.6% and 20.2% of the patients). The volume of last prior puncture and average volume of all previous punctures were comparable between the 2 treatment groups: Mean volume (± SD) of last prior puncture was 3496.3 ± 2190.4 mL in the overall group (catumaxomab group: 3523.5 ± 2269.69 mL; control group: 3436.9 ± 2033.9 mL). Mean average volume of all previous punctures was 3656.02 ± 2128.24 mL in the overall group (catumaxomab group: 3698.92 ± 2220.31 mL; control group: 3562.30 ± 1936.83 mL).

For the **non-ovarian** cancer group, 41.1% men and 58.9% women were enrolled in the study and 97.7% patients were of Caucasian origin. Gastric carcinoma was the most frequent (51.2%) primary tumor type at screening, followed by "other" tumor type and breast cancer. Each of the remaining tumour types had an overall frequency of <10%. There were no relevant differences between the treatment groups for distribution of tumour types at screening. Median (range) time since first cancer diagnosis was 11.0 (0 to 229) months in the catumaxomab group and 11.0 (0 to 343) months in the control group. Tumour, node, metastases (TNM) staging yielded 69.0% patients with a T classification of the primary tumour of 3 or 4, 60.9% patients with a

N classification of regional lymph nodes of 1, 2 or 3, and 61.0% patients with distant metastases. In general, the gastric cancer subpopulation had a worse TNM staging than the other non-ovarian cancer subpopulation. Most patients had undergone 0 or 1 surgeries (overall: 34.9% and 48.8% of the patients, respectively). The treatment groups were comparable regarding number of previous anti neoplastic medication regimens with 1.0 (0-10) in the catumaxomab group and 1.0 (0-9) in the control group. The treatment groups were comparable in terms of time since diagnosis of ascites with 2.0 (0 to 76) months in the catumaxomab group and 2.0 (0 to 58) months in the control group. The treatment groups were comparable in terms of time since last therapeutic ascites puncture with 14.0 (2 to 63) days in the catumaxomab group and 17.5 (2 to 35) days in the control group. The number of previous therapeutic ascites punctures ranged from 1 to 10 and was similar between the 2 treatment groups. Most of the patients had undergone 1 or 2 previous therapeutic ascites punctures (overall: 62.8% and 20.9% of the patients). The volume of last prior puncture and average volume of all previous punctures were comparable between the 2 treatment groups: Overall mean volume (± SD) of last prior puncture was 4526.6 ± 2941.6 mL (catumaxomab group: 4368.9 ± 2871.7 mL; control group: 4812.8 ± 3077.9 mL) and overall mean average volume of all previous punctures was 4488.09 ± 2788.83 mL (catumaxomab group: 4329.69 ± 2657.63 mL; control group: 4776.09 ± 3023.20 mL).

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

The median number of previous therapeutic ascites punctures at screening was 1 (range 1-5) in ovarian cancer patients and 2 (1-10) in nonovarian cancer patients.

- **Numbers analysed**

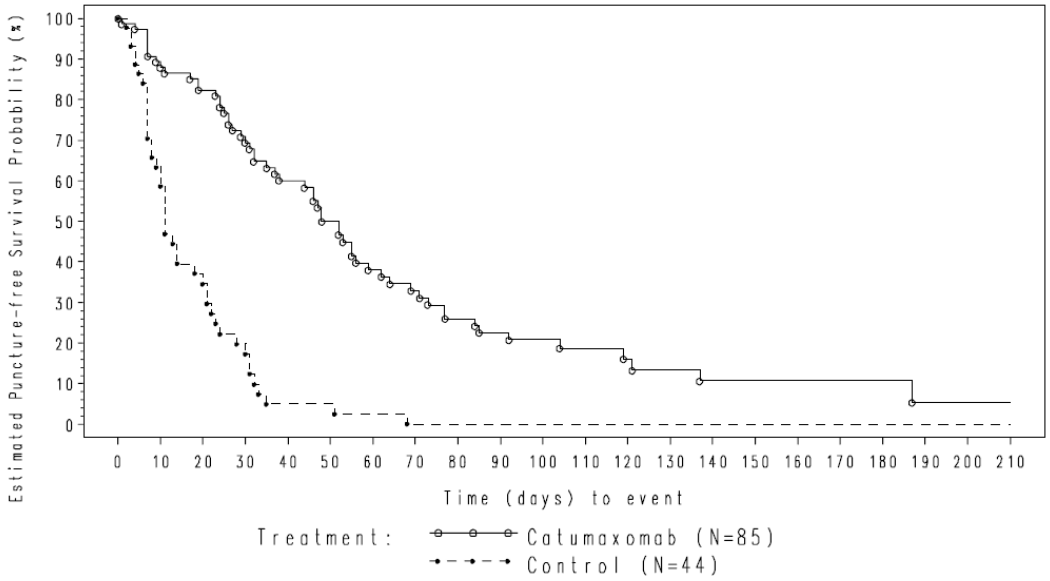
129 patients were randomised in the ovarian subgroup and 129 in the non-ovarian subgroup. For the efficacy analyses all randomised patients were analysed.

Outcomes and estimation

Primary efficacy endpoint

Puncture-free survival (PuFS)

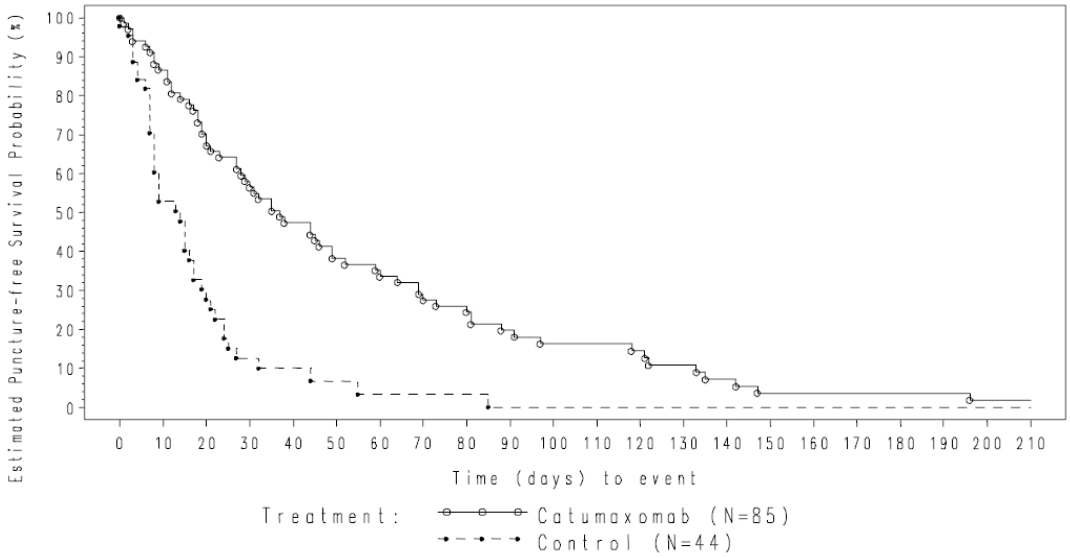
PuFS Ovarian (Primary per protocol analysis, original censoring rules)



N: number of patients in a treatment group.

Figure 7. Kaplan-Meier estimates of puncture-free survival in the ovarian population (full analysis set)

PuFS Non-ovarian (Primary per protocol analysis, original censoring rules)



N: number of patients in a treatment group.

Figure 8. Kaplan-Meier estimates of puncture-free survival in the non-ovarian population (full analysis set)

Table 11. Puncture-free survival, protocol defined censoring, ITT

	Ovarian cancer		Nonovarian cancer		Total	
	Catum.	Control	Catum.	Control	Catum.	Control
Patients, n	85	44	85	44	170	88
Patients with event, n (%)	56 (65.9)	42 (95.5)	63 (74.1)	40 (90.9)	119 (70.0)	82 (93.2)
Patients censored, n (%)	29 (34.1)	2 (4.5)	22 (25.9)	4 (9.1)	51 (30.0)	6 (6.8)
PuFS [days], median	52	11	37	14	46	11
95% CI	38, 62	9, 20	27, 49	8, 17	35, 53	9, 16
p-value[1]	<0.0001		<0.0001		<0.0001	
HR (95% CI)	0.205 (0.129, 0.327)		0.309 (0.199, 0.482)		0.254 (0.185, 0.350)	

[1] Log-rank test

Table 12. Puncture-free survival, protocol defined censoring, event types and censoring, ITT

	Ovarian cancer		Nonovarian cancer		Total	
	Catum.	Control	Catum.	Control	Catum.	Control
Patients, n	85	44	85	44	170	88
Patients with event, n (%)	56 (65.9)	42 (95.5)	63 (74.1)	40 (90.9)	119 (70.0)	82 (93.2)
Puncture	36 (42.4)	38 (86.4)	28 (32.9)	31 (70.5)	64 (37.6)	69 (78.4)
Death	20 (23.5)	4 (9.1)	35 (41.2)	9 (20.5)	55 (32.4)	13 (14.8)
Patients censored, n (%)	29 (34.1)	2 (4.5)	22 (25.9)	4 (9.1)	51 (30.0)	6 (6.8)
Reached study end[1]	3 (3.5)	0	2 (2.4)	0	5 (2.9)	0
Premature discontinuation	23 (27.1)	2 (4.5)	10 (11.8)	4 (9.1)	33 (19.4)	6 (6.8)
Consent withdrawn	7 (8.2)	2 (4.5)	3 (3.5)	0	10 (5.9)	2 (2.3)
Lost to follow-up	2 (2.4)	0	0	3 (6.8)	2 (1.2)	3 (3.4)
Protocol violation	7 (8.2)	0	2 (2.4)	0	9 (5.3)	0
AE	0	0	1 (1.2)	0	1 (0.6)	0
Other	7 (8.2)	0	4 (4.7)	1 (2.3)	11 (6.5)	1 (1.1)
Death before clock start	2 (2.4)	0	10 (11.8)	0	12 (7.1)	0
Start of new anticancer tx	1 (1.2)	0	0	0	1 (0.6)	0

Table 13. Puncture-free survival, sensitivity analyses with alternative censoring rules, ITT

	Total	
	Catumaxomab	Control
Patients, n	170	88
Sensitivity analysis: all deaths before clock start considered as PuFS events		
Patients with event, n (%)	131 (77.1)	82 (93.2)
PuFS [days], median	44	11
95% CI	31, 49	9, 16
p-value[1]	<0.0001	
HR (95% CI)	0.310 (0.228, 0.423)	
Sensitivity analysis: all censored events counted as PuFS events		
Patients with event, n (%)	170 (100.0)	88 (100.0)
PuFS [days], median	30	11
95% CI	24, 37	8, 14
p-value[1]	<0.0001	
HR (95% CI)	0.400 (0.300, 0.533)	

[1] Log-rank test

Table 14. Puncture-free survival, sensitivity analyses, all deaths before clock start, ITT

	Ovarian Cancer		Nonovarian Cancer		Total	
	Catumaxomab	Control	Catumaxomab	Control	Catumaxomab	Control
Patients, n	85	44	85	44	170	88
Patients with event, n (%)	58 (68.2)	42 (95.5)	73 (85.9)	40 (90.9)	131 (77.1)	82 (93.2)
PuFS [days], median	48	11	30	14	44	11
95% CI	37, 59	9, 20	20, 45	8, 17	31, 49	9, 16
p-value[1]	<0.0001		<0.0001		<0.0001	
HR (95% CI)	Not calculated		Not calculated		0.310 (0.228, 0.423)	

Patients who completed the study at the scheduled study end without therapeutic puncture were censored at the date of the scheduled study end. Patients who discontinued the study after randomisation but before the endpoint of puncture or death were censored at the date of premature discontinuation.

[1] Log-rank test

Secondary endpoints

Time to first need of therapeutic ascites puncture

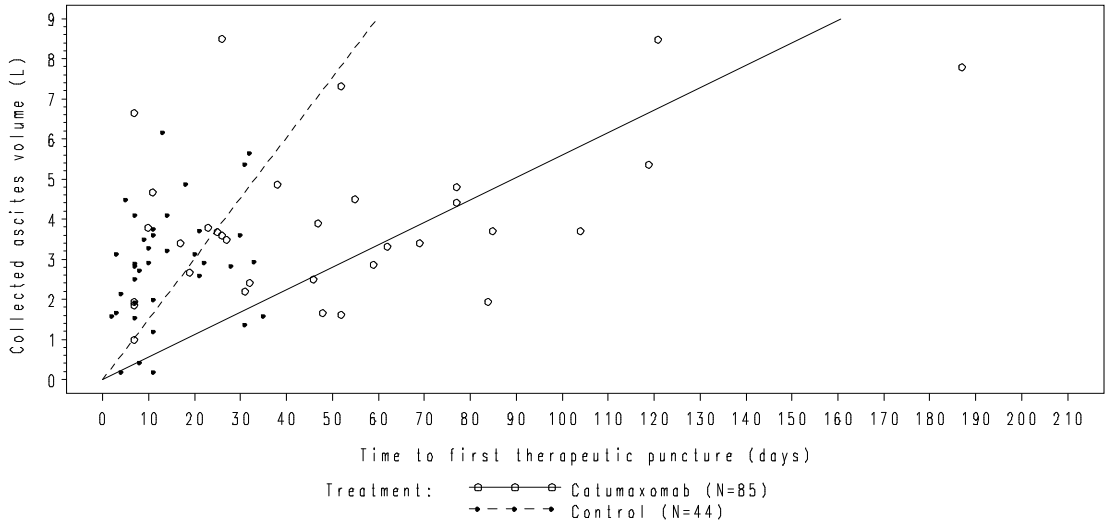
- Not presented here (see Discussion).

Correlation between collected ascites volume and time to puncture

Table 15. Correlation analysis: collected ascites volume at puncture vs. time to puncture (full analysis set)

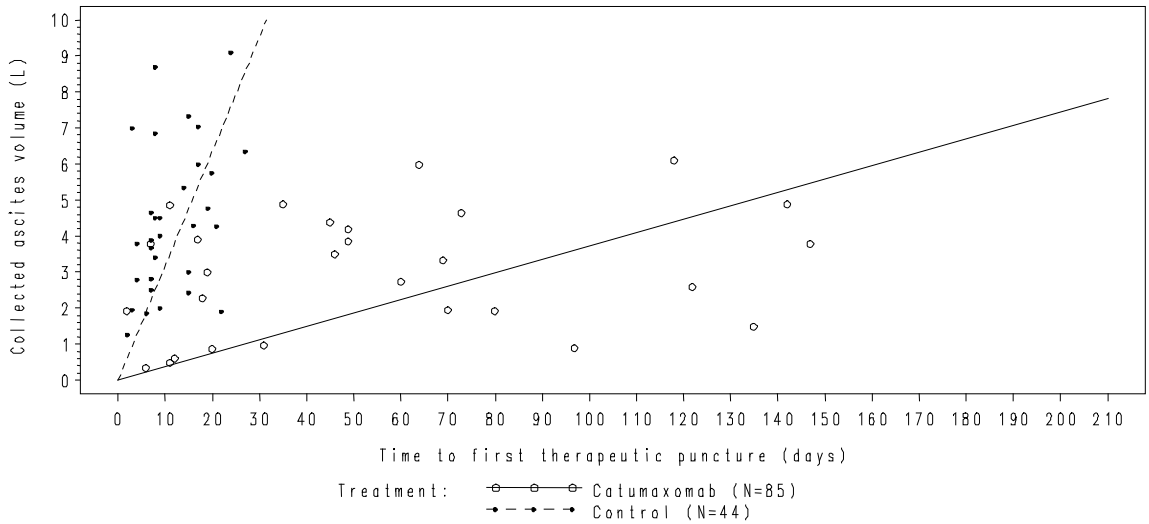
		Ovarian cancer patients		Non-ovarian cancer patients	
		Catumaxomab (N=85)	**Control (N=44)**	**Catumaxomab (N=85)**	**Control (N=44)**
Slope of regression line	Estimate	56.042	150.880	37.230	317.322
N: number of patients per treatment group.					

The figures below provide an overview of the correlation between collected ascites volume at puncture and time to puncture for both strata (including the related regression lines).



Note: Measurements with regression lines forced through the (0,0) origin

Figure 9. Collected ascites volume at puncture vs. time to puncture, ovarian cancer patients (full analysis set)



Note: Measurements with regression lines forced through the (0,0) origin

Figure 10. Collected ascites volume at puncture vs. time to puncture: all non-ovarian cancer patients, full analysis set

Daily collected ascites volume

Table 16. Median daily collected ascites volume (full analysis set)

	Ovarian cancer patients		Non-ovarian cancer patients	
	Catumaxomab (N=85)	Control (N=44)	Catumaxomab (N=85)	Control (N=44)
Median volume (mL/day)	81.8	271.0	55.10	414.35

Table 17. Collected volume on puncture visit

	Ovarian cancer		Nonovarian cancer		Total	
	Catum.	Control	Catum.	Control	Catum.	Control
Screening						
Patients, n	84	43	82	44	166	87
Ascites vol. [mL], mean (SD)	3277 (2404)	2955 (1786)	3782 (2486)	4277 (2770)	3527 (2450)	3623 (2416)
Ascites vol. [mL], median	2927	2927	3764	3951	3122	3375
Therapeutic puncture						
Patients, n	33	37	28	31	61	68
Ascites vol. [mL], mean (SD)	3939 (1960)	2884 (1417)	3011 (1690)	4441 (2074)	3513 (1885)	3594 (1901)
Ascites vol. [mL], median	3684	2927	3171	4273	3500	3251

Body weight and abdominal girth

- Will not be presented as inconclusive and without impact on B/R (see discussion)

Weight over time analyses

- Will not be presented as inconclusive and without impact on B/R (see discussion)

Total protein concentration in ascites

- Will not be presented as inconclusive and without impact on B/R (see discussion)

Time to death without therapeutic ascites puncture

Table 18. Time to death without therapeutic ascites puncture

	Ovarian cancer		Nonovarian cancer		Total	
	Catum.	Control	Catum.	Control	Catum.	Control
Patients, n	85	44	85	44	170	88
Patients with event, n (%)	20 (23.5)	4 (9.1)	35 (41.2)	9 (20.5)	55 (32.4)	13 (14.8)
Time to death without puncture [days], median	137	51	69	44	91	51
95% CI	73, NE	51, 68	37, 121	25, 55	64, 137	32, 68
p-value[1]	0.4643		0.3713		0.2170	

Abbreviation: NE= not estimable

[1] Log-rank test

Assessments to objectify need for / time to therapeutic puncture

1. Ascites symptoms assessed by interview

With the exception of fatigue, fewer ovarian cancer patients in the catumaxomab group had symptoms than in the control group for all symptoms assessed by interview. Ascites symptoms assessed by interview were reduced at Visit 6 in the catumaxomab group (compared to the control group) for abdominal pain, nausea, early satiety, abdominal swelling, and anorexia. For non-ovarian cancer patients, with the exception of heartburn, fewer patients in the catumaxomab group had symptoms than in the control group at Visit 6 for all signs and symptoms assessed. Ascites symptoms assessed by interview were reduced in the catumaxomab group (compared to the control group) for dyspnoea, abdominal pain and nausea.

2. Ascites signs assessed by physical abdominal examination

For ovarian cancer patients, the number of patients with ascites signs assessed by physical abdominal examination was reduced in the catumaxomab group for shifting dullness, fluid thrill and abdominal distension dull to percussion. Generally, fewer patients in the catumaxomab group had ascites signs than in the control group for all signs assessed by physical abdominal examination (table 17). For non-ovarian cancer patients, the number of patients with ascites signs assessed by physical abdominal examination was reduced in the catumaxomab group for shifting dullness, fluid thrill and abdominal distension dull to percussion. Generally, fewer patients in the catumaxomab group had ascites signs than in the control group for all signs assessed by physical abdominal examination.

Table 19. 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)**		**Catumaxomab (N=85)**	**Control (N=44)**	
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)		34 (63.0)	10 (38.5)	
Nausea	43 (64.2)	10 (41.7)		36 (66.7)	12 (46.2)	
Early satiety	37 (55.2)	6 (25.0)		32 (59.3)	13 (50.0)	
Abdominal swelling	39 (58.2)	9 (37.5)		30 (55.6)	11 (42.3)	
Anorexia	40 (59.7)	9 (37.5)		31 (57.4)	11 (42.3)	
Vomiting	46 (68.7)	14 (58.3)		38 (70.4)	18 (69.2)	
Heartburn	43 (64.2)	13 (54.2)		39 (72.2)	19 (73.1)	
Fatigue	42 (62.7)	17 (70.8)		33 (61.1)	15 (57.7)	
Swelling ankles	31 (46.3)	8 (33.3)		23 (42.6)	7 (26.9)	
Dyspnoea	39 (58.2)	13 (54.2)		33 (61.1)	8 (30.8)	
Signs assessed by abdominal examination as "none"						
Shifting dullness	39 (58.2)	5 (20.8)		33 (61.1)	8 (30.8)	
Fluid thrill	42 (62.7)	7 (29.2)		34 (63.0)	12 (46.2)	
Abdominal distension dull to percussion	33 (49.3)	4 (16.7)		30 (55.6)	8 (30.8)	

	Number (%) of patients					
	Ovarian cancer patients			Non-ovarian cancer patients		
	Catumaxomab (N=85)	Control (N=44)		Catumaxomab (N=85)	Control (N=44)	
Bulging flanks	39 (58.2)	9 (37.5)		33 (61.1)	12 (46.2)	

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 (ascending order).

3. Patients with ascites volume <1 L

- Will not be presented as inconclusive and without impact on B/R (see discussion)

4. Calculated ascites volume

- Will not be presented as inconclusive and without impact on B/R (see discussion)

5. Collected ascites volume

Table 20. Collected ascites volume

	Ovarian cancer		Nonovarian cancer		Total	
	Catum.	Control	Catum.	Control	Catum.	Control
Screening						
Patients, n	84	43	82	44	166	87
Ascites vol. [mL], mean (SD)	3277 (2404)	2955 (1786)	3782 (2486)	4277 (2770)	3527 (2450)	3623 (2416)
Ascites vol. [mL], median	2927	2927	3764	3951	3122	3375
Therapeutic puncture						
Patients, n	33	37	28	31	61	68
Ascites vol. [mL], mean (SD)	3939 (1960)	2884 (1417)	3011 (1690)	4441 (2074)	3513 (1885)	3594 (1901)
Ascites vol. [mL], median	3684	2927	3171	4273	3500	3251

6. Adherence to measures to objectify time of puncture

Table 21. Adherence to measures to objectify time of puncture

	Catumaxomab		Control	
	n	%	n	%
Patients	170		88	
With therapeutic puncture	64	100.0	69	100.0
With data on ascites signs and symptoms	64	100.0	69	100.0
With data on body weight at puncture	55	85.9	67	97.1
With data on abdominal girth at puncture	52	81.3	65	94.2
With data on ascites volume >1 L (radiologist)	43	67.2	57	82.6
With data on calculated ascites volume	44	68.8	54	78.3
With data on collected ascites volume	61	95.3	68	98.6

Overall survival

OS analysis as reported in the CSR has data cut-off date 31 May 2007. Reasons for censoring in the catumaxomab group were non-availability of post-study data (8%) and being alive (7%); censoring reasons in the control group were switch to catumaxomab (51%) and non-availability of post-study data (6%).

Table 22. Overall survival, ITT

	Ovarian cancer		Nonovarian cancer		Total	
	Catum.	Control	Catum.	Control	Catum.	Control
Patients, n	85	44	85	44	170	88
Patients with event, n (%)	66 (77.6)	14 (31.8)	78 (91.8)	24 (54.5)	144 (84.7)	38 (43.2)
Patients censored, n (%)						
Crossed over to catum.					0	45 (51.1)
No data					14 (8.2)	5 (5.7)
Premature discontinuation					4 (2.4)	0
Alive at data cut-off date					8 (4.7)	0
OS [days], median	110	81	52	49	72	68
95% CI	70, 164	68, 134	44, 74	33, 68	61, 98	49, 81
p-value[1]	0.1543		0.4226		0.0846	
HR (95% CI)	0.650 (0.357, 1.183)		0.825 (0.514, 1.324)		0.723 (0.498, 1.048)	

[1] Log-rank test

Control patients crossing over to catumaxomab open-label treatment were censored at the time of crossover.

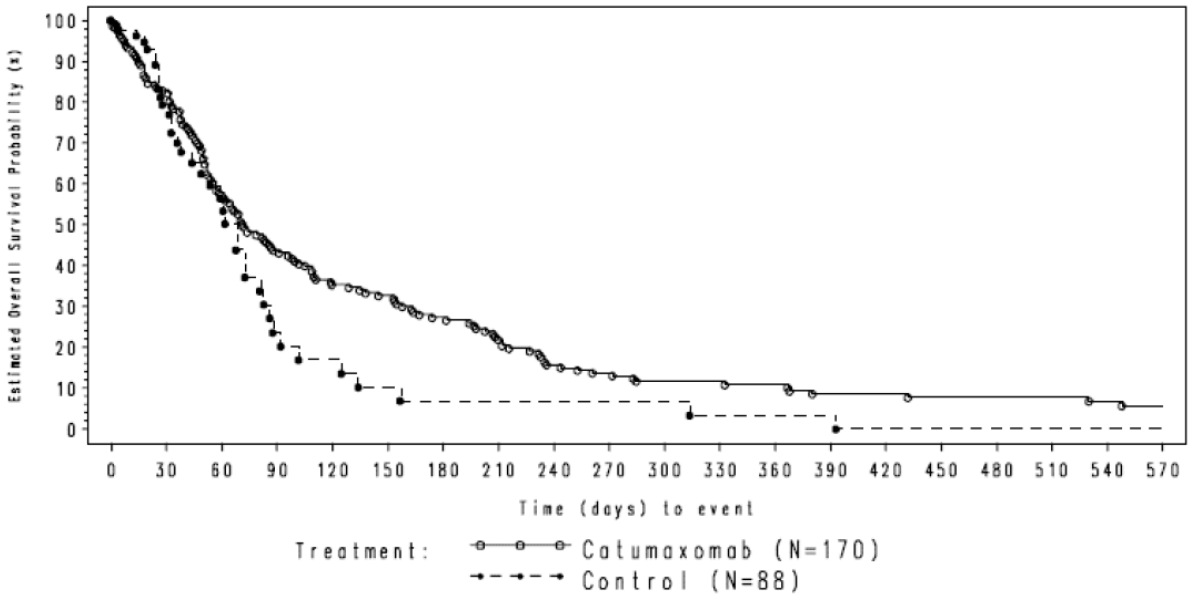


Figure 11. Overall survival (patients crossing over to experimental arm were censored at time of crossover) ITT

Sensitivity analyses of OS data

Two sensitivity analyses were performed.

a) In the first sensitivity analysis, control patients who crossed over to catumaxomab were analysed as randomised, and OS data observed after cross-over were used.

b) In the second sensitivity analysis, patients lost to follow-up were counted as death events.

As shown in the table below, this ensured comparable event rates in the 2 treatment arms, as compared to the primary OS analysis. Median OS as per these sensitivity analyses was consistent with the primary analysis.

Table 23. Overall survival, sensitivity analyses with alternative censoring rules, ITT

	Total	
	Catumaxomab	**Control**
Patients, n	170	88
Sensitivity analysis: crossover patients analysed as randomised and using crossover OS events		
Patients with event, n (%)	144 (84.7)	78 (88.6)
OS [days], median	72	71
95% CI	61, 98	54, 89
p-value[1]	0.1036	
HR (95% CI)	0.795 (0.602, 1.050)	
Sensitivity analysis: as above, and additionally patients lost to follow-up analysed as OS event		
Patients with event, n (%)	170 (100.0)	88 (100.0)
OS [days], median	66	65
95% CI	52, 83	49, 81
p-value[1]	0.0954	
HR (95% CI)	0.801 (0.617, 1.041)	

[1] Log-rank test

Source data: IP-REM-AC-01 CSR.04 Tables 5, 7, 9; IP-REM-AC-01 additional analyses Att-1 Q77.4, Att-2 Q77.4a, Att-3 Q77.4b, Att-13

Updated overall survival (cut-off Sep 2009)

An updated OS analysis became available with cut-off date on 10 Sep 2009. Control patients who did not enter the crossover period as well as all catumaxomab patients were censored at the date of their last post-study follow-up visit at which they were known to be alive or (if no post-study follow-up) at the date of their last visit documented on the study termination record.

In one analysis, control patients who rolled over into the crossover period were censored at the date of their first catumaxomab infusion. The analysis included 152 OS events in the catumaxomab arm vs 38 in the control arm i.e. 74% of patients having an OS event. Median OS was 72 vs 68 days. The HR was 0.718 (95% CI 0.495, 1.041), i.e. not formally reaching clinical significance.

In a second analysis, control patients receiving catumaxomab during the crossover period were not censored but were analysed together with the other control patients. The analysis included 152 OS events in the

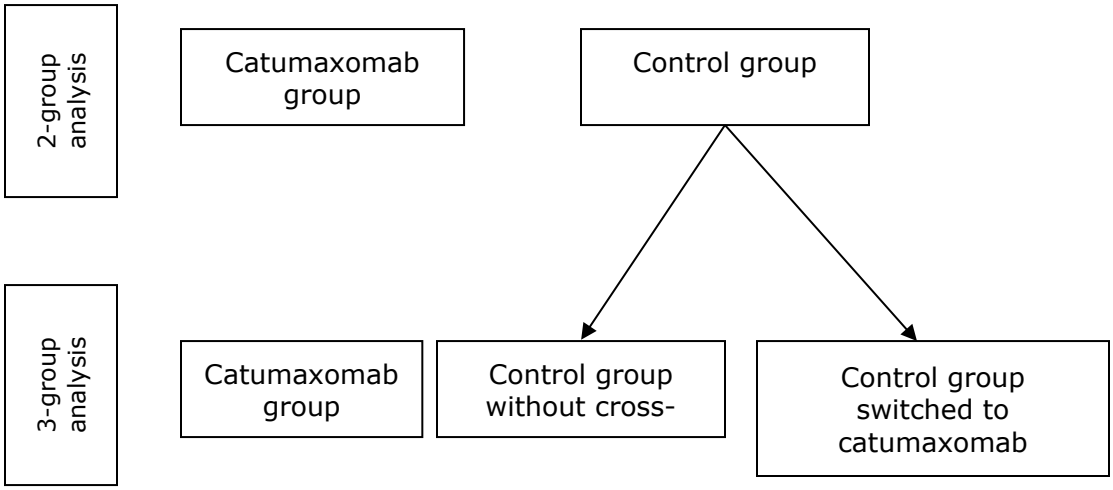
catumaxomab arm vs 79 in the control arm i.e. 90% of patients with OS event. Median OS was 72 vs 71 days. The HR was 0.798 (95% CI 0.606, 1.051), i.e. not formally reaching clinical significance.

In a sensitivity analysis of OS based on the safety set (i.e. including only catumaxomab patients who received at least one infusion, including 147 catumaxomab patients and 88 control patients), there were 144 OS events in the catumaxomab group and 38 OS events in the control group.

Median OS was 79 days with catumaxomab and 68 days with control (HR 0.649, 95% CI 0.446, 0.943).

3-group analysis of OS with cross-over as sensitivity analysis

Analysis approach in post-study part of Study IP-REM-AC-01



2-group analysis (only overall survival and time to progression analysed):

These approaches differed in the handling of the corresponding events (death or progression, respectively) occurring in control patients crossing over to catumaxomab. In the 2-group analysis such events were not considered; instead the time from randomisation until cross-over was used (and considered as censored observation). This conservative analysis is therefore based on the 2 groups as randomised and includes a log-rank test comparing the 2 randomised groups.

3-group analysis (all endpoints analysed):

In a second supportive analysis (3-group analysis), control-patients were further split to patients crossing-over to catumaxomab and patients not crossing-over. For patients crossing-over to catumaxomab all events (death or progression) were considered, including those events occurring after the cross-over. Different to the 2-analysis-approach there was no censoring performed for such post-cross-over events. For control-patients not crossing over to catumaxomab also all observed events were considered for this analysis.

Time within post-study period

During the post-study period the patients were observed until end of lifetime. Follow up differed between groups with shortest FU in the control group without cross-over

3-group analysis

In the 3-group analysis, best overall survival data were seen in all analysis groups for the cross-over group (controls switched to catumaxomab) with a difference between the cross-over group and the catumaxomab group of 24 days for ovarian cancer patients, 23 days for the pooled analysis, and 18 days for non-ovarian cancer patients (table 22). The least prolongation of overall survival was seen for the control group without cross-over in all analysis groups. The longest median overall survival was seen for all patients in the ovarian cancer group.

Table 24. Post-study: overall survival in the 2-group analysis (full analysis set)

	Pooled analysis		**Ovarian cancer patients**		**Non-ovarian cancer patients**	
2-group analysis	**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)**
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	

Table 25. Post-study: overall survival in the 3-group analysis (full analysis set) – Taken from Removab assessment

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

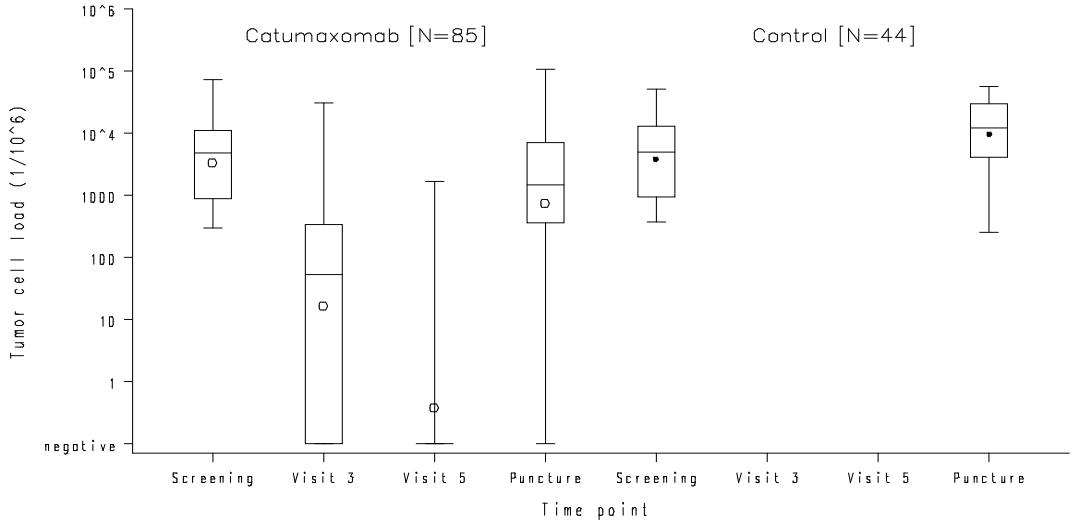
Progression-free survival

- PFS will not be presented as inconclusive and without impact on B/R (see discussion)

Tumour response rate

- TRR will not be presented as inconclusive and without impact on B/R (see discussion)

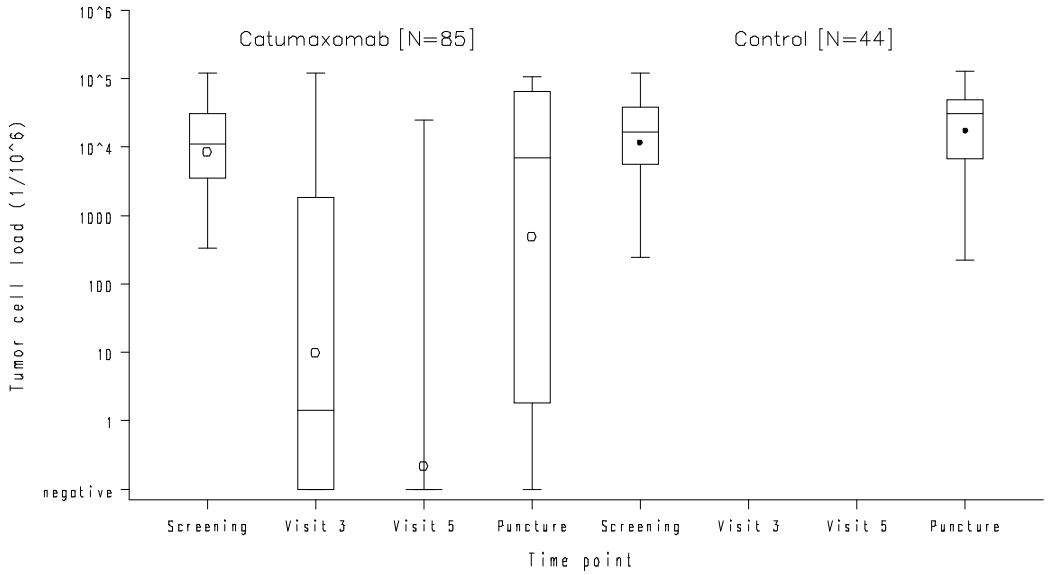
Tumour cell load



Note: Lower, upper end of box = 25., 75. percentiles, Line across box = Median,
Lower, upper end of vertical lines = Minimum, Maximum, Dot = Mean

Figure 12. Tumour cell load in ovarian cancer patients (full analysis set)

N: number of patients in a treatment group.



Note: Lower, upper end of box = 25., 75. percentiles, Line across box = Median,
Lower, upper end of vertical lines = Minimum, Maximum, Dot = Mean

Figure 13. Tumor cell load in non-ovarian cancer patients (full analysis set)

N: number of patients in a treatment group.

Triggered analysis on subsequent punctions

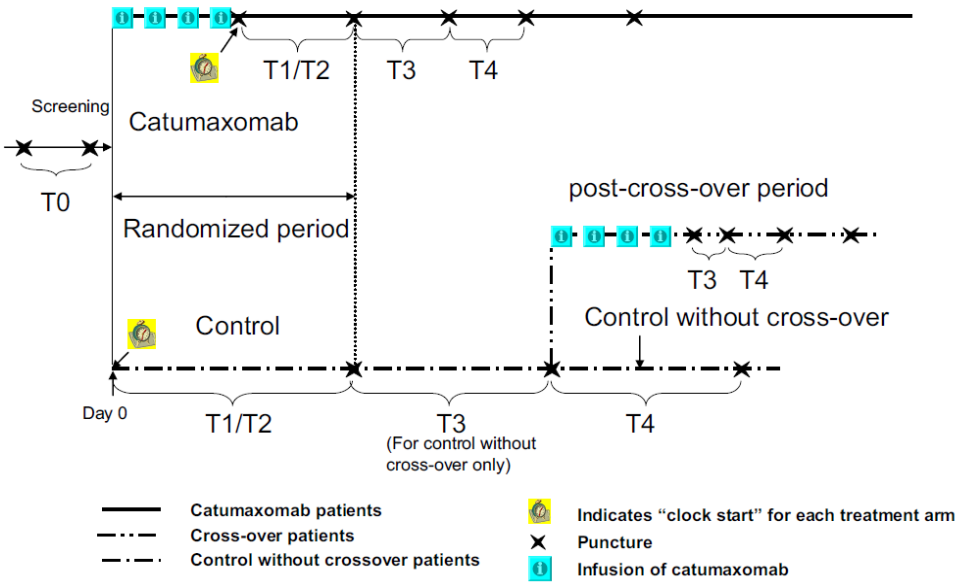


Figure 14. Schematic definitions of time intervals between punctures

Table 26. Time to therapeutic punctures: Ovarian cancer patients, full analysis set

	Catumaxomab N = 85	Controls without cross-over N = 16	Controls switched to Catumaxomab N = 28
T0: Time before screening puncture*		Control N = 44	
n	85	44	
Minimum	1	3	
Median	17.0	19.5	
Maximum	46	36	
T1: Time to puncture in randomized part of study			
n	36	10	28
Minimum	7	6	2
Median	44.5	12.5	10.0
Maximum	187	33	35
T2: Time to puncture in randomized part of study			
n	20	4	13
Minimum	7	7	4
Median	49.5	16.0	7.0
Maximum	187	31	30
T3: Time to 1st puncture in post-study/post-cross-over**			
n	20	4	13
Minimum	2	10	1
Median	26.0	25.0	8.0
Maximum	226	47	284
T4: Time from 1st to 2nd puncture in post-study/post-cross-over			
n	15	3	10
Minimum	1	20	1
Median	17.0	35.0	12.5
Maximum	164	150	89

Table 27. Time to therapeutic punctures: All non-ovarian cancer patients, full analysis set

	Catumaxomab N = 85	Controls without cross-over N = 27	Controls switched to Catumaxomab N = 17
T0: Time before screening puncture*		**Control N = 44**	
n	85	44	
Minimum	2	2	
Median	14.0	17.5	
Maximum	63	35	
T1: Time to puncture in randomized part of study			
n	28	14	17
Minimum	2	6	2
Median	47.5	15.5	7.0
Maximum	147	27	21
T2: Time to puncture in randomized part of study			
n	8	3	4
Minimum	11	7	2
Median	52.5	20.0	6.0
Maximum	147	22	15
T3: Time to 1st puncture in post-study/post-cross-over**			
n	8	3	4
Minimum	6	10	3
Median	23.5	18.0	9.5
Maximum	77	21	13
T4: Time from 1st to 2nd puncture in post-study/post-cross-over			
n	4	2	2
Minimum	7	8	18
Median	17.0	28.5	25.0
Maximum	31	49	32

Quality of Life

Currently, no validated questionnaire for malignant ascites is available, therefore a questionnaire for the underlying disease was used to investigate the QoL. The patients' QoL was assessed with the European Organization for Research and Treatment of Cancer (EORTC) QoL questionnaire (QLQ) C30. For ovarian cancer patients, the questionnaire EORTC QLQ-C28 was used in addition. For the pooled analyses, EORTC QLQ-C30 scores of most domains were similar in both treatment groups at screening and puncture visit. The data showed high individual variation in changes from screening to puncture visit.

Wimberger et al. 2012

Based on the data from study IP-REM-AC-01, Wimberger (2012) investigated and published QOL of patients. QOL was assessed using the EORTC QLQ-C30 questionnaire at screening, 1, 3 and 7 months after treatment and in, the case of re-puncture, on the day of paracentesis. Time to first deterioration in QOL was defined as a decrease in the QOL score of at least 5 points and compared between treatment arms (catumaxomab n=160; control n=85) groups using the log-rank test and Cox proportional hazards models adjusted for baseline score, country, and primary tumour type.

Thresholds for the interpretation of EORTC QLQ-C30 scores were established by Osoba (1994), were small, moderate, and large changes in QOL are defined by changes in the score from 5 to 10; 10 to 20; and >20, respectively.

Deterioration in QOL scores (i.e. decrease in score from screening of ≥5 points) was more rapid in the control group than in the catumaxomab group (Figure 15). Median time to first deterioration ranged from 19 to 26 days in the control group and from 47 to 49 days in the catumaxomab group. This is also reflected by the Kaplan-Meier curves, see Figure 16.

HRs ranged from 0.08 for nausea and vomiting score to 0.24 for emotional functioning score. Regarding covariables included in the models for adjustment, the baseline value of the respective QOL score was found to have an impact on QOL deterioration for all scores of primary interest, except for fatigue, i.e. the better the level of QOL or the lower the level of symptoms at baseline, the greater the risk of experiencing a deterioration in QOL or symptoms during the study (HR 1.02 for QOL scores; HR 0.97-0.99 for symptom scores). Primary tumour type and country had no (nominally) significant impact on time to deterioration in QOL.

Sensitivity analyses conducted with a 10-point threshold for the definition of deterioration in QOL provided similar results (HRs 0.08-0.23).

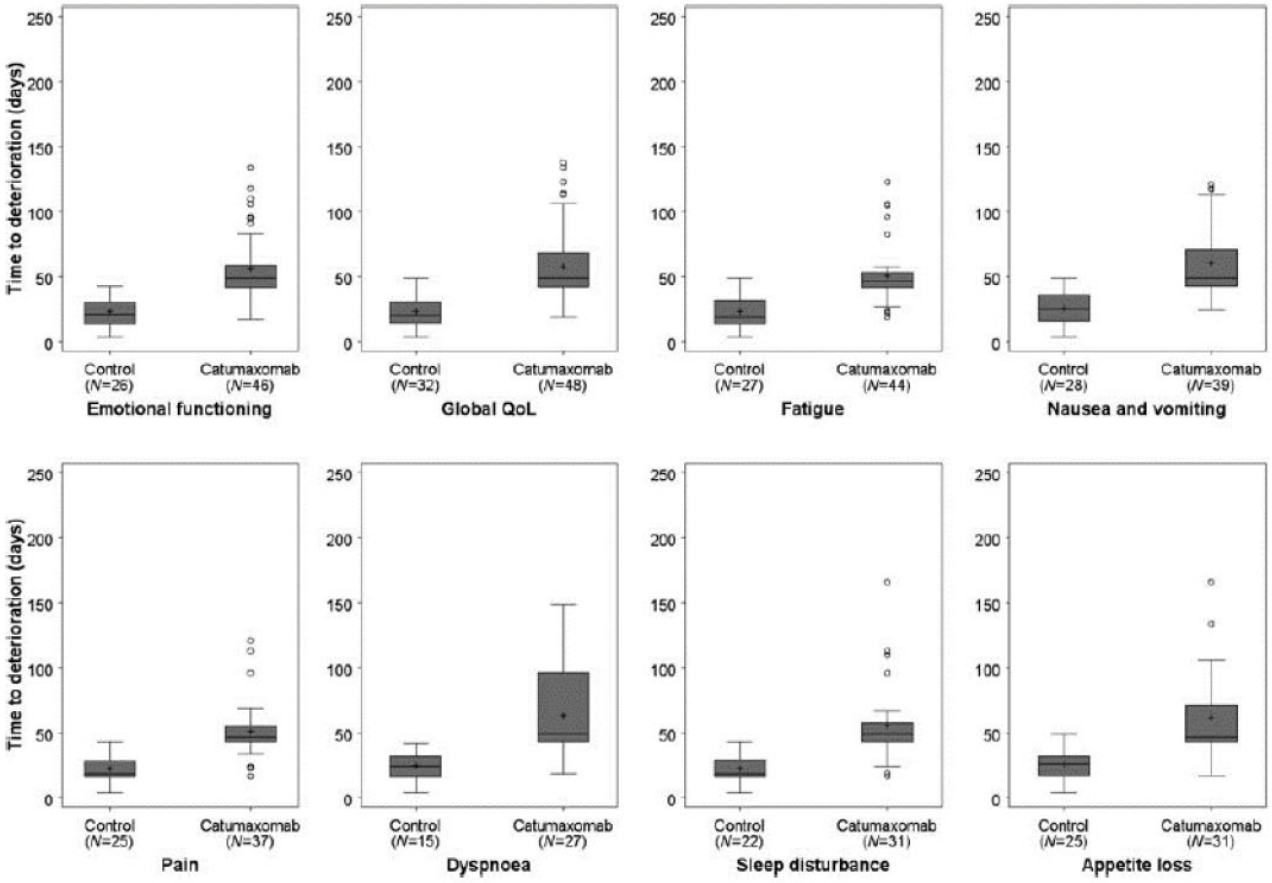
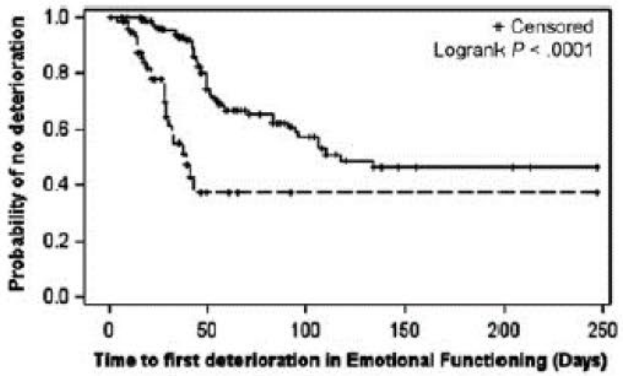
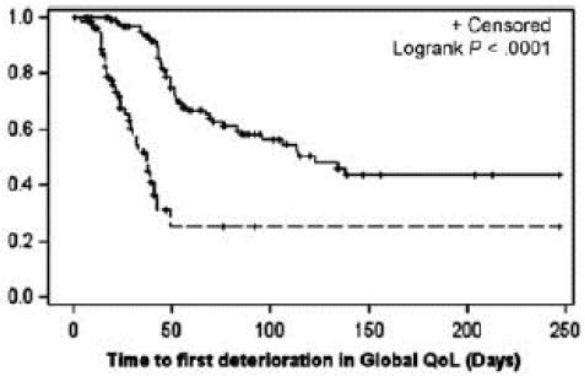
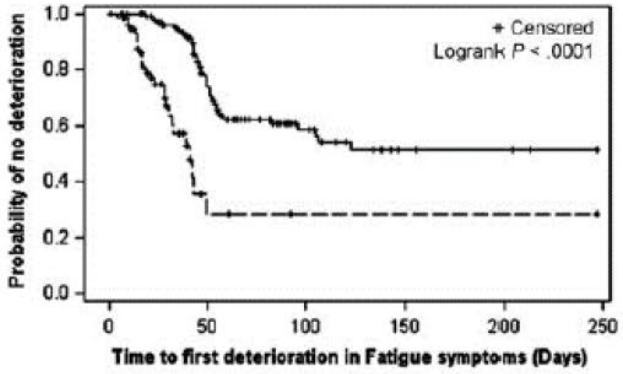
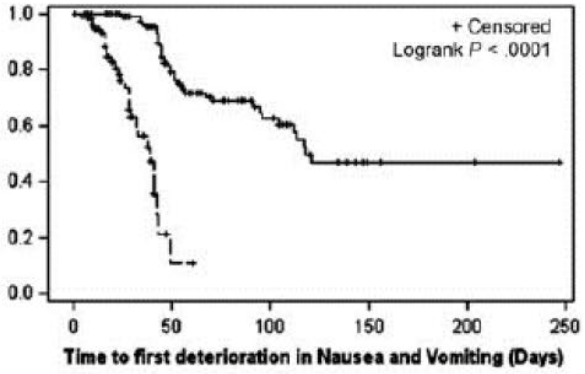


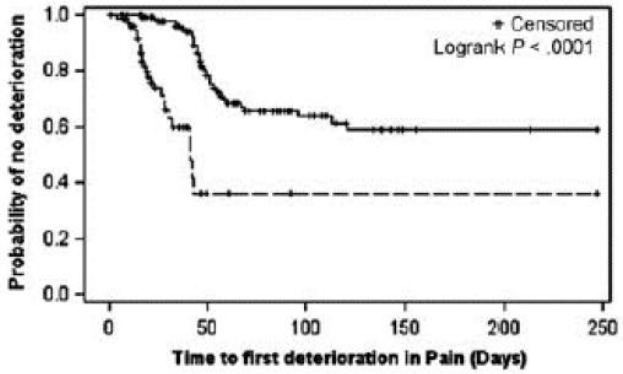
Figure 15. Box plots of EORTC QLQ-C30 scores of primary interest

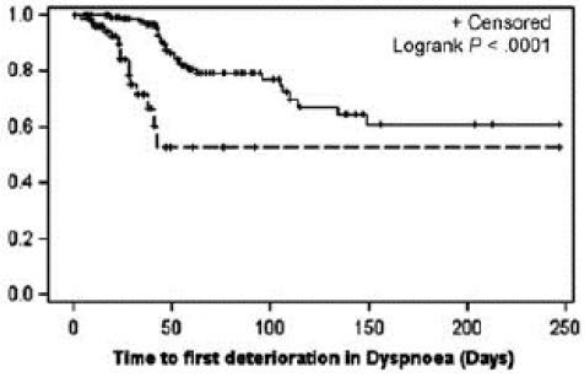

+ Censored
Logrank P < .0001
Probability of no deterioration
1.0
0.8
0.6
0.4
0.2
0.0
0
50
100
150
200
250
Time to first deterioration in Emotional Functioning (Days)

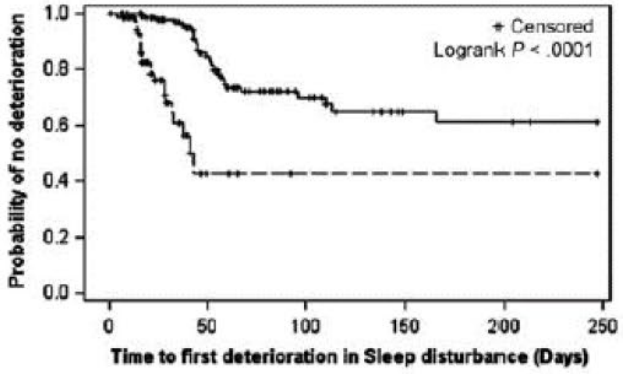

+ Censored
Logrank P < .0001
1.0
0.8
0.6
0.4
0.2
0.0
0
50
100
150
200
250
Time to first deterioration in Global QoL (Days)


+ Censored
Logrank P < .0001
Probability of no deterioration
1.0
0.8
0.6
0.4
0.2
0.0
0
50
100
150
200
250
Time to first deterioration in Fatigue symptoms (Days)


+ Censored
Logrank P < .0001
1.0
0.8
0.6
0.4
0.2
0.0
0
50
100
150
200
250
Time to first deterioration in Nausea and Vomiting (Days)


+ Censored
Logrank P < .0001
Probability of no deterioration
1.0
0.8
0.6
0.4
0.2
0.0
0
50
100
150
200
250
Time to first deterioration in Pain (Days)


+ Censored
Logrank P < .0001
1.0
0.8
0.6
0.4
0.2
0.0
0
50
100
150
200
250
Time to first deterioration in Dyspnoea (Days)


+ Censored
Logrank P < .0001
Probability of no deterioration
1.0
0.8
0.6
0.4
0.2
0.0
0
50
100
150
200
250
Time to first deterioration in Sleep disturbance (Days)

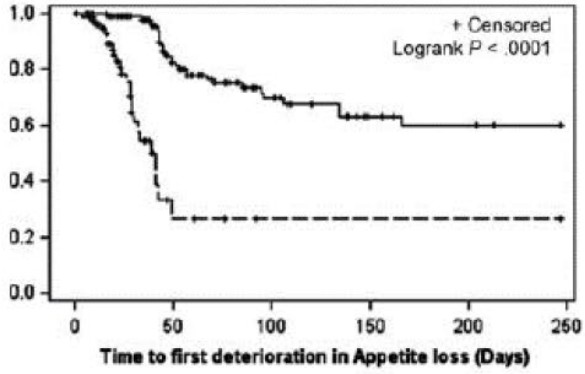

+ Censored
Logrank P < .0001
1.0
0.8
0.6
0.4
0.2
0.0
0
50
100
150
200
250
Time to first deterioration in Appetite loss (Days)

Figure 16. Kaplan-Meier curves of EORTC QLQ-C30 scores of primary interest

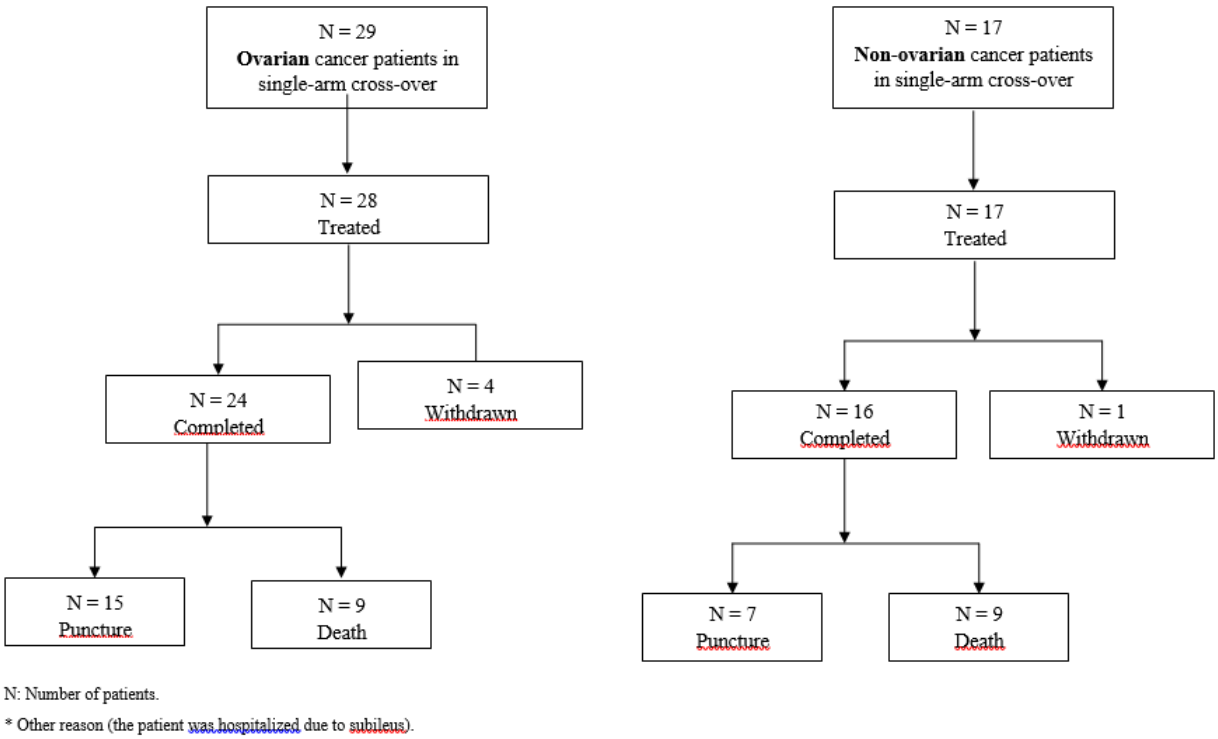
- **Ancillary analyses**

Ascites volume estimations as sensitivity analysis and concordance testing

The applicant provided an analyses of different ascites volume estimations (by local radiologist vs. central blinded reader vs. collected volume). This is an attempt to compensate for the fact that in this open-label study the assessment of the need for therapeutic paracentesis and the evaluation of the patients' symptoms may be biased. Only one subject did not fulfil the radiologic criteria for punction (more than 1 L) per local radiologist. A different subject did not fulfil criteria per central blinded readers.

Therefore, a high concordance has been demonstrated in fulfilling the radiologic criteria for punction. At puncture visit, ovarian cancer patients have had a trend to higher ascites volume per radiologic assessment and also in the collected volume in catumaxomab group. For non-ovarian cancer numerically higher values of collected volume were noted for the control arm, which is opposite to the trend finding in the ovarian cancer.

Results of the single arm cross over



N: Number of patients.

* Other reason (the patient was hospitalized due to subileus).

Figure 17. Disposition of patients (cross-over period)

Puncture free survival

Table 28. Cross-over study: puncture-free survival (full analysis set)

	Pooled analysis (N=46)	**Ovarian cancer patients (N=29)**	**Non-ovarian cancer patients (N=17)**
% of patients with event	83%	83%	82%
Median puncture-free survival (days)	27	27	25
95% CI	[17; 39]	[17; 54]	[7; 51]
N: total number of patients; CI: confidence interval			

Median PuFS in cross-over study was 25-27 days which is shorter than 37-52 days in the randomised part. This might be due to more advanced disease.

Intra-individual comparison of TTP

Table 29. Intra-individual comparison of time to first need for therapeutic ascites puncture before and during cross-over (full analysis set)

Cross-over	Ovarian cancer patients (N=29)			Non-ovarian cancer patients (N=17)		
	During randomised part of the study	During cross-over	Difference (cross-over minus randomised)	During randomised part of the study	During cross-over	Difference (cross-over minus randomised)
Number of patients with puncture	29	15	15	17	7	7
Median time to need for first therapeutic puncture (days)	10	41	33	7	52	50
95% CI	[7; 13]	[21; 80]	[10; 47]	[4; 14]	[21; 105]	[6; 88]
N: total number of patients. patients; CI: confidence interval. Intra-individual comparisons were based on patients who had events during the randomised part of the study and during cross-over.						

Cross-over design made an intra-individual analysis possible. In this intra-individual comparison, longer times to punction after catumaxomab than they have had in the randomised part in the control arm.

Concomitant treatment

As to concomitant treatment, all drug groups have been more frequently used in catumaxomab-treated patients.

Table 30. Most frequent (>20%) concomitant medications, safety set

ATC4 code	Ovarian cancer		Nonovarian cancer	
	Catumaxomab	Control	Catumaxomab	Control
Patients treated, n	80	44	77	44
Any concomitant medication	73 (91.3)	21 (47.7)	69 (89.6)	18 (40.9)
Anilides	52 (65.0)	4 (9.1)	40 (51.9)	2 (4.5)
Propulsives	46 (57.5)	8 (18.2)	37 (48.1)	7 (15.9)
Pyrazolones	31 (38.8)	7 (15.9)	24 (31.2)	2 (4.5)
Blood substitutes and plasma protein fractions	27 (33.8)	3 (6.8)	33 (42.9)	7 (15.9)
Electrolyte solutions	24 (30.0)	5 (11.4)	29 (37.7)	2 (4.5)
Proton pump inhibitors	24 (30.0)	5 (11.4)	6 (14.3)	0
Serotonin antagonists	24 (30.0)	3 (6.8)	25 (32.5)	5 (11.4)
Other opioids	23 (28.8)	6 (13.6)	6 (17.1)	1 (4.2)
Solutions for parenteral nutrition	16 (20.0)	4 (9.1)	28 (36.4)	4 (9.1)
Natural opium alkaloids	11 (13.8)	3 (6.8)	24 (31.2)	1 (2.3)

The table shows all concomitant medications reported >20% in at least one treatment group. Sort order is by decreasing frequency in the catumaxomab arm of the ovarian cancer stratum.

Analysis of specific cancer entities

Table 31. Distribution of cancer types, study IP-REM-AC-01, ITT, all patients

	Catumaxomab		Control		Total	
	n	%	n	%	n	%
Ovarian cancer	85	50.0	44	50.0	129	50.0
Gastric cancer	46	27.1	20	22.7	66	25.6
Breast cancer	5	2.9	8	9.1	13	5.0
Pancreas cancer	6	3.5	3	3.4	9	3.5
Colon cancer	4	2.4	4	4.5	8	3.1
Endometrial cancer	4	2.4	2	2.3	6	2.3
Lung cancer	1	0.6	0	0.0	1	0.4
Other[1]	19	11.2	7	8.0	26	10.1

[1] Including: carcinoma of unknown primary, cholangiocarcinoma, primary peritoneal cancer, primary liver cancer, oesophageal cancer, uterine cancer, fallopian tube neoplasm malignant, urothelial cancer, rectum cancer, and melanoma.

Table 32. Key efficacy results in gastric cancer patients, ITT

	Catumaxomab	Control	p-value[1]
Patients	46	20	
PuFS			
Patients with event	39	18	
Median [days], 95% CI	44 (27, 69)	15 (8, 21)	<0.0001
TTPu			
Patients with event	15	14	
Median [days], 95% CI	118 (64, 147)	15 (8, 24)	<0.0001
OS[2]			
Patients with event	43	12	
Median [days], 95% CI	71 (50, 98)	44 (28, 68)	0.0313
TTP[2]			
Patients with event	9	3	
Median [days], 95% CI	110 (99, 187)	35 (34, NE)	<0.0001

[1] Log-rank test.

[2] Control patients who crossed over to catumaxomab were censored at the time of crossover

ADAs and their impact on efficacy

Table 33. Key efficacy results by ADA status (Medac test), ITT

	Median time [days]			p-value[1]	
	Control (n=50)	Catumaxomab		Control vs ADA negative	ADA positive vs ADA negative
		ADA negative (n=27)	ADA positive (n=85)		
PuFS	21	27	64	0.0327	<0.0001
TTPu	21	46	104	0.0045	0.0002
OS	62	64	129	0.4009	0.0003

[1] Log-rank test.

Only control patients who attended Visit 6 were included in the analysis. For PuFS, patients who were lost to follow-up were censored at the time of their last visit. In addition, for OS, control patients who crossed over to open-label catumaxomab treatment were censored at the time of crossover.

- **Summary of main efficacy results**

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 34. Summary of efficacy for trial IP-REM-AC-01

Title: Two-arm, randomised (2:1), open-label phase II/III study in EPCAM-positive cancer patients with symptomatic malignant ascites using paracentesis plus the trifunctional antibody Removab (anti-EPCAM x anti-CD3) versus paracentesis alone			
Study identifier	IP-REM-AC-01 EudraCT number 2004-000723-15		
Design	Phase II/III, randomised (2:1 for catumaxomab to control), open-label study Patients in the control group who had undergone a second therapeutic ascites puncture after Day 0 were permitted to cross over into an optional single-arm cross-over period to active catumaxomab Results presented in this study narrative are from the randomised main study part and for the overall patient population (regardless of stratum), unless otherwise stated Multicentre study		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		Treatment on Days 0, 3, 7, 10; follow-up visits after the last infusion (catumaxomab) or Day 0 (control), at 8 days, and 1, 3, 5, and 7 months Not applicable Not applicable
Hypothesis	Superiority		
Treatments groups	Catumaxomab		Catumaxomab infusions (n=4) i.p. of 6-h duration at doses of 10 µg (Day 0), 20 µg (Day 3), 50 µg (Day 7), and 150 µg (Day 10) Prior to each of the 4 infusions (Days 0, 3, 7, 10) and after the last infusion, fluid was discharged from the peritoneal cavity (‘draining to dryness’) n=170 patients randomised 39% of patients discontinued prematurely.
	Control		Fluid was discharged from the peritoneal cavity on Day 0 n=88 patients randomised 15% of patients discontinued prematurely.
Endpoints and definitions	Puncture-free survival (primary)	PuFS	PuFS was a composite endpoint that comprised time to first need for therapeutic ascites puncture or death, whatever occurred first. For catumaxomab patients, PuFS was defined as the time after drainage to dryness following the last catumaxomab infusion until the first need for therapeutic puncture or death, whichever occurred first. For control patients, PuFS was defined as time after the therapeutic ascites puncture on Day 0.

	Overall survival	OS	OS was defined as time from randomisation to death due to any cause
Database lock	Not specified		
Results and Analysis			
Analysis description	**Primary Analysis: PuFS (primary endpoint)**		
Analysis population	Intent to treat; protocol-defined censoring; data cut-off date Nov 2006		
Descriptive statistics and estimate variability	Treatment group	Catumaxomab	Control
	Number of patients	170	88
	Patients with event, n (%)	119 (70)	82 (93)
	Median PuFS (days)	**46**	**11**
	95% CI (days)	35, 53	9, 16
Effect estimate per comparison	Primary endpoint PuFS	Comparison groups	Catumaxomab vs control
		Hazard ratio	0.254
		Hazard ratio 95% CI	0.185, 0.350
		p-value (log rank test)	<0.0001
Analysis description	**OS (secondary endpoint)**		
Analysis population	Intent to treat; protocol-defined censoring; data cut-off date May 2007		
Descriptive statistics and estimate variability	Treatment group	Catumaxomab	Control
	Number of patients	170	88
	Patients with event, n (%)	144 (85)	38 (43)
	Median OS (days)	72	68
	95% CI (days)	61, 98	49, 81
Effect estimate per comparison	OS	Comparison groups	Catumaxomab vs control
		Hazard ratio	0.723
		Hazard ratio 95% CI	0.498, 1.048
Analysis description	**OS (secondary endpoint) – update with later data cut-off**		
Analysis population	Intent to treat; protocol-defined censoring; data cut-off date Sep 2009		
Descriptive statistics and estimate variability	Treatment group	Catumaxomab	Control
	Number of patients	170	88
	Patients with event, n (%)	152 (89)	38 (43)

	Median OS (days)	72	68
	95% CI (days)	n.a.	n.a.
Effect estimate per comparison	OS	Comparison groups	Catumaxomab vs control
		Hazard ratio	0.718
		Hazard ratio 95% CI	0.495, 1.041

2..6.5.3. Clinical studies in special populations

	Age 65-74 (Older subjects number /total number)	Age 75-84 (Older subjects number /total number)	Age 85+ (Older subjects number /total number)
Controlled Trials	37 / 157	8 / 157	1 / 157
Non-Controlled trials	80 / 360	25 / 360	4 / 360

2..6.5.4. *In vitro* biomarker test for patient selection for efficacy

Assay

Table 35. Bioanalytical methods used in clinical studies with catumaxomab

Test	Method	Sample matrix	Parameters	Sensitivity	Reports	Validation	Use in clinical study
Pharmacokinetics							
Tumour cells in ascites fluid	Immuno-histochemistry	Cells from ascites fluid	EpCAM+ cells	1 cell/slide (2.5×10^5 cells)	TR-VAL-060100-V01 [3] TR-VAL-060200-V01 TR-KF-0001-07	Yes	IP-REM-AC-01 IP-REM-PK-01-EU STP-REM-01

In predose samples, the anti-EpCAM antibody HO-3 (TRION Pharma, Munich, Germany) was used for staining of EpCAM+ tumour cells. HO-3 is the parental antibody of catumaxomab's EpCAM-specific arm. In parallel, staining for cytokeratin was performed to confirm the epithelial nature of the cells detected, using antibody A45/B/B3. In post-dose samples, the anti-EpCAM antibody VU1D9 (TRION Research, Martinsried, Germany) was used in order to prevent competitive inhibition of the staining antibody by residual catumaxomab. VU1D9 recognises a different EpCAM epitope than HO-3. Either antibody (HO-3, VU1D9) was directly labelled with Texas Red fluorescence dye.

Three validation studies were performed:

1. Validation of preparation and counting of viable cells from ascites fluid (TR-VAL- 060100-V01),

2. Validation of detection of EpCAM+ cells and cytokeratin+ cells in malignant ascites (TR-VAL-060200-V01),

3. Evaluation of simultaneous reduction of EpCAM+ cells and cytokeratin+ cells in ascites samples collected after treatment with catumaxomab (TR-VAL-060200-V01).

Threshold in the pivotal study

A total of 465 patients were screened for EpCAM-positivity; 205 ovarian cancer patients and 260 non-ovarian cancer patients. The threshold for positivity was set at 400 EpCAM-positive cells in 10^6 total cells. 99 (30 ovarian and 69 non-ovarian) from 465 patients were excluded due to EpCAM-negativity.

Development of a future assay

Currently, there is no available biomarker assay. The applicant proposes an *in vitro* diagnostic assay, i.e. Medicover EpCAM In-house Assay, to be manufactured and used only in a single health institution established in the Union ("in-house assay"). A cut-off will be applied to determine which patients are considered eligible for treatment with Korjuny, based on the cut-off from the pivotal clinical trial. As no clinical trial samples remain from the pivotal trial that could be used in a clinical bridging study, and because the CTA from the pivotal study is no longer available, clinical performance of the Medicover EpCAM In-house Assay will be demonstrated by showing statistically equivalent analytical performance to the CTA. To demonstrate analytical concordance between the Medicover EpCAM In-house Assay and the CTA the applicant will repeat the analytical validation study as it was performed for the CTA reported by Trion1, using contrived samples with a known EpCAM-positive cell count prepared exactly as those prepared in the original validation study:

- Studies will be conducted with PBMC of healthy donors in PBS or supernatant of cell free ascites fluid, spiked with cells from an EpCAM-expressing cell line (SW480 cells).
- The same antibody as the CTA (anti-EpCAM HO-3) will be used, for which the selectivity / specificity is already known and published.
- Robustness of the assay in terms of sample stability, antibody concentration, incubation time and centrifugation conditions were confirmed for the CTA and will be identical for the Medicover EpCAM In-house Assay.
- Linearity will be determined by 6-fold determination of 6 different concentrations of SW480 tumour cells. This study will also determine range, LoD and LoQ.
- Trueness will be determined by 6 repeats with three different tumour cell concentrations. This study will also determine within-run precision, between-run precision (repeatability) and uncertainty of measurement.
- Acceptance criteria will be the analytical performance achieved by the CTA.

2..6.5.5. Analysis performed across trials (pooled analyses and meta-analysis)

n/a

2..6.5.6. Supportive study(ies)

For efficacy claims, three supportive studies have been submitted.

Study STP-REM-01 was a non-randomised, multi-centre, dose-escalation study with up to 5 i.p. infusions of catumaxomab to establish the maximum tolerated dose (MTD) in patients with malignant ascites due to ovarian carcinoma and investigated the safety, tolerability and preliminary efficacy of catumaxomab. 23 patient**s** were included. Each infusion lasted 6 h. A follow-up visit was done 7 days after the last infusion; an end of trial visit was performed 28 days after the last infusion.

The actual doses the patients received in each dose groups until the MTD was reached are shown below.

Table 36. Dosing scheme in Study STP-REM-01

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	
i.v.	10 μg	20 μg	50 μg	200 μg	
V	10 μg	20 μg	50 μg	200 μg	200 μg

Free peritoneal ascites flow rate was calculated from the collected ascites volume (minus lavage volumes if appropriate) and time of collection. On the morning of Day 0, ascites flow rate was calculated since the time of catheter placement; collection of the first fraction of ascites lasted at least 20 h. In the morning of Days 1 to 10, ascites flow rate was calculated for the past 24 h. Necessity of peritoneal puncture before the end-of-trial visit was to be documented as an AE or documented as comment in the end-of-trial page on the CRF. Data were analysed using descriptive statistics only.

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 was shown.

Table 37. Ascites flow rate (mL/h) in Study STP-REM-01 (ITT population)

	Statistic	**All dose groups (mL/h)**
Before first infusion (baseline)	N	20
	Median (range)	104.7 (6.3 ; 1200.0)
Day 1 after the fourth infusion	N	18
	Median (range)	23.2 (0.0 ; 240.0)
Change from baseline to Day 1 day after the fourth infusion	N	15
	Median (range)	−51.7 (−1200.0 ; 42.1)
N: total number of patients, ITT: intention to treat		

Secondary endpoints, i.e. necessity of peritoneal puncture and tumor cell load, confirmed the effect of catumaxomab and supported the claims of the main study (data not shown).

Maximum tolerated dose (MTD)

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.

This study determined the dose for the pivotal study.

Study IP-REM-PK-01-EU was a non-randomised 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. From efficacy point of view, Time to ascites puncture was assessed up to Day 38. A total of 13 patients received catumaxomab at 3 sites in Romania and 4 sites in Germany. The efficacy value of this study is limited. Although tumour cells have been reduced, no reduction in ascites volume has been shown here.

Study IP-REM-AC-02-US was a Phase II, single-arm, open-label study performed at 15 active sites in the US. This study has not been included in the original Removab dossier. This study applied the 3h infusion (see also Clinical safety). Interpretation of efficacy is very limited due to lack of comparator and subjective indication for paracentesis (patient's request) after administration of catumaxomab. EpCAM positivity was not required.

Primary efficacy endpoint was the proportion of patients who achieved a 4-fold increase in puncture/paracentesis-free interval following catumaxomab.

Time-related endpoints used as secondary endpoints have very limited value in SAT and are not presented.

Puncture-free interval was longer after catumaxomab treatment. However, the pre-defined threshold of study success >60% has not been achieved. Moreover, only 28% of patients achieved a 4-fold prolongation interval, this is lower than 30% which was considered the limit to assess the efficacy as low.

IP-CAT-AC-03 (CASIMAS) (Sehouli 2014) was a randomised, open-label, phase III study investigating the safety and efficacy of a 3-h catumaxomab infusion with/without prednisolone premedication to reduce catumaxomab-related adverse events. Patients with malignant ascites due to epithelial cancer received four 3-h intraperitoneal catumaxomab infusions with/without intravenous prednisolone (25 mg) premedication before each infusion. where positive EpCAM status was not required for inclusion. This study is used for safety aspects and in support of the 3-h infusion rate. Summarised data are presented below.

Table 38. Efficacy data, study IP-CAT-AC-03

	Catumaxomab + prednisolone	Catumaxomab
Patients, n	111	108
Tumour types, n (%)		
Ovarian	58 (52.3)	51 (47.2)
Breast	17 (15.3)	9 (8.3)
Gastric	10 (9.0)	8 (7.4)

	Catumaxomab + prednisolone	Catumaxomab
Pancreas	5 (4.5)	6 (5.6)
Colon	4 (3.6)	7 (6.5)
Endometrial	5 (4.5)	4 (3.7)
Lung	1 (0.9)	1 (0.9)
Other	11 (9.9)	22 (20.4)
Efficacy		
PuFS [days] median, 95% CI	30.0 (23.0; 67.0)	37.0 (24.0; 61.0)
OS [days] median, 95% CI	124.0 (97.0; 169.0)	86.0 (72.0; 126.0)

2.6.6. Discussion on clinical efficacy

Dose response study: The proposed dosing regimen was selected based on the results of 2 phase I/II studies assessing the maximum tolerated dose (MTD) in malignant ascites and in peritoneal carcinomatosis, respectively. The dose escalation scheme employing a low starting dose was selected because i.p. administration of catumaxomab is associated with symptoms attributed to cytokine release and that the patients did not tolerate high starting doses. The gradually increased doses of catumaxomab in subsequent infusions were, however, generally well tolerated. The interval between infusions was selected to allow for a sufficient recovery of the patients from symptoms and laboratory abnormalities following each infusion (see also Clinical Safety).

Primarily the efficacy claim is 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. 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 II Study IP-REM-AC-02-US has been also provided. The sought indication was initially:

"KORJUNY is indicated for the intraperitoneal treatment of malignant ascites in adults with EpCAM-positive carcinomas where **standard therapy is not available or no longer feasible**."

Design and conduct of clinical studies

The efficacy objective of the pivotal study was to demonstrate the superiority of a treatment with paracentesis plus catumaxomab over a treatment with paracentesis alone in terms of puncture-free survival. This is from a palliative care point of view clinically relevant objective. Based on literature reference it is clear that paracentesis is still the most used method and a valid comparator. There is no clear rule whether paracentesis or permanent catheter or any alternative method should be used in these patients.

The open-label design of the study is agreed as it would be unacceptable to do four punctures with i.p. infusion of placebo in the control arm.

Patients in the catumaxomab group received catumaxomab as four 6-hour constant-rate i.p. infusions as specified above. Up to 5 follow-up visits were scheduled after the last infusion (catumaxomab group) or Day 0 (control group) at: 8 days, 1 month, 3 months, 5 months and 7 months. An end of study (EoS) visit

was performed in case of necessity of peritoneal puncture, necessity of anti-tumour-treatment, 7 months follow-up or drop out for other reasons. A cut-off date for efficacy follow-up was set at 4 months after the last patient was randomised applicable for all patients who were in follow-up at that date; the safety follow-up was continued for up to 7 months.

After participation in the randomised part of the study, patients in the control group could be treated with catumaxomab in an optional single-arm cross-over period. The study design is in principle acceptable for the primary endpoint. However, the optional cross-over for patients in the control arm makes it difficult to detect possible survival benefit and, as it strongly reduces the follow-up time in the (already small) control group, and hampers assessment of other endpoints as well. This was addressed through additional sensitivity analyses of catumaxomab vs. controls switched to catumaxomab vs. controls without cross-over, and provided reassurance for the primary endpoint.

EpCAM positive subjects with ascites requiring therapeutic puncture without appropriate causal treatment were recruited. EpCAM positivity was defined as ≥ 400 EpCAM-positive cells/10^6 analysed ascites cells. As currently there is no available assay, the applicant presented a plan for the development of an in-house assay. All aspects of the proposed assay are identical to the CTA one used in the pivotal study, with only one difference that the Medicover EpCAM In-house Assay utilises manual counting of cells while the CTA utilised automatic counting of cells. The demonstration of an equivalent performance with spiked cell lines as was seen in study TR-VAL-060200-V01 will confirm that manual and automatic cell counting can provide statistically similar specificity and sensitivity. Therefore, applying the same cut-off of 400 EpCAM positive cells / 10^6 analysed ascites cells would have resulted in the Medicover EpCAM In-house Assay selecting the same patient population for treatment with Korjuny as was selected by the CTA in the pivotal clinical trial. The applicant was recommended to provide the validation data for the biomarker assay as a PAM-REC. Relevant information on EpCAM testing is reflected in SmPC sections 4.2 and 5.1.

The pivotal study population is adequate with regard to the indication wording. EpCAM related criteria were defined in 3 of 4 studies in malignant ascites in a way that evolved over time, as part of analytical, supportive pharmacodynamic monitoring to elucidate the mode of action of catumaxomab *in vivo*, as requested in EMEA Scientific Advice dated 19 Nov 2004.

Patients in the experimental arm received 4 catumaxomab infusions i.p. of 6 h duration each at doses of 10 µg on Day 0, 20 µg on Day 3, 50 µg on Day 7, and 150 µg on Day 10 via an indwelling catheter. The proposed infusion time in the SmPC is 3 hours compared to 6 hours in the pivotal study. This was based on the single arm study IP-REM-AC-02-US showing median PuFS of 29 days in the 32 subjects treated. Although the study formally failed, the mean and median value of the punction-free interval was prolonged, which supports the efficacy of catumaxomab and is considered supportive for the conclusion of the pivotal study. In addition, a total of 219 subjects treated with catumaxomab (111 and 108 patients with or without prednisolone pre-treatment) were infused for 3 hours in the phase III, open-label, randomised study IP-CAT-AC-03 with a median PuFS of 30 days with catumaxomab plus prednisolone, vs 37 days with catumaxomab alone, which confirmed the safety and feasibility of catumaxomab administered as 3-hr i.p. infusion and underlined the robustness of the efficacy and safety data for catumaxomab in the treatment of patients with malignant ascites (Sehouli 2014). A 3-hour infusion has a lower burden for patient and healthcare provider, and could improve the quality of life in this palliative setting. No clinically relevant impact is expected from the difference in t_{max} from 6-hr to 3-hr infusion.

In this palliative setting, mostly relevant endpoints considered to be:

- Puncture-free survival (PuFS),

- ascites volume at punction visit and respectively calculated daily ascites production,
- ascites signs and symptoms,
- overall survival (OS),
- quality of life (QoL).

Patients in the experimental arm had punctures to dryness on day 0, 3, 7, and 10, whereas patients in the control arm had only one puncture to dryness on day 0. This could be a source of bias. Ideally, a second puncture to dryness should be done in the control arm at the point in time where the patients in the experimental arm had their last catumaxomab infusion, in order for both groups to have the same interval from randomisation to clock start. However, this extra puncture in the control arm would possibly not be clinically indicated. To omit this ethical problem in the palliative care setting, the clock started for the primary endpoint at the first puncture to dryness in the control group, whereas the clock only started after the last catumaxomab infusion with subsequent drainage to dryness in the experimental arm. This was not considered optimal and additional analyses were requested in this regard, where subjects who died after randomisation but before clock-start are considered a PuFS event at time 0. This is considered the most suitable analysis for benefit/risk assessment, which largely addresses the previous issues and can substantiate the efficacy in terms of PuFS. It is noted that further intercurrent events with possible relation to the treatment exist, which were all considered as censoring events in that analysis.

It is noted that a separate enrolment and separate type 1 error control in the cancer entity strata were planned to be used. Accordingly, SmPC section 5.1 shows stratum-specific analyses for PuFS.

Of all subjects randomised to catumaxomab 131 (of 170 = 77.1%) received all four scheduled doses. No apparent differences between the two treatment cancer strata were observed. However, subjects who did not receive any infusion or one, two or three were included in the primary analysis of PuFS (in the FAS) which is acceptable.

Per Amendment 1 (11 May 2004) required calculated ascites volume to perform a therapeutic ascites punction was reduced from 2 L to 1 L. This change is medically acceptable. Per Amendment 1 also the time for removal of the catheter was shortened to 1 day after last catumaxomab infusion. It is understood, that this was necessary to do for the primary endpoint. The resulted SmPC wording in section 6.6 reflects this measure as studied per protocol by specifying that the day after the last infusion, a drainage of ascites is performed until cessation of spontaneous flow, and, subsequently, the catheter can be removed.

As per Amendment 2, the decision for therapeutic puncture was to be based on ascites signs and symptoms in addition to the assessment of ascites volume per CT, making more objective the timepoint of therapeutic puncture and minimising the bias of the open-label design.

Per Amendment 5, efficacy data cut-off was clarified as 4 months after randomisation, which seemed inappropriate as efficacy evaluation was shorter in the treatment arm, but it was clarified that this would only have minor impact on PuFS, with only 5 patients (2.9%) being censored in the catumaxomab arm due to end of study, which is a very low number.

The updated sample size is in principle acceptable.

Efficacy data and additional analyses

In non-ovarian cancer group there were slightly more women (59%), also, slight difference in previous volume extraction in non-ovarian cancer between catumaxomab and control group has been noted, which could somehow favour the catumaxomab group. However, in scope of the distribution of other baseline data variables it is considered, that in general both in the ovarian cancer group and in the non-ovarian cancer group, baseline data seem evenly distributed between treatment arms, and do not give cause for concern.

Based on the initial sample size calculations a sufficient number of patients was randomised in both subgroups.

Puncture-free survival (PuFS) – primary endpoint

PuFS is a composite endpoint, as it is measures time to therapeutic puncture or death. In all analysis groups, puncture-free survival was longer 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).

While these results looked remarkable at first glance, there were uncertainties that needed further clarification. The main issue was that a rather high number of patients who died were censored prior to clock start in the experimental arm. This was most pronounced in the non-ovarian carcinoma group where there were 10 deaths in the experimental arm prior to clock start which were censored per protocol. Therefore, supportive analyses were provided (similarly during the Removab submission), where deaths also prior to clock start were included as events (table 18). This is considered the most suitable analysis for benefit/risk assessment, which largely addresses the previous issues and substantiates the efficacy in terms of PuFS, showing a longer PuFS in catumaxomab with a difference in median of 33 days (HR 0.31, 95% CI: 0.23; 0.42).

Correlation between collected ascites volume and time to puncture

According to a correlation analysis of ascites volume collected at puncture and time to puncture, the ascites fluid production occurred more rapidly in the control group compared to the catumaxomab group. Although this could be biased in an open-label study due to a more efficient drainage before administration of catumaxomab, and the lack of objective criteria in the protocol to define the need for the next paracentesis, the analysis provided on the collected ascites volume and time to puncture (correlation analysis and collected ascites volume per arm) indicate a magnitude of effect that counterbalances these uncertainties and any imprecisions. In conclusion, this endpoint is considered to support the efficacy claim, alongside the supportive sensitivity analysis.

Daily collected ascites volume

The median daily fluid production was 3.3 times lower in the ovarian cancer catumaxomab group compared to control and 7.0 times lower in the non-ovarian cancer catumaxomab group compared to control. This calculated value would suggest that the fluid production in catumaxomab-treated subjects is markedly lower than in the control group.

Collected volume on puncture visit

At therapeutic puncture visit, lower volumes were seen in the catumaxomab arm in non-ovarian cancer patients. This could suggest a bias, however, in the ovarian group, catumaxomab had higher volume of therapeutic puncture compared to control. Therefore, it is concluded that these findings are not interpretable.

Body weight and abdominal girth

Body weight and abdominal girth are useful for individual non-invasive patient monitoring, but do not provide any value in determining the efficacy of catumaxomab. In the pivotal study IP-REM-AC-01, patients with a Karnofsky performance score of < 60 and with a BMI of < 17 or > 40 kg/m2 have not been investigated. Treating these patients with Korjuny is at the discretion of the treating physician.

Weight over time analysis

The mean body weight curves did not contribute to establishing efficacy.

Total protein concentration

A provided analysis showed an increase in serum albumin levels after visit 6 in catumaxomab-treated patients and decrease in the control arm which would suggest a protective role of catumaxomab infusions on total protein loss after completing treatment (data not shown).

Assessments to objectify need for / time to therapeutic puncture

A non-validated questionnaire was used to assess ascites signs and symptoms. The results are of limited value due to the open-label design of the study. Only one subject in the non-ovarian group did not have confirmed the need for at least 1L volume in a centralised review post punction, which adds validity to this criterion. The fact that ascites volume at puncture was higher with catumaxomab than with control in the ovarian cancer stratum, while the opposite was seen in the nonovarian cancer stratum could indicate against a systematic bias.

Overall survival

During the post-study period the patients were observed until end of lifetime. OS assessment was impacted by the possibility of crossing-over of control patients into an open-label, single-arm catumaxomab period. Follow-up differed between groups with shortest FU in the control group without cross-over questioning the validity of the results. In the 31 May 2007 DCO, median OS was comparable between catumaxomab and control. Two sensitivity analyses were performed showing comparable results to the primary OS analysis.

An updated OS analysis with cut-off date on 10 Sep 2009 with different censoring rules was provided. No detrimental effect of catumaxomab has been observed in this long-time survivor analysis.

An additional approach to make a 3-group analysis, although of limited value, showed numerically longer survival times in the crossed over patients compared to the randomised catumaxomab patient that may be attributed to a patient selection for crossing-over.

A further OS-analysis was provided, following the ITT principle, where subjects were not censored when they cross-over to catumaxomab but are followed for OS. This comparison provided sufficient reassurance that there is no detrimental effect of catumaxomab but avoided the issues mentioned above and it was included in the SmPC. Furthermore, it allowed to assess whether an earlier treatment with catumaxomab is beneficial to no catumaxomab or later treatment with catumaxomab.

Triggered analysis on subsequent punctions

An assessment of time to next punctions after the punction visit used for calculation of PuFS has been made. It has been shown that time to second punction in the post-study period was shorter in catumaxomab treated subjects, compared to controls. The numbers of patients in all groups was however very low, with particularly low numbers for control group patients without crossover (n=2-4), so that no meaningful conclusions could be drawn. Due to lack of sufficient patient numbers, the issue was not pursued further.

QoL

The data collected in QLQ-C30 showed high individual variation in changes from screening to puncture visit. The applicant revises for assessment of these high individual variations in a publication (Wimberger et al. 2012) that tried post-hoc to analyse QoL in the pivotal study in a more powerful and meaningful way. In this analysis, where EORTC QLQ-C30 questionnaire responses were analysed, using a post-hoc algorithm where time to first deterioration in QoL was defined as a decrease in the QoL score of at least five points (Osoba et al.) and compared between the catumaxomab (n = 160) and control (n = 85) groups using the log-rank test and Cox proportional hazards models adjusted for baseline score, country and primary tumour type. These post-hoc results showed that deterioration in QoL scores appeared more rapidly in the control than in the catumaxomab group (median 19–26 days versus 47–49 days). The hazard ratios ranged from 0.08 to 0.24. Although these are post hoc analyses, a benefit in QoL is shown.

Ancillary analyses

Results of the single arm cross over

Cross-over subjects have shown efficacy in terms of PuFS comparing to randomised control and also have shown longer time to puncture if compared intra-individually. All results of the assessments within the cross-over period should be interpreted on the background that a certain selection of patients occurred: Only a part of the control patients of the randomised part switched to the cross-over arm, and of those patients only a part had therapeutic puncture. The population of control patients who did not cross over were probably a subgroup with a worse prognosis, and, hence, the analysis of overall survival may exaggerate the treatment effect. However, the overall survival analysis is not the analysis supporting this application, and is only regarded as an interesting observation.

Concomitant treatment

As to concomitant treatment, all drug groups have been more frequently used in catumaxomab-treated patients, which could be explained by the higher AE incidences in catumaxomab patients overall, and the more frequent follow-up and were observed longer. The use of blood substitutes and plasma protein fractions in catumaxomab patients was primarily due to human albumin administrations. In the pivotal study, only paracetamol has been used as pre-treatment. In the SmPC however, analgesic, antipyretic and non-steroidal antiphlogistic are recommended, which is agreed, as they are part of standard medications in all products that cause CRS.

Most common cancer type was ovarian cancer. The second most represented cancer type was gastric cancer, where efficacy results were similar as in the whole population. Numerically also other included cancer types like breast cancer (n=13), pancreatic cancer (n=9), colorectal cancer (n=9= and other (n=32) seemed to benefit in the primary endpoint mostly with low patient numbers and without statistical significance. Patients with distant metastases also seemed to benefit from catumaxomab in PuFS (data not shown).

ADAs and impact on efficacy

Patients with positive ADAs have had longest PuFS and TTpu and OS comparing to control or ADA negative subjects treated with catumaxomab. This is an interesting finding, as ADAs should have a neutralising potential. It is assumed that catumaxomab was able in the short time until ADAs have been build deplete tumour cells in peritoneal space and ADA positivity will have for the short dosing time not so much influence on efficacy. Interesting finding, outside of the currently requested indication, was published for the SECIMAS study, where it seems that even in patients after one course of catumaxomab, a second course, even if ADAs have been developed, could be safe and efficacious.

Supportive studies are considered to have limited supportive value for the indication claimed as they were small and had different endpoints.

As the term "standard therapy is not available or no longer feasible" could be misinterpreted the wording of the final indication was revised for clarity and to better reflect the indicated population (i.e. chemotherapy refractory/resistant patients):

"Korjuny is indicated for the intraperitoneal treatment of malignant ascites in adults with epithelial cellular adhesion molecule (EpCAM)-positive carcinomas, **who are not eligible for further systemic anticancer therapy**."

2.6.7. Conclusions on the clinical efficacy

The efficacy was considered demonstrated regarding the chosen primary endpoint (PuFS), supported also by various sensitivity analysis. Despite the limitations of the pivotal study, supportive analyses, including analysis with alternative censoring rules, confirmed the clinical efficacy of catumaxomab in the treatment of EpCAM positive malignant ascites. It is also clear, that catumaxomab had no detrimental OS effect compared to control. Although there seems to be also efficacy in other chosen endpoints, for methodological reasons it may be difficult to clearly describe it.

2.6.8. Clinical safety

2..6.8.1. Patient exposure (test)

The focus of this MAA is on the safety profile of catumaxomab from the main, controlled study part of pivotal study IP-REM-AC-01, and additionally on the safety data from the overall population exposed to catumaxomab i.p. as per Integrated Summary of Safety 2 (ISS2). A total of 157 patients were treated with catumaxomab in the main study period of the pivotal study. Of these patients, 83% received all 4 infusions as planned. Overall, 517 patients were exposed to catumaxomab (ISS2 population) and 74% received all planned infusions. In patients receiving catumaxomab as 6-hr infusion, 80% received all planned infusions, vs 67% in the 3-hr group.

Data from the pivotal study are frequently presented without data for the control group. As catumaxomab was effective in prolonging puncture-free survival, the observation period of adverse events was distinctly longer in the catumaxomab than in the control group which needs to be considered for the direct comparison between catumaxomab and control group.

2..6.8.2. Adverse events

Table 39. Overall summary of AEs in pivotal study and in catumaxomab exposed patients overall; safety set, catumaxomab treated patients only

	IP-REM-AC-01[1]	ISS2, 3h pooled	ISS2, 6h pooled	ISS2, Total
Patients	157	224	293	517
AE	154 (98)	224 (100)	288 (98)	512 (99)
AE ≥grade 3	125 (80)	176 (79)	224 (77)	400 (77)
Related AEs	133 (85)	219 (98)	260 (89)	479 (93)
SAE	91 (58)	103 (46)	150 (51)	253 (49)
Related SAE	23 (15)	57 (25)	41 (14)	98 (19)
AE leading to tx disc.	11 (7)	50 (22)	32 (11)	82 (16)
Death	71 (45)	14 (6)	103 (35)	117 (23)

Abbreviations: AE= adverse event; inf.= infusion, n.a.= not available; SAE= serious adverse event; tx disc.= treatment discontinuation

[1] Main (randomised controlled) study part, catumaxomab patients only (ISS1)

Note: The key safety studies are also included in the 3-h or 6-h groups (according to the respective study design). All key safety studies are also included in the catumaxomab overall-group.

Table 40. Most frequent (>20%) AEs; pooled patient population (ISS2), safety set

	3h pooled	6h pooled	Catum. overall
Patients, n	224	293	517
Any event	224 (100)	288 (98.3)	512 (99.0)
Gastrointestinal disorders	206 (92.0)	247 (84.3)	453 (87.6)
Abdominal pain	124 (55.4)	154 (52.6)	278 (53.8)
Nausea	123 (54.9)	150 (51.2)	273 (52.8)
Vomiting	104 (46.4)	139 (47.4)	243 (47.0)
Constipation	62 (27.7)	58 (19.8)	120 (23.2)

	3h pooled	6h pooled	Catum. overall
Diarrhoea	65 (29.0)	47 (16.0)	112 (21.7)
General disorders and administration site cond.	205 (91.5)	241 (82.3)	446 (86.3)
Pyrexia	148 (66.1)	186 (63.5)	334 (64.6)
Fatigue	81 (36.2)	68 (23.2)	149 (28.8)
Metabolism and nutrition disorders	97 (43.3)	133 (45.4)	230 (44.5)
Blood and lymphatic system disorders	90 (40.2)	112 (38.2)	202 (39.1)
Anaemia	70 (31.3)	54 (18.4)	124 (24.0)
Respiratory, thoracic and mediastinal disorders	106 (47.3)	82 (28.0)	188 (36.4)
Infections and infestations	80 (35.7)	69 (23.5)	149 (28.8)
Skin and subcutaneous tissue disorders	78 (34.8)	64 (21.8)	142 (27.5)
Vascular disorders	75 (33.5)	53 (18.1)	128 (24.8)
Psychiatric disorders	70 (31.3)	51 (17.4)	121 (23.4)
Musculoskeletal and connective tissue disorders	70 (31.3)	40 (13.7)	110 (21.3)

Source data: ISS2 Table 4.2.2.2

While grade ≥3 events were frequently reported (77% of all catumaxomab exposed patients and 80% of all patients in the pivotal study), median duration was one to two days for most events except anaemia and hypotension.

The patients in the control group in the pivotal trial only received paracentesis, no placebo. Overall, the incidence of any AEs, AEs ≥ Grade 3, related AEs, SAEs and related SAEs was higher in the catumaxomab compared to the control group. 80% in the catumaxomab and 29.5% of the control group had events recorded as AE of CTCAE grade 3 or higher (Table 41).

Table 41. Overall summary of AEs; IP-REM-AC-01, main study period, safety set

	Ovarian cancer		Nonovarian cancer	
	Catumaxomab	Control	Catumaxomab	Control
Patients, n	80	44	77	44
Patients with any AE	80 (100.0)	24 (54.5)	74 (96.1)	27 (61.4)
AE ≥grade 3	60 (75.0)	11 (25.0)	65 (84.4)	15 (34.1)
Related AE	75 (93.8)	n.a.	58 (75.3)	n.a.
SAE	38 (47.5)	7 (15.9)	53 (68.8)	14 (31.8)
Related SAE	13 (16.3)	n.a.	10 (13.0)	n.a.

	Ovarian cancer		Nonovarian cancer	
	Catumaxomab	Control	Catumaxomab	Control
AE leading to tx disc.	5 (6.3)	n.a.	6 (7.8)	n.a.
Related AE leading to tx discontinuation	3 (3.8)	n.a.	3 (3.9)	n.a.
AE leading to death	26 (32.5)	4 (9.1)	45 (58.4)	9 (20.5)
Related AE leading to death	0	n.a.	0	n.a.

Abbreviations: n.a.= not assessed; tx= treatment

Source data: IP-REM-AC-01-CSR.01 Appendix A1.1, Table 1.1.1, Appendix A1.3, Tables 5.1.1, 5.1.2; IP-REM-AC-01-CSR.02, Appendix A1.1, Table 1.1.1, Appendix A1.3.1, Tables 5.1.1, 5.1.2, Section 8.2.5

To allow a better comparison of the frequency of safety events, the applicant provided analyses for safety of the pivotal study which was based on fixed follow-up periods, once from randomisation (in both arms) and once from the respective clock-start.

- ***Safety analysis by time period relative to randomisation***

The high number of AEs in the catumaxomab group occurred during the first and second time window, which corresponds to the catumaxomab infusion period. In general, there was a trend for AE incidences, Grade ≥3 AEs and SAEs to decrease over time during the first three-time windows in the catumaxomab treatment group and in the control arm (Table 42 and Table 43). Thereafter, an increase in AE incidences, grade ≥3 AEs and SAEs was observed in the catumaxomab treatment group but not in the control arm. Drug-related AEs incidences decreased over time. There was no relevant difference between ovarian and nonovarian cancer patients (Table 42 and Table 43).

Table 42. AE overall summary by time window relative to randomisation; IP-REMAC-01, ovarian cancer patients

	Days 0-7				Days 8-14				Days 15-21				>21 Days			
	Catum.		Control		Catum.		Control		Catum.		Control		Catum.		Control	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Patients with AE	70	(87.5)	16	(36.4)	72	(90.0)	10	(22.7)	49	(61.3)	2	(4.5)	58	(72.5)	7	(15.9)
AE grade ≥3	24	(30.0)	5	(11.4)	24	(30.0)	2	(4.5)	12	(15.0)	2	(4.5)	32	(40.0)	4	(9.1)
Related AE	63	(78.8)	0		66	(82.5)	0		35	(43.8)	0		12	(15.0)	0	
AE-discont.	3	(3.8)	0		1	(1.2)	0		1	(1.2)	0		0	(0.0)	0	
SAE	8	(10.0)	2	(4.5)	10	(12.5)	1	(2.3)	5	(6.2)	1	(2.3)	25	(31.2)	3	(6.8)
Related SAE	2	(2.5)	0		9	(11.2)	0		2	(2.5)	0		2	(2.5)	0	
Fatal AE	4	(5.0)	1	(2.3)	2	(2.5)	1	(2.3)	2	(2.5)	0	(0.0)	18	(22.5)	2	(4.5)

Number of patients (100%): 80 - Catumaxomab, 44 - Control

Source data: Appendix Table 1.1

Table 43. AE overall summary by time window relative to randomisation; IP-REMAC-01, nonovarian cancer patients

	Days 0-7				Days 8-14				Days 15-21				> 21 Days			
	Catum.		Control		Catum.		Control		Catum.		Control		Catum.		Control	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Patients with AE	58	(75.3)	13	(29.5)	60	(77.9)	9	(20.5)	42	(54.5)	5	(11.4)	48	(62.3)	8	(18.2)
AE grade ≥3	28	(36.4)	5	(11.4)	33	(42.9)	3	(6.8)	20	(26.0)	2	(4.5)	37	(48.1)	5	(11.4)
Related AE	46	(59.7)	0		49	(63.6)	0		33	(42.9)	0		12	(15.6)	0	
AE -discont.	2	(2.6)	0		3	(3.9)	0		1	(1.3)	0		0		0	
SAE	12	(15.6)	4	(9.1)	16	(20.8)	3	(6.8)	10	(13.0)	1	(2.3)	31	(40.3)	6	(13.6)
Related SAE	5	(6.5)	0		6	(7.8)	0		2	(2.6)	0		3	(3.9)	0	
Fatal AE	5	(6.5)	3	(6.8)	8	(10.4)	2	(4.5)	6	(7.8)	0		27	(35.1)	4	(9.1)

Number of patients (100%): 77 - Catumaxomab, 44 - Control

Source data: Appendix Table 1.2

- ***Safety Analyses by Time Period Relative to Clock Start***

Incidence of related AEs and of related SAEs (reported in catumaxomab patients only) appeared to decline over time (Table 44 and Table 45).

Table 44. AE overall summary by time window relative to clock Start; IP-REMAC-01, ovarian cancer patients

	Days 0-7				Days 8-14				Days 15-21				>21 Days			
	Catum.		Control		Catum.		Control		Catum.		Control		Catum.		Control	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Patients with AE	55	(68.8)	17	(38.6)	22	(27.5)	6	(13.6)	15	(18.8)	1	(2.3)	44	(55.0)	7	(15.9)
AE grade ≥3	18	(22.5)	5	(11.4)	4	(5.0)	1	(2.3)	7	(8.8)	1	(2.3)	24	(30.0)	4	(9.1)
Related AE	38	(47.5)	0		9	(11.2)	0		3	(3.8)	0		3	(3.8)	0	
AE-discont.	4	(5.0)	0		0		0		0		0		0		0	
SAE	10	(12.5)	3	(6.8)	2	(2.5)	1	(2.3)	8	(10.0)	0		19	(23.8)	3	(6.8)
Related SAE	7	(8.8)	0		0		0		1	(1.2)	0		1	(1.2)	0	
Fatal AE	4	(5.0)	2	(4.5)	0		0		3	(3.8)	0		15	(18.8)	2	(4.5)

Number of patients (100%): 80 - Catumaxomab, 44 - Control

Source data: Appendix Table 2.1

Table 45. AE overall summary by time window relative to clock start; IP-REMAC-01, nonovarian cancer patients

	Days 0-7				Days 8-14				Days 15-21				> 21 Days			
	Catum.		Control		Catum.		Control		Catum.		Control		Catum.		Control	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Patients with AE	52	(67.5)	15	(34.1)	24	(31.2)	5	(11.4)	13	(16.9)	6	(13.6)	34	(44.2)	7	(15.9)
AE grade ≥3	27	(35.1)	6	(13.6)	12	(15.6)	3	(6.8)	10	(13.0)	1	(2.3)	23	(29.9)	5	(11.4)
Related AE	29	(37.7)	0		10	(13.0)	0		3	(3.9)	0		4	(5.2)	0	
AE -discont.	4	(5.2)	0		0		0		0		0		0		0	
SAE	21	(27.3)	5	(11.4)	6	(7.8)	3	(6.8)	7	(9.1)	0		19	(24.7)	6	(13.6)
Related SAE	6	(7.8)	0		0		0		0		0		1	(1.3)	0	
Fatal AE	14	(18.2)	3	(6.8)	4	(5.2)	2	(4.5)	7	(9.1)	0		17	(22.1)	4	(9.1)

Number of patients (100%): 77 - Catumaxomab, 44 - Control

Source data: Appendix Table 2.2

Table 46. AEs in >10 patients in at least one time window (by clock start) and treatment group; IP-REM-AC-01, ovarian cancer patients

	0-7 Days				8-14 Days				15-21 Days				> 21 Days			
	Catum.		Control		Catum.		Control		Catum.		Control		Catum.		Control	
	n	E	n	E	n	E	n	E	n	E	n	E	n	E	n	E
Blood and lymphatic system dis.	**15**	**17**	**0**	**0**	**4**	**4**	**1**	**1**	**1**	**1**	**0**	**0**	**6**	**8**	**0**	**0**
Gastrointestinal disorders	**25**	**41**	**8**	**16**	**11**	**17**	**3**	**4**	**7**	**16**	**0**	**0**	**17**	**37**	**2**	**5**
General disorders and admin. site conditions	**26**	**34**	**5**	**6**	**8**	**8**	**0**	**0**	**4**	**5**	**0**	**0**	**8**	**13**	**1**	**1**
Pyrexia	15	15	2	2	1	1	0	0	0	0	0	0	1	1	0	0
Neoplasms	**3**	**3**	**2**	**2**	**1**	**1**	**1**	**1**	**3**	**4**	**0**	**0**	**15**	**15**	**3**	**3**
Malignant neoplasm progression	3	3	2	2	1	1	1	1	3	3	0	0	15	15	3	3
Respiratory, thoracic and mediastinal disorders	**7**	**8**	**0**	**0**	**0**	**0**	**1**	**1**	**2**	**2**	**0**	**0**	**11**	**15**	**2**	**2**

Number of patients (100%): 80 - Catumaxomab, 44 - Control

Sorted alphabetically

n= number of patients; E= number of events

Source data: Appendix Table 2.3

Table 47. AEs in >10 patients in at least one time window (by clock start) and treatment group; IP-REM-AC-01, nonovarian cancer patients

	0-7 Days				8-14 Days				15-21 Days				> 21 Days			
	Catum.		Control		Catum.		Control		Catum.		Control		Catum.		Control	
	n	E	n	E	n	E	n	E	n	E	n	E	n	E	n	E
Blood and lymphatic system dis.	**11**	**12**	**3**	**3**	**4**	**6**	**0**	**0**	**0**	**0**	**0**	**0**	**3**	**4**	**1**	**1**
Gastrointestinal disorders	**19**	**31**	**7**	**14**	**9**	**14**	**3**	**3**	**4**	**10**	**3**	**3**	**13**	**30**	**2**	**3**
General disorders and amin. site conditions	**15**	**17**	**3**	**3**	**3**	**4**	**0**	**0**	**4**	**5**	**1**	**1**	**3**	**3**	**1**	**2**
Investigations	**14**	**19**	**3**	**10**	**6**	**13**	**0**	**0**	**1**	**1**	**0**	**0**	**7**	**12**	**0**	**0**
Metabolism and nutrition dis.	**11**	**11**	**3**	**4**	**7**	**7**	**2**	**2**	**3**	**4**	**1**	**1**	**7**	**9**	**0**	**0**
Neoplasms	**8**	**8**	**2**	**2**	**2**	**2**	**2**	**2**	**6**	**6**	**0**	**0**	**17**	**17**	**4**	**4**
Malignant neoplasm progression	8	8	2	2	2	2	2	2	6	6	0	0	15	15	4	4

Number of patients (100%): 77 - Catumaxomab, 44 - Control
Sorted alphabetically
n= number of patients; E= number of events
Source data: Appendix Table 2.4

- ***Adverse drug reactions considered for inclusion in the SmPC***

Adverse drug reactions (ADRs) are based on a comprehensive assessment of the pivotal study IP-REM-AC-01, in the indication of malignant ascites. During the assessment of this application, the proposed ADR table was based on n=11 studies including 517 patients from the ISS2 population.

AEs were included in the updated list of ADRs if they fulfilled the following criteria:

1. AE was assessed as at least possibly related to catumaxomab, i.e. qualifying as adverse drug reaction (ADR); AND
2. ADR occurred in 2 or more patients treated with catumaxomab;
   AND one of the following (#3 or #4):
3. ADR incidence (% of patients) was at least twice the incidence among catumaxomab patients as compared to control patients of the pivotal study IP-REM-AC-01; OR
4. If the ADR was reported in catumaxomab patients only (across all 4 malignant ascites studies) but not in control patients of the pivotal study IP-REM-AC-01 and if it fulfilled the first 2 criteria, the event was also included in the table as an ADR

The ADR table is presented below. ADRs are marked with an asterisk if reported only in studies in indications other than malignant ascites (e.g. in cancer patients undergoing curative surgery and intraoperative administration of catumaxomab).

Table 48. ADR table for catumaxomab based on the pooled analysis (ISS2) (by decreasing frequency)

MedDRA PT	Patients (%)	SmPC Frequency
PYREXIA	62,16%	Very common
Abdominal pain	42,47%	Very common
NAUSEA	40,73%	Very common
VOMITING	38,22%	Very common
FATIGUE	18,92%	Very common

CHILLS	17,37%	Very common
Diarrhoea	14,48%	Very common
C-reactive protein increased	10,81%	Very common
PAIN	10,23%	Very common
Anaemia	8,88%	Common
Gamma-glutamyltransferase increased	8,88%	Common
Lymphopenia	8,49%	Common
Tachycardia	8,30%	Common
Hypotension	8,30%	Common
Leukocytosis	7,92%	Common
Blood alkaline phosphatase increased	7,14%	Common
RASH	7,14%	Common
Aspartate aminotransferase increased	6,56%	Common
Alanine aminotransferase increased	6,37%	Common
Systemic inflammatory response syndrome	4,63%	Common
Abdominal distension	4,25%	Common
Abdominal pain upper	4,25%	Common
Dehydration	4,25%	Common
Erythema	4,05%	Common
Hypertension	3,86%	Common
BACK PAIN	3,67%	Common
Myalgia	3,47%	Common
OEDEMA	3,28%	Common
FLATULENCE	2,70%	Common
Blood potassium decreased	2,70%	Common
Cholangitis	2,51%	Common
BLOOD CREATININE INCREASED	2,51%	Common
Body temperature increased	2,51%	Common
Neutrophil count increased	2,51%	Common
White blood cell count increased	2,51%	Common
HYPOKALAEMIA	2,51%	Common
Arthralgia	2,51%	Common
HYPERBILIRUBINAEMIA	2,32%	Common
Blood bilirubin increased	2,32%	Common
SUBILEUS	2,12%	Common
Dizziness	2,12%	Common
HYPONATRAEMIA	1,93%	Common
INFECTION	1,54%	Common
Haemoglobin decreased	1,54%	Common
Hepatic enzyme increased	1,54%	Common
Protein total decreased	1,54%	Common
Weight decreased	1,54%	Common
Hypoalbuminaemia	1,54%	Common
ANXIETY	1,54%	Common
HYPERHIDROSIS	1,54%	Common
Abdominal discomfort	1,35%	Common
Gastroesophageal reflux disease	1,35%	Common
CHEST PAIN	1,35%	Common
Cytokine release syndrome	1,35%	Common
Gamma-glutamyltransferase	1,35%	Common
LYMPHOCYTE COUNT DECREASED	1,35%	Common
Procalcitonin increased	1,35%	Common

Pruritus	1,35%	Common
FLUSHING	1,35%	Common
Inflammation	1,16%	Common
Malaise	1,16%	Common
HYPERSENSITIVITY	1,16%	Common
HAEMATURIA	1,16%	Common
Hypoxia	1,16%	Common
DERMATITIS ALLERGIC	1,16%	Common
Hot flush	1,16%	Common
Thrombocythaemia	0,97%	Uncommon
Vertigo	0,97%	Uncommon
Abdominal pain lower	0,97%	Uncommon
Gastric disorder	0,97%	Uncommon
Catheter site erythema	0,97%	Uncommon
Anastomotic complication	0,97%	Uncommon
Blood albumin decreased	0,97%	Uncommon
Paraesthesia	0,97%	Uncommon
Leukopenia	0,77%	Uncommon
Sinus tachycardia	0,77%	Uncommon
PERITONITIS	0,77%	Uncommon
Stomach discomfort	0,77%	Uncommon
Jaundice	0,77%	Uncommon
Activated partial thromboplastin time	0,77%	Uncommon
Blood alkaline phosphatase	0,77%	Uncommon
Blood glucose increased	0,77%	Uncommon
Blood lactate dehydrogenase increased	0,77%	Uncommon
Lipase increased	0,77%	Uncommon
SYNCOPE	0,77%	Uncommon
Tremor	0,77%	Uncommon
Leukocyturia	0,77%	Uncommon
Oliguria	0,77%	Uncommon
Renal failure acute	0,77%	Uncommon
Pulmonary embolism	0,77%	Uncommon
Respiratory failure	0,77%	Uncommon
Skin reaction	0,77%	Uncommon
Urticaria	0,77%	Uncommon
Coagulopathy	0,58%	Uncommon
Thrombocytopenia	0,58%	Uncommon
ASCITES	0,58%	Uncommon
ILEUS PARALYTIC	0,58%	Uncommon
IMPAIRED GASTRIC EMPTYING	0,58%	Uncommon
Catheter site pain	0,58%	Uncommon
Extravasation	0,58%	Uncommon
Injection site reaction	0,58%	Uncommon
THIRST	0,58%	Uncommon
CYTOLYTIC HEPATITIS	0,58%	Uncommon
HEPATIC FAILURE	0,58%	Uncommon
Hepatic function abnormal	0,58%	Uncommon
Erythema induratum	0,58%	Uncommon
ORAL CANDIDIASIS	0,58%	Uncommon
Wound dehiscence	0,58%	Uncommon
Blood fibrinogen increased	0,58%	Uncommon

Blood pressure increased	0,58%	Uncommon
ELEVATED LIVER ENZYMES	0,58%	Uncommon
Gamma-glutamyltransferase increased	0,58%	Uncommon
Haematocrit decreased	0,58%	Uncommon
HEART RATE INCREASED	0,58%	Uncommon
LABORATORY TEST ABNORMAL	0,58%	Uncommon
Liver function test abnormal	0,58%	Uncommon
Transaminases increased	0,58%	Uncommon
Urobilin urine present	0,58%	Uncommon
Bone pain	0,58%	Uncommon
Musculoskeletal pain	0,58%	Uncommon
Dysgeusia	0,58%	Uncommon
LETHARGY	0,58%	Uncommon
Peripheral sensory neuropathy	0,58%	Uncommon
Agitation	0,58%	Uncommon
Renal failure	0,58%	Uncommon
Acute respiratory distress syndrome	0,58%	Uncommon
HICCUPS	0,58%	Uncommon
Night sweats	0,58%	Uncommon
Rash pruritic	0,58%	Uncommon
Neutropenia	0,39%	Uncommon
Arrhythmia	0,39%	Uncommon
Cardiac failure	0,39%	Uncommon
Palpitations	0,39%	Uncommon
Vision blurred	0,39%	Uncommon
ABDOMINAL CRAMPS	0,39%	Uncommon
ABDOMINAL RIGIDITY	0,39%	Uncommon
Dry mouth	0,39%	Uncommon
Duodenogastric reflux	0,39%	Uncommon
Gastrointestinal hypomotility	0,39%	Uncommon
HEARTBURN	0,39%	Uncommon
Retching	0,39%	Uncommon
Small intestinal obstruction	0,39%	Uncommon
Application site inflammation	0,39%	Uncommon
Early satiety	0,39%	Uncommon
FEELING COLD	0,39%	Uncommon
Feeling hot	0,39%	Uncommon
HYPERTHERMIA	0,39%	Uncommon
Mucosal inflammation	0,39%	Uncommon
RIGORS	0,39%	Uncommon
Cholestasis	0,39%	Uncommon
HEPATITIS TOXIC	0,39%	Uncommon
HEPATOTOXICITY	0,39%	Uncommon
Herpes simplex	0,39%	Uncommon
LOCALISED INFECTION	0,39%	Uncommon
Skin infection	0,39%	Uncommon
Procedural pain	0,39%	Uncommon
Alanine aminotransferase	0,39%	Uncommon
BILIRUBIN CONJUGATED INCREASE	0,39%	Uncommon
Blood iron decreased	0,39%	Uncommon
Blood magnesium decreased	0,39%	Uncommon
BLOOD URINE PRESENT	0,39%	Uncommon

BODY TEMPERATURE DECREASED	0,39%	Uncommon
Cells in urine	0,39%	Uncommon
Oxygen saturation decreased	0,39%	Uncommon
Red blood cell count decreased	0,39%	Uncommon
FLUID RETENTION	0,39%	Uncommon
HYPOGLYCAEMIA	0,39%	Uncommon
Hypomagnesaemia	0,39%	Uncommon
Polydipsia	0,39%	Uncommon
Flank pain	0,39%	Uncommon
CONVULSION	0,39%	Uncommon
Polyneuropathy	0,39%	Uncommon
Depression	0,39%	Uncommon
Dysuria	0,39%	Uncommon
Renal pain	0,39%	Uncommon
White blood cells urine positive	0,39%	Uncommon
Pelvic pain	0,39%	Uncommon
Bronchospasm	0,39%	Uncommon
Lung infiltration	0,39%	Uncommon
Pharyngolaryngeal pain	0,39%	Uncommon
Respiratory distress	0,39%	Uncommon
Tachypnoea	0,39%	Uncommon
Wheezing	0,39%	Uncommon
Palmar erythema	0,39%	Uncommon

Systemic inflammatory response syndrome (SIRS, with concurrent fever, increased heart rate and respiratory rate, and abnormal leukocyte count) was reported in 2 patients out of 203 patients in the pivotal study. In both patients, SIRS was of Grade 4, required hospitalisation/prolongation of hospitalisation, and led to discontinuation of the treatment. In addition, 2 patients were reported as having SIRS after i.p. administration of catumaxomab in patients with malignant ascites according to post-marketing data sources. In one patient, death due to the suspected SIRS event or (the differential diagnosis of sepsis) was considered related to treatment by investigator. SIRS has been added to the list of ADRs in the SmPC and has been included under Warning & Precautions in SmPC Section 4.4.

In 38.9% of patients in the main study period of the pivotal study, abdominal pain was reported as an adverse reaction, reaching grade 3 or higher in 8.9% of patients, but it resolved under symptomatic treatment.

- ***3-hr versus 6-hr infusion***

Overall, the AE profile was also comparable between the 6-hr and 3-hr infusion durations treatment groups in terms of events/preferred terms. There have been no new side effects observed with only the 3-hr infusion that would not have been seen with the 6-hr infusion. The main difference was that there was higher incidences for some side effects with the 3-hr application. Differences of >10% in AEs overall were seen for diarrhoea (29% with the 3-hr infusion, vs 16% with the 6-hr infusion), fatigue (36% vs 23%), anaemia (31% vs 18%), chills (28% vs 13%), and pleural effusion (22% vs 9%). Lymphopenia was less frequent with the 3-hr infusion (5% vs 16%) (Module 2.7.4 Section 2.1.2.5.1). The profile of AEs ≥grade 3 was generally balanced between the 2 groups, but the 6-hr group included more patients with lymphopenia (11% vs 4%). Drug-related AEs were comparable between the 3-hr and 6-hr infusion duration, except for the following preferred terms being more frequent after the shorter infusion: fatigue (3-hr infusion: 26%, 6-hr infusion: 13%); chills (25% vs 12%), diarrhoea (21% vs 10%), rash (12% vs 6%), and hypotension (13% vs 6%).

Again, lymphopenia was less frequent with the 3-hr infusion (5% vs 12%). No relevant impact of infusion duration was seen for SAEs, except for vomiting and nausea. Both were more frequent with the 3-hr than the 6-hr infusion (vomiting 7% vs 2%; nausea 6% vs 1%).

As noted earlier, the 6-hr infusion group included mostly patients with the malignant ascites while studies in the 3-hr infusion group included predominantly patients with other indications undergoing surgery which curative intend i.e. these patients tended to have a better prognosis.

- Safety data based on the number of previous therapeutic ascites puncture in the controlled part of the Study IP-REM-AC-01

Analyses of key safety data by the number of previous punctures of patients, were provided separately for patients in the ovarian and the non-ovarian cancer stratum. Overall, there was no systematic or consistent effect of the number of previous ascites punctures on the safety profile of catumaxomab in ovarian cancer patients (Table 49). For non-ovarian cancer patients, there seemed to be a trend for higher incidence of several AEs with the number of previous punctures (Table 50) (diarrhoea (14%, 29%, and 44%); dyspepsia (9%, 14%, 22%); nausea (30%, 43%, 44%); asthenia (2%, 10%, 11%); pyrexia (39%, 76%, 78%); anorexia (15%, 39%, 44%); weight decreased (5%, 14%, 22%); hypokalaemia (5%, 19%, 22%)).

Table 49. AE overall summary; study IP-REM-AC-01, main study period, ovarian cancer

	1 Puncture				2-3 Punctures				≥4 Punctures			
	Catum.		Control		Catum.		Control		Catum.		Control	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Patients, n	44		24		20		13		16		7	
With event…												
AE	44	(100.0)	12	(50.0)	20	(100.0)	6	(46.2)	16	(100.0)	6	(85.7)
SAE	20	(45.5)	5	(20.8)	11	(55.0)	2	(15.4)	7	(43.8)	0	
AE grade ≥3	34	(77.3)	7	(29.2)	16	(80.0)	3	(23.1)	10	(62.5)	1	(14.3)
Related AE	42	(95.5)	0		18	(90.0)	0		15	(93.8)	0	
Related SAE	6	(13.6)	0		5	(25.0)	0		2	(12.5)	0	
AE discont.[1]	1	(2.3)	0		2	(10.0)	0		2	(12.5)	0	
Fatal AE	14	(31.8)	3	(12.5)	7	(35.0)	1	(7.7)	5	(31.2)	0	

[1] AE leading to discontinuation

No drug-related fatal AE leading to death were observed.

Source data: Q164 ovarian_summary

Table 50. AE overall summary; study IP-REM-AC-01, main study period, nonovarian cancer

	1 Puncture				2-3 Punctures				≥4 Punctures			
	Catum.		Control		Catum.		Control		Catum.		Control	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Patients, n	46		28		22		10		9		6	
With event…												
AE	44	(95.7)	19	(67.9)	21	(95.5)	5	(50.0)	9	(100.0)	3	(50.0)
SAE	33	(71.7)	11	(39.3)	16	(72.7)	2	(20.0)	4	(44.4)	1	(16.7)
AE grade ≥3	39	(84.8)	11	(39.3)	19	(86.4)	3	(30.0)	7	(77.8)	1	(16.7)
Related AE	32	(69.6)	0		18	(81.8)	0		8	(88.9)	0	
Related SAE	3	(6.5)	0		5	(22.7)	0		2	(22.2)	0	
AE discont.[1]	4	(8.7)	0		2	(9.1)	0		0		0	
Fatal AE	31	(67.4)	8	(28.6)	12	(54.5)	1	(10.0)	2	(22.2)	0	

[1] AE leading to discontinuation

No drug-related fatal AE leading to death were observed.

Source data: Q164 nonovarian_summary

2..6.8.3. Serious adverse events, deaths, and other significant events

Deaths

In the pivotal study, incidences of fatal AEs for catumaxomab are 45% for the main study period and 45% (i.e. 91/202 patients, including cross-over patients) of all patients exposed to catumaxomab, vs 15% for control.

Of all catumaxomab exposed patients (ISS2), 21% experienced an AE of grade 5. The most frequent AE was malignant neoplasm progression (16%); all other AEs at the preferred term level were reported in <1% of patients. Patients receiving catumaxomab as 6-hr infusion had a higher incidence of AEs of grade 5 (32%) than patients receiving the 3-hr infusion (7%). This difference was driven by malignant neoplasm progression (6-hr: 24%, 3-hr: 6%) and is thought to reflect different patient populations. One AE of grade 5 was judged as being drug-related, i.e. hypovolaemic shock in a gastric cancer patient in the crossover period of the pivotal study (see above).

Serious adverse events

Table 51. SAEs in ⩾2 patients overall by MedDRA system organ class and corresponding SADRs: IP-REM-AC-01, main study period, safety set, catumaxomab only

	SAEs	SADRs
Patients	157	157
Patients with events, n (%)	91 (58.0)	23 (14.6)
Neoplasms benign, malignant and unspecified	56 (35.7)	0
Gastrointestinal disorders	30 (19.1)	17 (10.8)
General disorders and administration site conditions	14 (8.9)	8 (5.1)
Cardiac disorders	10 (6.4)	0
Respiratory, thoracic and mediastinal disorders	7 (4.5)	1 (0.6)
Metabolism and nutrition disorders	7 (4.5)	2 (1.3)
Infections and infestations	4 (2.5)	0
Renal and urinary disorders	4 (2.5)	2 (1.3)
Nervous system disorders	4 (2.5)	1 (0.6)
Hepatobiliary disorders	2 (1.3)	0
Vascular disorders	3 (1.9)	2 (1.3)
Investigations	2 (1.3)	2 (1.3)
Blood and lymphatic system disorders	2 (1.3)	0

Abbreviation: SADR= serious adverse drug reaction; SAE= serious adverse event

Sorted by overall incidence

Source data: ISS1 Tables 5.3.2, 5.5.1

Table 52. Most frequent (>2% overall) SAEs; pooled patient population (ISS2), safety set

	3h pooled	6h pooled	Catum overall
Patients, n	224	293	517
Patients with event, n (%)	103 (46.0)	150 (51.2)	253 (48.9)
Gastrointestinal disorders	47 (21.0)	53 (18.1)	100 (19.3)
Vomiting	16 (7.1)	6 (2.0)	22 (4.3)
Ileus	5 (2.2)	15 (5.1)	20 (3.9)
Nausea	14 (6.3)	3 (1.0)	17 (3.3)
Abdominal pain	7 (3.1)	5 (1.7)	12 (2.3)
Neoplasms benign, malignant and unspecified	14 (6.3)	78 (26.6)	92 (17.8)
Malignant neoplasm progression	14 (6.3)	78 (26.6)	92 (17.8)
Respiratory, thoracic and mediastinal disorders	28 (12.5)	21 (7.2)	49 (9.5)
Pleural effusion	6 (2.7)	12 (4.1)	18 (3.5)
General disorders and administration site conditions	24 (10.7)	23 (7.8)	47 (9.1)
Pyrexia	6 (2.7)	6 (2.0)	12 (2.3)
Infections and infestations	20 (8.9)	9 (3.1)	29 (5.6)
Injury, poisoning and procedural complications	17 (7.6)	2 (0.7)	19 (3.7)
Cardiac disorders	2 (0.9)	14 (4.8)	16 (3.1)
Metabolism and nutrition disorders	7 (3.1)	7 (2.4)	14 (2.7)
Vascular disorders	9 (4.0)	4 (1.4)	13 (2.5)
Renal and urinary disorders	5 (2.2)	6 (2.0)	11 (2.1)

Source data: ISS2, Table 4.3.2.2

2..6.8.4. Laboratory findings

Analyses of laboratory data for all patients exposed to catumaxomab (ISS2) are not available, and all presentations of laboratory data were at the study level. Of these, results for the main part of the pivotal study IP-REM-AC-01 are considered to be of particular relevance and are summarised and discussed in the following.

Changes in laboratory parameters were expected (LFTs, leukocytosis, lymphopenia), and they were rarely clinically relevant.

Hepatic toxicity by increase of AST, ALT, GGT and AP with a tendency to accumulate by the end of the treatment period was noted. The following AEs Gamma-GT increased, ALT increased, AST increased, Bilirubin conjugated increased, Blood AP increased, Blood Bilirubin increased, were added to the list of ADR of the SmPC. Cytokine levels were transiently increased after each infusion.

Twelve patients fulfilling criteria for potential Hy's law with elevations of ALT or AST of >3 ULN in conjunction with bilirubin >2 ULN were identified. All patients but one had relevant AEs reported; in the majority, increased liver values were reported as (S)AEs, in 4 patients, events suggested clinical consequences (jaundice, toxic hepatitis, cholestasis, hepatic failure in one patient each). AEs with fatal outcome were reported in cholestasis and hepatic failure in one patient each although considered not being drug related. The risk of hepatotoxicity reported with Korjuny which may lead to drug-induced liver injury (DILI), hepatitis and may result in cases of hepatic failure and fatal cases, has been adequately reflected Section 4.4 of the

SmPC. Overall, 11% of patients reported hepatobiliary AEs, most frequently hyperbilirubinaemia (2.9%), cholangitis (2.5%), jaundice (1.4%), hepatic function abnormal (1.0%), and cholestasis (1.0%).

In the Overall Population, the most frequently reported laboratory abnormalities reported as TEAEs were increased C-reactive protein (15%) and GGT (13%). C-reactive protein is an indicator for inflammatory processes and may also consequently be influenced by the release of pro-inflammatory cytokines as part of the mode of action of catumaxomab.

Transient increases in hepatic enzymes (alanine transaminase [ALT], aspartate transaminase [AST], alkaline phosphatase [ALP], gamma-glutamyl transferase [GGT]) and total bilirubin were commonly observed after the administration of catumaxomab. In general, the changes in laboratory parameters were not clinically relevant and mostly returned to baseline after end of treatment. In the pivotal trial, 12 patients (5.6%) treated with catumaxomab experienced elevations of ALT of > 3 × upper limit of normal (ULN) in conjunction with bilirubin > 2 × ULN. In 2 of 12 patients, values continued to increase after end of infusion whereas in 10 of 12 patients, the increased values were reversible and showed a trend to improve shortly after the last catumaxomab infusion. Only in case of clinically relevant or persisting increase further diagnostics or therapy should be considered.

2..6.8.5. *In vitro* biomarker test for patient selection for safety

Not applicable

Hospitalisation

According to the study protocol of the pivotal study, patients were to be hospitalised for 24 hours at each dose. In practice, however, median stay in hospital due to application of catumaxomab was 13 days (which is in line with the planned treatment schedule of 11 days for catumaxomab). In total mean (SD) cumulative duration of hospitalisation was 21.1 (13.3) days in catumaxomab patients and 15.2 (41.5) days in control patients; median duration was 18 vs 4 days. It is noted that the number of hospital days is based on different follow-up times but are still of concern. The applicant was therefore asked to provide a sensitivity analysis for hospitalisation.

This analysis should have included

a) A frequency table for number of hospital days from randomisation to death, end-of study, cross-over or similar terminal events (preferably not only until the time of first ascites puncture) separated by cancer strata and arms and

b) Suitable summary measures (e.g. mean, median, quartiles, range) for a)

c) Additionally, the relative length of hospitalisation should be computed individually per patient (number hospital days / observation period) and suitable summary statistics (e.g. mean, median, quartiles, range) should be provided for this new variable.

No new analysis was provided by the applicant. This issue was not further pursued.

An analysis of the relative length of hospitalisation was provided as requested. As described by the applicant, data issues were identified when reanalysing hospitalisation data. Hospitalisation duration could be recreated for the ovarian cancer stratum. For non-ovarian cancer, minor differences were identified by reanalysis: in the catumaxomab group, the SD of hospitalisation duration was 11.0 days not 11.7 days; in the control

group, mean hospitalisation duration was 10.5 days not 10.4 days. Results of the re-analysis are depicted in Table 53. In the control groups, 27% (17/44) of ovarian cancer patients and 48% (21/44) of nonovarian cancer patients had no hospitalisation episodes reported. In contrast, there were almost no catumaxomab patients without hospitalisation (ovarian cancer: 1%; nonovarian cancer: 5%). Most catumaxomab patients had been admitted once or twice (ovarian cancer: 78%; nonovarian cancer: 78%). Overall, these trends are in line the original analysis although numerical values differ between the historical analysis and the new analysis, for the above-listed methodological reasons. Mean relative hospitalisation duration is comparable in catumaxomab patients of 2 strata (ovarian cancer: 0.38, or 38%; nonovarian cancer: 0.42, or 42%), as well as in control patients of 2 strata (ovarian cancer 0.23, or 23%; nonovarian cancer 0.25, or 25%). Patients receiving catumaxomab had a longer mean relative hospitalisation duration of 0.38-0.42, (38-42%) vs 0.23-0.25 (23-25%) in control patients.

Table 53. Hospitalisation episodes and total and relative hospitalisation duration, by stratum, Approach 2; IP-REM-AC-01

	Ovarian cancer		Nonovarian cancer	
	Catumaxomab	Control	Catumaxomab	Control
Patients, n (%)	80 (100.0)	44 (100.0)	77 (100.0)	44 (100.0)
Episodes/patient				
0	1 (1.3)	17 (38.6)	4 (5.2)	21 (47.7)
1	40 (50.0)	18 (40.9)	46 (60.7)	17 (38.6)
2	22 (27.5)	6 (13.6)	14 (18.2)	6 (13.6)
3	9 (11.3)	2 (5.0)	6 (7.8)	0
4	8 (10.0)	1 (2.0)	3 (3.9)	0
5	0	0	3 (3.9)	0
6	0	0	1 (1.3)	0
Total hospitalisation duration/patient				
Patients with values	79	42	75	43
Mean (SD)	16.3 (11.2)	5.5 (8.7)	15.0 (7.5)	3.4 (5.4)
Median	15.0	1.5	14.0	0.0
Range (min, max)	0, 81	0, 34	0, 35	0, 24
Relative hospitalisation duration/patient				
Patients with values	79	42	75	43
Mean (SD)	0.38 (0.29)	0.23 (0.33)	0.42 (0.31)	0.25 (0.37)
Median	0.27	0.07	0.32	0.00
Range (min, max)	0, 1	0, 1	0, 1	0, 1

The duration of hospitalisation as reported in the pivotal trial was preliminary driven by the study design and most hospitalisations in catumaxomab patients were for study drug infusions (81%). The length of hospitalisation in the catumaxomab group can also be explained by the study procedures as patients who received at least one infusion (safety set) were only once hospitalised, meaning that patients stayed in hospital from admission until the end of treatment. In this context it should be noted that the pivotal study was initiated almost 20 years ago (Sep 2004) and by that time CRS was a relatively new and poorly understood phenomenon explaining the requirement for hospitalisation for 24 hours after each dose. This situation has been fundamentally changed and CRS is now considered to be a manageable toxicity of modern

immunotherapies. The hospitalisation time is expected to be significantly reduced to 5-7 days for the majority (>70%) of patients. In the pivotal trial around 23% of patients experienced CSR episodes (based on Post hoc assessment of CRS (data not shown)) which is in line with the AE-driven hospitalisation rate of 28.3%. As most of the CRS episodes started on the day or the day after catumaxomab infusion, close medical supervision for at least 24 h is considered sufficient for the first infusion only, while for the remaining infusions (i.e. #2-4), medical monitoring can be reduced to 6 h (reflected in the SmPC).

2..6.8.6. Safety in special populations

Based on the pooled population of catumaxomab treated patients (ISS2), an analysis of safety by patient age was performed according to the categories of ≤64 years vs >64 years.

Table 54. Most frequent (>5% overall in either subgroup) AEs of ⩾grade 3; pooled patient population (ISS2), safety set

	≤64 years			>64 years		
	3h pooled	6h pooled	Overall	3h pooled	6h pooled	Overall
Patients, n	149	199	348	75	94	169
Patients with any event	116 (78)	152 (76)	268 (77)	60 (80)	72 (77)	132 (78)
Blood and lymphatic system dis.	18 (12)	29 (15)	47 (14)	13 (17)	19 (20)	32 (19)
Anaemia	12 (8)	7 (4)	19 (6)	8 (11)	7 (7)	15 (9)
Lymphopenia	4 (3)	20 (10)	24 (7)	5 (7)	12 (13)	17 (10)
Cardiac disorders	1 (<1)	14 (7)	15 (4)	5 (7)	6 (6)	11 (7)
Gastrointestinal disorders	51 (34)	62 (31)	113 (33)	23 (31)	27 (29)	50 (30)
Abdominal pain	20 (13)	23 (12)	43 (12)	7 (9)	11 (12)	18 (11)
Nausea	11 (7)	7 (4)	18 (5)	3 (4)	5 (5)	8 (5)
Vomiting	13 (9)	17 (9)	30 (9)	5 (7)	5 (5)	10 (6)
General disorders and administration site cond.	24 (16)	36 (18)	60 (17)	21 (28)	16 (17)	37 (22)
Pyrexia	5 (3)	10 (5)	15 (4)	5 (7)	5 (5)	10 (6)
Hepatobiliary disorders	10 (7)	9 (5)	19 (6)	3 (4)	3 (3)	6 (4)
Infections and infestations	18 (12)	9 (5)	27 (8)	8 (11)	2 (2)	10 (6)
Injury, poisoning, and procedural complications	17 (11)	1 (<1)	18 (5)	6 (8)	1 (1)	7 (4)
Investigations	35 (24)	44 (22)	79 (23)	23 (31)	28 (30)	51 (30)
GGT increased	12 (8)	14 (7)	26 (8)	5 (7)	8 (9)	13 (8)

	≤64 years			>64 years		
	3h pooled	**6h pooled**	**Overall**	**3h pooled**	**6h pooled**	**Overall**
Metabolism and nutrition dis.	22 (15)	26 (13)	48 (14)	13 (17)	16 (17)	29 (17)
Hyponatraemia	1 (<1)	5 (3)	6 (2)	4 (5)	8 (9)	12 (7)
Neoplasms	10 (7)	60 (30)	70 (20)	6 (8)	22 (23)	28 (17)
Malignant neoplasm progression	10 (7)	58 (29)	68 (20)	6 (8)	22 (23)	28 (17)
Respiratory, thoracic and mediastinal disorders	17 (11)	20 (10)	37 (11)	16 (21)	11 (12)	27 (16)
Vascular disorders	7 (5)	10 (5)	17 (5)	10 (13)	5 (5)	15 (9)

2..6.8.7. Immunological events

In general, CRS is expected, as it is part of the mechanism of action of catumaxomab.

According to the original MAA, 72% of catumaxomab exposed patients (ISS2) experienced CRS. The assessment of CRS assessment used in the original MAA was regarded as highly unspecific. Therefore, a new algorithm was used in the pivotal study to identify patients with symptoms suggestive of CRS according to current standards using a combination of symptoms.

It should be noted that in the "original analysis" of the pivotal study, CRS was observed in 79.6% of all patients, whereas in the post-hoc analysis, only 37/157 (36.9%) of all patients experienced CRS.

Post-hoc assessment of CRS based on algorithm

In the main study period of IP-REM-AC-01, 23% of all exposed patients had episodes of suspected CRS according to this algorithm, which was comparable to the crossover period. Patients with ovarian and nonovarian cancer had comparable incidences (26% vs 20% in the main study period, Table 55). No patient in the control group was identified with a suspected CRS episode.

Table 55. Suspected CRS episodes (as per post hoc analysis); study IP-REM-AC-01, safety set, main study period

	Ovarian		Non-ovarian	
	Catumaxomab	Control	Catumaxomab	Control
Patients, n	80	44	77	44
Patients with suspected CRS episode[1], n (%)	21 (26.3)	0	15 (19.5)	0
Suspected CRS episodes, n	23	0	18	0

[1] Patient nos. 0102-07; 1102-05; 0118-08; 1205-01; 0125-03; 0125-06; 0129-02; 0129-04; 1301-01; 1301-11 (2 episodes; 1301-07 (2 episodes, one with infection at the same time); 0139-03; 0201-02; 0202-05; 0403-01; 0702-03; 0710-14; 0710-02; 0710-03; 0803-03; 0806-01; 1101-04; 1104-12; 1204-02; 1303-04 (2 episodes); 0201-12; 0202-11; 0210-03; 0302-01; 0302-02; 0404-04 (2 episodes); 0602-06; 0602-07; 0704-13; 0706-03; 0710-05 (2 episodes)

In the pivotal study, even using the new algorithm, of the 41 suspected CRS episodes in the 36 patients, 3 were mild/grade 1, 27 moderate/grade 2, 10 severe/grade 3, and 1 was life threatening/grade 4. Twenty-four of 36 episodes (67%) started on day of or the day after the first catumaxomab infusion. It is, therefore, not considered acceptable to reduce the time of hospitalisation to 6 hours after the first dose of Korjuny. Therefore, upon request of the CHMP the applicant reworded Section 4.2 of the SmPC to "Patients should remain under close medical supervision for at least 24 hours after the first infusion of KORJUNY. For the remaining doses, patients may be hospitalised for at least 6 hours or for a longer time after infusions of KORJUNY at the discretion of the treating physician to safeguard patient safety" which is accepted.

In order avoid or ameliorated symptoms of pain and pyrexia, paracetamol was routinely administered at a dose of 1000 mg, 30 minutes prior to each catumaxomab infusion in study IP-REM-AC-01. Prednisolone at 25 mg did not result in a significant reduction in the main catumaxomab-related adverse events which was demonstrated in study IP-CAT-AC-03 (Sehouli 2014).

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

In general, a notable increase in the proportion of ADA positive patients were observed between screening and end of study/follow-up. However, data across studies indicate differences between studies in ADA dynamic, in particular when ADAs occur in patients. This may be due to different factors, such as the patient population included in each study as well as the assays used (Gallati, Medac, double antigen-binding assay [DABA]). It also needs to be considered that all study protocols defined time windows for both catumaxomab infusion time points and ADA sampling time points.

Formal subgroup analyses of safety by ADA status have not been performed. The majority of patients developed ADAs in response to catumaxomab treatment. Thus, the safety of catumaxomab as described in this MAA is for a generally ADA positive patient population.

There were no safety signals detected regarding infusion reactions, anaphylaxis, immune complex-mediated diseases, or more serious AEs with catumaxomab that might potentially be a consequence of ADAs.

2..6.8.8. Safety related to drug-drug interactions and other interactions

No clinical data were presented.

2..6.8.9. Discontinuation due to adverse events

Study IP-REM-AC-01

Overall in the pivotal study, 16 patients (8%) had 27 AEs that led to treatment discontinuation, 11 patients in the main study period (7%) and 5 patients in the crossover period (11%). Preferred terms were malignant neoplasm progression in 4 patients; ileus/subileus in 3 patients; and abdominal pain in 2 patients. No other preferred term was reported in more than a single patient.

All catumaxomab patients (ISS2)

Most frequent AEs leading to discontinuation by preferred term in catumaxomab exposed patients overall were ileus, abdominal pain, pyrexia, systemic inflammatory response syndrome (SIRS), and malignant neoplasm progression.

Patients who received catumaxomab as 3-hr infusion had twice the incidence of AEs leading to-treatment discontinuation (22%) than those who received the 6-hr infusion (11%) (Table 56). At the preferred-term level, the greatest differences were seen for vomiting, nausea, peritonitis, dyspnoea, CRS, and anastomotic complications (each 2% vs 0% for 3-hr vs 6-hr infusion duration), and SIRS (2% vs <1%). Not all of these terms are shown in the below table due to the cut-off.

Table 56. Most frequent (>1% overall) AEs leading to treatment discontinuation; pooled patient population (ISS2), safety set

	3h pooled	6h pooled	Catum. overall
Patients, n	224	293	517
Patients with event, n (%)	50 (22.3)	32 (10.9)	82 (15.9)
Gastrointestinal disorders	19 (8.5)	13 (4.4)	32 (6.2)
Ileus	1 (0.4)	6 (2.0)	7 (1.4)
Abdominal pain	4 (1.8)	2 (0.7)	6 (1.2)
General disorders and administration site conditions	9 (4.0)	7 (2.4)	16 (3.1)
Pyrexia	3 (1.3)	4 (1.4)	7 (1.4)
SIRS	5 (2.2)	1 (0.3)	6 (1.2)
Respiratory, thoracic and mediastinal disorders	14 (6.3)	0	14 (2.7)
Infections and infestations	9 (4.0)	2 (0.7)	11 (2.1)
Immune system disorders	5 (2.2)	1 (0.3)	6 (1.2)
Injury, poisoning and procedural complications	10 (4.5)	1 (0.3)	11 (2.1)

2..6.8.10. Post marketing experience

Patient exposure to commercial catumaxomab was approximated as 2082 patients, based on the number of Removab packages delivered in the market. Patients exposed to catumaxomab in clinical studies that were ongoing during the different PSUR reporting periods were included in the safety analyses i.e. ISS2, with the exception of patients treated in clinical studies IP-CAT-AC-03 (CASIMAS study) and IP-CAT-AC-04 (SECIMAS study). For both studies conducted in patients with malignant ascites, safety information is summarised below.

Several investigator-initiated trials with catumaxomab have been performed. CSRs are not available, and the applicant has no right to the study databases. Other than numbers of exposed patients, no safety information is available from these studies.

Overall, the summary of SARs reported in PSURs 1 to 10 confirmed the side effect profile of catumaxomab, with most frequent SARs of pyrexia, abdominal pain, vomiting, nausea, asthenia, fatigue, general physical health deterioration, SIRS, and ileus/subileus. This side effect profile was in line with catumaxomab's mode of action, consequences of the paracentesis procedure, and generally poor health of patients with advanced malignant disease. Unlisted SARs did not represent a clear safety signal.

IP-CAT-AC-03 (CASIMAS)

While failing to show that prednisolone at 25 mg premedication is able to reduce the rate of typical catumaxomab related AEs, the results of this second phase III study confirmed the safety and feasibility of catumaxomab administered as 3-h i.p. infusion and underlined the robustness of the efficacy and safety data for catumaxomab in the treatment of patients with malignant ascites (Sehouli 2014). The proportion of patients who discontinued catumaxomab due to AEs (catumaxomab + prednisolone 16%; catumaxomab alone 15%) was within the range seen for the ISS2 population.

Study IP-CAT-AC-04 (SECIMAS) – catumaxomab repeated treatment

This study showed that a second cycle of catumaxomab treatment is feasible in a selected patient population, with tolerability and safety of catumaxomab comparable to that after one cycle. Presence of ADAs did not seem to affect the safety or efficacy of catumaxomab. However, of note, patients in this study were highly selected, as they needed to have a puncture free interval of ≥60 days after Cycle 1 of catumaxomab and still had to be in a good general health condition despite their already advanced stage of disease; this was confirmed by the fact that only 8 patients could be included in this study.

2.6.9. Discussion on clinical safety

Characterisation of the safety profile of catumaxomab is focused on information from the main, controlled study part of the pivotal study, and additionally on the safety data from the overall population exposed to catumaxomab i.p. as per Integrated Summary of Safety 2 (ISS2). The patients were exposed to catumaxomab at least by one infusion. Data from the pivotal study and the ISS2 are not fully comparable. Patients in the pivotal study had advanced cancer disease, in many cases metastatic, and were heavily pre-treated. However, patients with malignant ascites made up only part of the ISS2 population, while other patients had cancers responding to chemotherapy or scheduled for surgery with curative intent. Such patients would have a better prognosis and less previous anticancer treatment, likely impacting their safety profile. In addition, the infusion duration is partly confounded. In the pivotal study and in the other early clinical studies, catumaxomab was given as a 6-hr infusion; but in later studies (including indications other than malignant ascites), the infusion duration was shortened to 3-hr.

Exposure

A total of 157 patients were treated with catumaxomab in the main study period of the pivotal study. Of these patients, 83% received all 4 infusions as planned. Overall, 517 patients were exposed to catumaxomab (ISS2 population) and 74% received all planned infusions. In patients receiving catumaxomab as 6-hr infusion, 80% received all planned infusions, vs 67% in the 3-hr group.

Adverse drug reactions (ADRs) in the SmPC section 4.8 are based on complete ISS2 population, which is acceptable.

Adverse Events

Almost all patients in the main part of the pivotal study and in the overall population had at least 1 TEAE. Half of catumaxomab patients overall (49%) had serious adverse events (SAEs), in 19% of patients, at least one SAE was drug-related. The SAE incidence was somewhat higher in the pivotal study (58%), but a comparable proportion had drug-related SAEs in the pivotal study (15%). In the control arm of the pivotal study (paracentesis only), 58% of patients had adverse events (AEs) and 29.3% had SAEs and 29.5 % TEAEs of grade 3 or higher. To allow a better comparison of the frequency of safety events, the applicant provided an analysis for safety of the pivotal study which is based on fixed follow-up periods, e.g., 7 days, 14 days, 21 days, once from randomisation (in both arms) and once from the respective clock-start.

Starting AE analysis from clock start onwards (Day 0 for control patients, after last infusion/drainage to dryness in catumaxomab patients), excluded AEs with onset during the infusion period in catumaxomab patients (excluding a considerably large proportion of adverse events related to drugs), resulting in more comparable AE profiles between the 2 treatment arms. Nevertheless, the incidence of all adverse event categories was higher in the catumaxomab arm compared to the control arm. As noted by the applicant, this might be related to the substantially longer observation time in catumaxomab patients due to the delay of therapeutic puncture achieved in these patients. For most categories there was a trend for incidences to decrease from the first (Day 0-7) to the third time window (Day 15-21). However, despite the decrease in the catumaxomab arm, the incidences remained higher compared to those in the control arm, which is of concern. Subsequently, incidences increased again in the last time window (>21 days) in the catumaxomab arm and to a lesser extend in the control arm. As noted by the applicant, this was likely in line with the fact that the last time window was the longest, with the most exposure data. Incidence of related AEs and of related SAEs (reported in catumaxomab patients only) appeared to decline over time.

Adverse events in more than 10 ovarian cancer patients included pyrexia and malignant neoplasm (Table 46). As expected, pyrexia (a typical event associated with CRS) decreased over time whereas malignant neoplasm progression occurred with the highest incidence in the last time window. This trend was observed for all patients, although more pronounced in catumaxomab patients for ovarian and non-ovarian cancer patients (Table 46 and Table 47). The most frequent drug related AEs occurred with a similar pattern in ovarian and non-ovarian cancer patients, with highest numbers in the first-time window, i.e. directly after clock start. No conclusion can be drawn from most frequent SAEs due to low number with the exception of malignant neoplasm progression in the catumaxomab arm which occurred with the highest frequency in the fourth and largest time window (>21 days).

Analyses of key safety data by the number of previous punctures of patients, were provided separately for patients in the ovarian and the non-ovarian cancer stratum. Overall, there was no systematic or consistent effect of the number of previous ascites punctures on the safety profile of catumaxomab in ovarian cancer patients. It seems that nonovarian cancer patients with more previous ascites punctures had a greater likelihood to experience gastrointestinal AEs, pyrexia and unspecific symptoms of asthenia and anorexia. This might be a reflection that non-ovarian cancer patients generally have more advanced disease, and a worse prognosis. However, number of patients in each of the subcategories by stratum and treatment group was very low, which hamper to draw robust conclusions on the effect of the number of previous punctures on safety results. In catumaxomab patients and control patients with nonovarian cancer with ≥4 previous punctures, incidence of SAEs, AEs ≥grade 3, AEs leading to discontinuation, and fatal AEs were lower than in patients with 1 or 2-3 previous punctures. On the other hand, the incidence of related AEs increased with

previous puncture number. This may be explained by the fact that patients able to achieve high puncture numbers were in relatively good condition, compared to frail patients who generally received less punctures and died or discontinued treatment with catumaxomab.

Isolated incidence of SIRS (with concurrent fever, increased heart rate and respiratory rate, and abnormal leukocyte count) have been reported during and after treatment with catumaxomab. Patients should be counselled to seek immediate medical attention if signs or symptoms of SIRS occur at any time. SIRS should be treated as medically indicated and according to the current standard of care.

In presence of factors interfering with the immune system, in particular acute infections, the administration of catumaxomab is not recommended. Patients should be monitored for signs and symptoms of infection, before and after Korjuny administration and treated appropriately.

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

Adequate monitoring of the patient after end of Korjuny infusion is recommended with close medical supervision for at least 24 hours after the first infusion of Korjuny and for at least 6 hours after subsequent infusions.

In the pivotal study IP-REM-AC-01, patients with a Karnofsky performance score of < 60 and with a BMI of < 17 or > 40 kg/m^2 have not been investigated. Treating these patients with Korjuny is at the discretion of the treating physician.

Fatal events

In the pivotal study, incidences of fatal AEs for catumaxomab are 45% for the main study period and 45% (i.e. 91/202 patients, including cross-over patients) of all patients exposed to catumaxomab, vs 15% for control. As already suggested, the higher incidence of fatal AEs with catumaxomab is thought to be linked to the substantially longer observation time in these patients that is due to the delay of therapeutic puncture achieved in patients receiving catumaxomab on top of paracentesis. This supposingly higher death rate is not linked to the different OS analyses with various censoring rules which did not show any detrimental effect on OS. In most patients, regardless of treatment and study period, the preferred term of the fatal AE was malignant neoplasm progression. One fatal AE was judged as being related to catumaxomab i.e. hypovolaemic shock in a patient with gastric cancer.

Of all catumaxomab exposed patients, 21% experienced an AE of grade 5. The most frequent AE was malignant neoplasm progression (16%); all other AEs at the preferred term level were reported in <1% of patients. Patients receiving catumaxomab as 6-hr infusion had a higher incidence of AEs of grade 5 (32%) than patients receiving the 3-hr infusion (7%). This difference was driven by malignant neoplasm progression (6-hr: 24%, 3-hr: 6%) and is thought to reflect different patient populations. One AE of grade 5 was judged as being drug-related, i.e. hypovolaemic shock in a gastric cancer patient in the crossover period of the pivotal study (see above).

Serious adverse events

The reported SAEs, were mainly within the anticipated risk pattern and were reported in 58% of catumaxomab patients (14% of these SAEs were considered related to catumaxomab) and in 23.9% of control patients in the main study part of the pivotal study. The most frequent SAE was malignant neoplasm progression (36% in the catumaxomab and 31.8% in the control arm). Next most frequent were GI SAEs, reported in 19% of patients; including SAEs of ileus or subileus reported in 13 patients (8%). Only a subset

of SAEs was related to catumaxomab. In general, higher numbers of patients with drug-related SAEs were seen in the SOCs of gastrointestinal disorders (most frequently ileus, 7 patients) and of general disorders and administration site conditions (most frequently pyrexia, 4 patients).

The SAE incidence in catumaxomab patients overall was 49%, with comparable incidences in the 6-hr group (51%) and 3-hr group (46%). The most frequent SAE was malignant neoplasm progression (18%), with a higher incidence in the 6-hr group (27%), vs 6% in the 3-hr group. Notable differences between the 3-hr and 6-hr infusion groups, apart from malignant neoplasm progression, were vomiting and nausea, both being more frequent with the 3-hr infusion.

3-hour versus a 6-hour infusion time

The 3-hr vs 6-hr application of catumaxomab have generally comparable side effect profiles in terms of events/preferred terms. There have been no new side effects observed with only the 3-hr infusion that would not have been seen with the 6-hr infusion.

Drug-related AEs were comparable between the 3-hr and 6-hr infusion duration, except for the following preferred terms being more frequent after the shorter infusion: fatigue (3h infusion: 26%, 6h infusion: 13%); chills (25% vs 12%), diarrhoea (21% vs 10%), rash (12% vs 6%), and hypotension (13% vs 6%). Lymphopenia was less frequent with the 3-h infusion (5% vs 12%). Notable differences between the 3-hr and 6-hr infusion groups, apart from malignant neoplasm progression, were vomiting and nausea, both being more frequent with the 3-hr infusion. Patients receiving the 3-hr infusion had twice the incidence of AEs leading to treatment discontinuation (22%) as the 6-hr infusion group (11%).

Accidental i.v. administration is considered a safety concern and a warning was added in the SmPC to highlight that the product must not be administered as a bolus or by any route other than i.p. (see RMP and SmPC section 4.4).

Laboratory findings

Analyses of laboratory data for all patients exposed to catumaxomab (ISS2) are not available, and all presentations of laboratory data were at the study level. Of these, results for the main part of the pivotal study IP-REM-AC-01 are considered to be of particular relevance and are summarised and discussed in the following.

Changes in laboratory parameters were expected (LFTs, leukocytosis, lymphopenia), and they were rarely clinically relevant.

Hepatic toxicity by increase of AST, ALT, GGT and AP with a tendency to accumulate by the end of the treatment period was noted, which has been adequately reflected in the SmPC. Furthermore, the risk of hepatotoxicity reported with Korjuny which may lead to drug-induced liver injury (DILI), hepatitis and may result in cases of hepatic failure and fatal cases, has been described in Section 4.4 of the SmPC, where it states that transient elevations of liver parameters after catumaxomab infusions were observed in clinical studies which subsequently improved in the majority of patients shortly after completion of the last catumaxomab infusion. In rare cases, catumaxomab -drug induced liver injury (DILI) or hepatitis may occur, potentially leading to hepatic failure including fatal outcome. Patients treated with Korjuny should be closely monitored for signs of clinically significant elevated liver parameters. This was also considered as a safety concern and reflected in the RMP as missing information (see RMP).

Cytokine levels were transiently increased after each infusion.

Hospitalisation

Median stay in hospital due to application of catumaxomab was 13 days which is in line with the planned treatment schedule of 11 days for catumaxomab.

Based on re-analysed data, 27% (17/44) of ovarian cancer patients and 48% (21/44) of nonovarian cancer patients in the control group had no hospitalisation episodes reported. In contrast, there were almost no catumaxomab patients without hospitalisation (ovarian cancer: 1%; nonovarian cancer: 5%). Most catumaxomab patients had been admitted once or twice (ovarian cancer: 78%; nonovarian cancer: 78%). Patients receiving catumaxomab had a longer mean relative hospitalisation duration of 0.38-0.42, (38-42%) vs 0.23-0.25 (23-25%) in control patients. Analysis of hospitalisation might be misleading, as (i) in the catumaxomab arm, screening was conducted as ambulatory visit, while in the control group the ambulatory visit might not have been counted as hospitalisation by some investigators, (ii) some catumaxomab patients had up to 4 short hospitalisations (for 4 catumaxomab infusions) while others were admitted and remained hospitalised through the end of the 4 infusions. Hence, more hospitalisation episodes per patient might in fact reflect good treatment tolerability because the patient could leave the hospital after each infusion, (iii) the difference in observation period between the catumaxomab patients and control patients likely contributed to higher hospitalisation rates (in analogy to higher AE incidences).

The duration of hospitalisation as reported in the pivotal trial was preliminary driven by the study design and that most hospitalisations in catumaxomab patients were for study drug infusions (81%). According to the study protocol of the pivotal study, patients were to be hospitalised for 24 hours at each dose. The length of hospitalisation in the catumaxomab group can also be explained by the study procedures as patients who received at least one infusion (safety set) were only once hospitalised, meaning that patients stayed in hospital from admission until the end of treatment. In this context it should be noted that the pivotal study was initiated almost 20 years ago (Sep 2004) and by that time CRS was a relatively new and poorly understood phenomenon explaining the requirement for hospitalisation for 24 hours after each dose. This situation has been fundamentally changed and CRS is now considered to be a manageable toxicity of modern immunotherapies. The hospitalisation time is expected to be significantly reduced to 5-7 days for the majority (>70%) of patients in current practice compared to time period of the pivotal trial. In the pivotal trial around 23 % of patients experienced CSR episodes (Post hoc assessment of CRS (data not shown)) which is in line with the AE-driven hospitalisation rate of 28.3%. As most of the CRS episodes started on the day or the day after catumaxomab infusion, close medical supervision for at least 24 h is considered sufficient for the first infusion only, while for the remaining infusions (i.e. #2-4), medical monitoring can be reduced to 6 h (as currently reflected in the SmPC).

In conclusion, it is anticipated that hospitalisation duration and burden will be much less in the current clinical practice compared to the pivotal trial, and thus, it is not considered a major concern in this disease setting.

Age

Overall, the safety profile was comparable between patients below or above 64 years.

Immunological events

In general, CRS is expected, as it is part of the mechanism of action of catumaxomab.

Seventy-two percent (72%) of catumaxomab exposed patients (ISS2) experienced CRS. An algorithm to identify patients with symptoms suggestive of CRS according to current standards using a combination of symptoms was used.

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 have been reported during and after catumaxomab administration, including events of fever, hypotension, gastrointestinal symptoms, headache, myalgia, arthralgia, tachycardia, chills, respiratory symptoms, skin symptoms, and fatigue. Despite pre-medication, patients may experience CRS as described above with an intensity of up to grade 4. Patients should be counselled to seek immediate medical attention if signs or symptoms of CRS occur at any time. CRS should be treated as medically indicated and according to the current standard of care (see sections 4.2, 4.4, 4.8 and 5.1 of the SmPC). As a consequence, patients should remain under close medical supervision for at least 24 hours after the first infusion of catumaxomab. For the remaining doses, patients may be hospitalised for at least 6 hours or for a longer time after infusions of catumaxomab at the discretion of the treating physician to safeguard patient safety.

Prior to the intraperitoneal infusion, medication for the prophylactic treatment of cytokine release symptoms, including analgesic, antipyretic and non-steroidal antiphlogistic medicinal products is recommended (see section 4.2 of the SmPC).

CRS/SIRS is considered as an important identified risk and a patient card was agreed as an aRMM (see RMP). The patient card describes the common signs and symptoms of CRS and SIRS and provides instructions on when a patient should seek medical attention.

Section 4.4 of the SmPC highlights that appropriate medical management of ascites drainage is a prerequisite for Korjuny treatment in order to assure stable circulatory and renal functions. This must at least include ascites drainage until stop of spontaneous flow or symptom relief. Blood volume, blood protein, blood pressure, pulse and renal function should be assessed before each Korjuny infusion. Conditions such as hypovolaemia, hypoproteinaemia, hypotension, circulatory decompensation and acute renal impairment must be resolved prior to each Korjuny infusion.

Immunogenicity of catumaxomab

There were no safety signals detected regarding infusion reactions, anaphylaxis, immune complex-mediated diseases, or more serious AEs with catumaxomab that might potentially be a consequence of ADAs.

Discontinuation due to adverse events

In 16% of patients overall (ISS2), AEs led to treatment discontinuation, vs 7% in the pivotal study. Patients receiving catumaxomab as 3-hr infusion had a higher incidence of AEs leading to discontinuation (22%) compared with 11% for the longer infusion duration. The incidence of drug-related AEs leading to discontinuation was 16% in the 3-hr infusion group and 7% in the 6-hr group.

2.6.10. Conclusions on the clinical safety

The safety profile of catumaxomab is in line with its mode of action. The safety results of the pivotal study and the overall population confirm the specific pattern of the commonly observed catumaxomab adverse events that are mainly related to its immunologic mode of action. Symptoms (e.g., pyrexia, vomiting and nausea) associated with the release of proinflammatory, modulatory and cytotoxic cytokines were very common and are a well-known consequence of antibody therapy. In general, in the pivotal study, catumaxomab treated patients had higher AEs, AEs ≥ grade 3 and SAEs than control (paracentesis only) for all SOC and preferred terms. Even though CRS were generally manageable and short lasting, 30% were of grade 3 and 4% included a symptom of grade 4 in the pivotal study. Such events trigger or prolong

hospitalisation. In the control group of the pivotal study, no CRS were observed. However, CRS is an anticipated reaction with the use of immunomodulating mAbs and generally manageable in clinical practice. In addition, hospitalisation duration and burden is expected to be much less in the current clinical practice compared to the pivotal trial, and thus, it is not considered a major concern in this disease setting. Therefore, the safety profile of catumaxomab can be considered acceptable in the agreed indication.

2.7. Risk Management Plan

2.7.1. Safety concerns

Table 57. Summary of safety concerns

Summary of safety concerns	
Important identified risks	Cytokine release syndrome/systemic inflammatory response syndrome
Important potential risks	More severe adverse reactions due to accidental i.v. infusions instead of i.p.
Missing information	Patients with at least severe hepatic dysfunction and/or with at least 70% of the liver affected by metastases

2.7.2. Pharmacovigilance plan

There are no planned or ongoing additional pharmacovigilance activities.

2.7.3. Risk minimisation measures

Table 58. Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	**Risk minimisation measures**	**Pharmacovigilance activities**
Cytokine release syndrome (CRS)/Systemic inflammatory response syndrome (SIRS)	Routine risk minimisation measures: SmPC Sections 4.2, 4.4 and 4.8 SmPC Section 4.2, where recommendations are given on patient supervision and advice on use of medication for the prophylactic treatment of cytokine release symptoms SmPC Section 4.4 where recommendations are given to ensure circulatory stability before treatment, on patient counselling, and on post-treatment monitoring	None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	PIL Sections 2, 3, 4 Additional risk minimisation measures: Patient card	
More severe adverse reactions due to accidental i.v. infusions instead of i.p.	Routine risk minimisation measures: SmPC Sections 4.2, 4.4, 6.6 PIL Section 3 Warning sticker for the syringe containing the diluted Korjuny solution indicating the name (Korjuny) and route of application (i.p.)	None
Patients with at least severe hepatic dysfunction and/or with at least 70% of the liver affected by metastases	Routine risk minimisation measures: SmPC Sections 4.2 and 4.4 PIL Section 2	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Specific follow-up questionnaire

2.7.4. Conclusion

The CHMP considers that the risk management plan version 0.3 is acceptable.

2.8. Pharmacovigilance

2.8.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.8.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did not request alignment of the PSUR cycle with the international birth date (IBD). The new EURD list entry will therefore use the EBD to determine the forthcoming Data Lock Points.

2.9. Product information

2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Korjuny is indicated for the intraperitoneal treatment of malignant ascites in adults with epithelial cellular adhesion molecule (EpCAM)-positive carcinomas, who are not eligible for further systemic anticancer therapy.

3.1.2. Available therapies and unmet medical need

Malignant ascites (MA) carries a poor prognosis, often becoming symptomatic in patients with only weeks to months to live. Despite this, the presence of MA can have a significant detrimental impact on QoL, with increasing abdominal distention, pain, and dyspnoea. Diuretics and dietary sodium restriction, the traditional first-line therapies for ascites in cirrhosis, do not work well for MA (Seah 2022).

Treatment depends on the cause; the severity of symptoms; the cancer type, extent of spread, suitability of anticancer treatments and patient preferences.

Methods are listed below:

- Treatment of the cancer itself with systemic therapy
    - Advantages: possibly life prolonging
    - Disadvantages: often not possible as ascites is a symptom of relapsed and refractory end-stage metastatic cancer
- Paracenteses as indicated +/- albumin substitutions (chosen comparator for the current submission)
    - Advantages: providing relief, uncomplicated and relatively safe procedure possible also in out-patient setting,
    - Disadvantages: procedure to be repeated, rarely GI perforation, infection, bleeding
- Permanent catheters – surgical procedure of insertion of tunnelised catheter required. Surgical tunnelisation is required for infection prophylaxis. However, also non-tunneled catheters exist.
    - Benefits: no additional paracenteses needed; home management
    - Risks: Infections, Bleeding, GI perforation
- Other solutions: indwelling peritoneal ports, peritoneovenous shunts (PVSs), or hyperthermic i.p. chemotherapy (HIPEC)

Last three do not improve overall survival, although they may improve QoL and decrease hospital visits and interventions in an end-stage disease palliative care (RCOG 2014).

An unmet medical need can be recognised as there is no medicinal product currently approved in this setting, and there is a need for an alternative therapy in this highly-individualised palliative care setting.

3.1.3. Main clinical studies

Study IP-REM-AC-01 was a Phase II/III, randomised, open-label study in epithelial cancer patients with symptomatic malignant ascites requiring therapeutic ascites puncture investigated treatment with paracentesis plus catumaxomab vs. paracentesis alone. The study population consisted of a total of 258 patients, divided into 2 strata: 129 patients with ovarian cancer and 129 patients with non-ovarian cancer. In each cancer stratum, 85 patients were randomised to treatment with paracentesis plus catumaxomab (catumaxomab group), and 44 patients were randomised to treatment with paracentesis alone (control group). The primary 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.

3.2. Favourable effects

- Puncture-free survival (PuFS). For ovarian cancer patients, the median difference between the groups was 37 days and for all non-ovarian cancer patients 16 days. This in favour of catumaxomab. Analyses with alternative censoring rules confirmed this advantage.
- Overall Survival (OS). OS-analysis following the ITT principle where subjects are not censored when they cross-over to catumaxomab showed a median OS of 72 days in the catumaxomab arm and 71 days in the control arm. This comparison provided sufficient reassurance that there is no detrimental effect of catumaxomab.
- Daily collected ascites volume. The median daily fluid production was 3.3 times lower in the ovarian cancer catumaxomab group and 7.0 times lower in the non-ovarian cancer catumaxomab group.
- Ascites signs and symptoms. At Visit 6 (8 days after the last infusion for the catumaxomab group, 8 days after Day 0 for the control group), fewer patients had signs and symptoms of ascites in the catumaxomab group than in the control group. All analysed signs (abdomen examination by investigator), according to physical examination like shifting dullness, fluid thrill, abdominal distension and bulging flanks are in favour of catumaxomab.

3.3. Uncertainties and limitations about favourable effects

The possibility to cross-over after second therapeutic puncture in control arm markedly reduced follow up time, impacting on the possibility to properly assess efficacy over time. Most notably it impacts the determination of OS and hampers the determination of the durability of the effect. Nevertheless, OS is at least not detrimental in catumaxomab treated subjects.

The open-label study design might induce bias in endpoints, e.g. in the time to first therapeutic puncture, and—as it seems that only minimal firewall measures (e.g., restricted access to database) were in place—might impact the conduct of study as decisions might have been taken in the light of accruing data.

The timing of visits was scheduled from time of last infusion (catumaxomab group) and time of randomisation (control group), respectively, hampering the comparability of data especially during the treatment phase itself.

3.4. Unfavourable effects

The safety profile is based on the pooled safety data from 517 catumaxomab exposed patients as per Integrated Summary of Safety 2 (ISS2).

Half of catumaxomab patients (49%) had serious adverse events (SAEs) with comparable incidences in the 6-hr group (51%) and 3-hr group (46%), in 19% of patients, at least one SAE was drug-related. Almost all patients experienced TEAEs. 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. The incidence of all adverse event categories was higher in the catumaxomab arm compared to the control arm in the pivotal study. Incidence of related AEs and of related SAEs (reported in catumaxomab patients only) appeared to decline over time.

The most frequent AE attributed to catumaxomab included cytokine release-related symptoms (fever, nausea and vomiting) and abdominal pain and were generally consistent between the pivotal study and the ISS2 population.

The most frequent SAE was malignant neoplasm progression (18%), with a higher incidence in the 6-hr group (27%), vs 6% in the 3-hr group.

In 16% of patients AEs led to treatment discontinuation, vs 7% in the pivotal study. Patients receiving catumaxomab as 3-hr infusion had a higher incidence of AEs leading to discontinuation (22%) compared with 11% for the longer infusion duration. The incidence of drug-related AEs leading to discontinuation was 16% in the 3-hr infusion group and 7% in the 6-hr group. At the preferred term level, the greatest differences were seen for vomiting, nausea, peritonitis, dyspnoea, CRS, and anastomotic complications (each 2% vs 0% for 3h vs 6h infusion duration), and SIRS (2% vs <1%).

The AE-driven hospitalisation rate was 28.3%. Patients receiving catumaxomab had a longer mean relative hospitalisation duration of 0.38-0.42, (38-42%) vs 0.23-0.25 (23-25%) in control patients.

3.5. Uncertainties and limitations about unfavourable effects

The patients in the control group in the pivotal trial only received paracentesis, not placebo. As catumaxomab was effective in prolonging puncture-free survival and as subjects in the control group could cross over to catumaxomab after the second therapeutic paracentesis, the observation period for adverse events was distinctly longer in the catumaxomab than in the control group which needs to be considered for the direct comparison between catumaxomab and control group. Moreover, patient follow-up was more intensive in catumaxomab patients: catumaxomab patients were followed during the infusion period, while control patients did not undergo the visits used in the catumaxomab patients for study drug administration. Thus, reporting of events is more likely during active treatment.

3.6. Effects Table

***T*able 59. Effects table for Korjuny for the intraperitoneal treatment of malignant ascites in adults with epithelial cellular adhesion molecule (EpCAM)-positive carcinomas, who are not eligible for further systemic anticancer therapy.**

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Favourable Effects						
PuFS	Composite primary endpoint: death or puncture *Note: From sensitivity analysis when all deaths before clock start are recognised as events*	days	48 (37; 59) (ovarian) 30 (20; 45) (non-ovarian)	11 (9; 20) (ovarian) 14 (8; 17) (non-ovarian)	Overall strong evidence as supported by various analyses Methodological issues regarding censoring and definition of time 0.	AR, section 2.5.2
Ascites signs and symptoms	% of patients without clinical signs or symptoms of ascites at Visit 6 Mean values calculated by assessor	%	59.9% (Symptoms - ovarian) 57.1% (Signs - ovarian) 60.9% (Symptoms - non-ovarian) 60.2% (Signs – non-ovarian)	44.2% (Symptoms - ovarian) 26.1% (Signs - ovarian) 47.7% (Symptoms - non-ovarian) 38.5% (Signs – non-ovarian)	Intermediate strength of evidence. Subject to bias due to open-label design Non-validated questionnaire Mean values calculated by assessor	AR, section 2.5.2
OS	OS analysis following the ITT (subjects are not censored when they cross-over)	median (days)	72 days	71 days	Excludes a detrimental effect of catumaxomab	AR, section 2.5.2
Unfavourable Effects						

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
CRS	Pivotal ISS2	n/N (%)	36/157 (23%) 373/517 (72.1%)	0/88	Retrospective analysis (not according to current guidelines) Original analysis	AR, section 2.8.8
SAE	Pivotal ISS2	n/N (%)	91/157 (58%) 253/517 (48.9%)	21/88 (23.9%)	Longer observation time in the catumaxomab arm compared to the control arm	AR, section 2.8.3
Grade 3/4	Pivotal ISS2	n/N (%)	125/157 (79.6%) 400/517 (77.4%)	26/88 (29.5%)		AR, section 2.8.3
SADR	Pivotal	n/N (%)	23/157 (14.6)	0		AR, section 2.8.3
Hospitalisation	Pivotal	Mean (SD) (days) Relative hospitalisation duration Mean (SD)	Ovarian cancer: 22.2 (14.7) Nonovarian: 19.9 (11.7) Ovarian cancer: 0.38 (0.29) Nonovarian: 0.42 (0.31)	Ovarian cancer: 20.1 (57.5) Nonovarian: 10.4 (13.4) Ovarian cancer: 0.23 (0.33) Nonovarian: 0.25 (0.37)	Longer observation time in the catumaxomab arm compared to the control arm Uncertainties in documentation	AR, section 2.8.3

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Malignant ascites is a manifestation of end stage disease in a variety of cancers and is associated with a significant morbidity. The onset and prognosis of malignant ascites is associated with deterioration in quality of life and poor prognosis.

Efficacy of catumaxomab has been demonstrated in an open-label randomised trial using a time-to event endpoint "puncture-free survival". The trial met its primary endpoint, supported by additional sensitivity analysis and using different censoring rules. Due to the currently marginal role of alternative treatment

options and their uncertain benefits over paracenteses alone (e.g. permanent catheters), paracenteses is still a valid comparator.

The prolongation of PuFS was from 11 [9; 20] days in control to 48 [37; 59] days in the catumaxomab group for ovarian cancer and from 14 [18; 17] days in control to 30 [20; 45] days in the catumaxomab group for non-ovarian cancer. This could be due to lower production of ascites fluid, which is 3.3 (ovarian) to 7.5 (non-ovarian) times lower than in the respective control group (this is supported by the analysis provided on the collected ascites volume and time to puncture (correlation analysis and collected ascites volume per arm)): see daily collected ascites volume). Even if the underlying reason for the lower production of ascites fluid is not completely resolved, there is still an anticipated benefit from such an improvement in PuFS, namely that, in the case of similar OS in both groups, it is expected to reduce the number of punctions needed during this time. Ascites signs and symptoms showed at Visit 6 lower subjective experience of ascites symptoms, which was confirmed by physical examination (signs). Median time to deterioration of QoL was longer in catumaxomab group compared to control. Without clear evidence of prolonging patient´s survival, such effects could be considered important but hampered due to uncertainties about QoL evaluation in the treatment period.

The safety results of the pivotal study and the overall population confirm the specific pattern of the commonly observed catumaxomab adverse events that are mainly related to its immunologic mode of action. Symptoms (e.g., pyrexia, vomiting and nausea) associated with the release of proinflammatory, modulatory and cytotoxic cytokines were observed in more than 70% of catumaxomab treated patients (ISS2 population). Even though CRS were generally manageable and short lasting, 30% were of grade 3 and 4% included a symptom of grade 4 in the pivotal study. Such events trigger or prolong hospitalisation. In the control group of the pivotal study, no CRS were observed. Prolonged hospitalisation seems not to be a trigger of major concern, as only 24h hospitalisation will be required post-marketing, based on incidence rates of CR predominantly after the first injection.

3.7.2. Balance of benefits and risks

The established benefit is a prolongation of time to the next therapeutic puncture, which is associated with lower ascites fluid production after catumaxomab treatment.

PuFS is a relevant endpoint in the treatment of malignant ascites only to study a prolongation of the time to first punction after treatment.

OS analyses allowed to conclude that there is no detrimental effect of catumaxomab treatment comparing to ascites punctions.

A benefit in QoL and ascites signs and symptoms is shown, but the strength of evidence is limited due to the open-label design, the post-hoc analyses and the failure to cover the treatment period itself. Acknowledging these limitations, these results are still considered to support the benefit of catumaxomab treatment.

There are uncertainties in the precise determination of the benefits of catumaxomab treatment due to the open-label design, the different starting points between the two arms, the multiple punctures that were required before administration of catumaxomab arm (but not performed in the control arm) and the lack of objective criteria in the protocol to define the need for the next paracentesis. However, based on the provided sensitivity analyses (also including different censoring rules), and the magnitude of the observed effects in the various analysis, a clinically relevant reduction in the number of needed punctures can be considered established.

The impact of hospitalisation has been assessed and accepted. CRS was the main driver for increased hospitalisation in the pivotal trial. In the current clinical practice, management of CRS has greatly improved.

The frequency and severity of AEs especially CRS as well as the necessary hospitalisation are not considered a major drawback in a palliative setting for the following reasons: most SAEs in the pivotal study were related to disease progression which can be explained by the longer observation period in the catumaxomab treatment group. Furthermore, only a minority of these SAEs were considered as related to catumaxomab. Clinical management of CRS has significantly changed and has strongly improved in the past decade. Nowadays, CRS is a well-known and manageable side effect of immune-oncology drugs. Thus, it can be anticipated that hospitalisation duration and burden will be reduced compared to the pivotal trial.

Currently, there is no medicinal product approved in this setting, and there is a need for an alternative therapy in this highly-individualised palliative care setting. Catumaxomab is considered as alternative to paracenteses or other treatment methods for malignant ascites

In conclusion, it is considered that there is an established benefit, in terms of PuFS, that is expected to reduce the number of needed punctures. This outweighs the safety profile, mainly driven by CRS, which is considered acceptable in this disease setting. Therefore, the benefit-risk balance is considered positive.

3.7.3. Additional considerations on the benefit-risk balance

The applicant proposes to develop an *in vitro* diagnostic assay to be manufactured and used only in a single health institution established in the Union ("in-house assay"). Applying the same cut-off of 400 EpCAM positive cells / 10^6 analysed ascites cells would have resulted in the EpCAM in-house assay selecting the same patient population for treatment with Korjuny as was selected by the CTA in the pivotal clinical trial, resulting in the same benefit-risk balance as was seen in the pivotal clinical trial.

3.8. Conclusions

The overall benefit/risk balance of Korjuny is positive, subject to the conditions stated in section 'Recommendations'.

Divergent position(s) are appended to this report.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by majority decision that the benefit-risk balance of Korjuny is favourable in the following indication(s):

Korjuny is indicated for the intraperitoneal treatment of malignant ascites in adults with epithelial cellular adhesion molecule (EpCAM)-positive carcinomas, who are not eligible for further systemic anticancer therapy.

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Other conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

The MAH shall ensure that in each Member State where Korjuny is marketed, all patients/carers who are expected to use catumaxomab have access to/are provided with the Patient Card which will inform and explain to patients the risks of cytokine release syndrome (CRS) and systemic inflammatory response syndrome (SIRS). The Patient Card also includes a warning message for healthcare professionals treating the patient that the patient is receiving catumaxomab.

The **Patient Card** shall contain the following key messages:

- A description of the key signs and symptoms of cytokine release syndrome/systemic inflammatory response syndrome.
- A description of when to seek urgent attention from the healthcare provider or seek emergency help, should signs and symptoms of cytokine release syndrome/systemic inflammatory response syndrome present themselves.
- The prescribing physician’s contact details.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.

Divergent position(s)

Divergent position(s) to the majority recommendation are appended to this report.

APPENDIX

DIVERGENT POSITION DATED 17 OCTOBER 2024

DIVERGENT POSITION DATED 17 OCTOBER 2024

Korjuny EMEA/H/C/005697/0000

The undersigned members of the CHMP did not agree with the CHMP's positive opinion recommending the refusal of the granting of the marketing authorisation of Korjuny indicated for the intraperitoneal treatment of malignant ascites in adults with epithelial cellular adhesion molecule (EpCAM)-positive carcinomas, who are not eligible for further systemic anticancer therapy.

The reason for divergent opinion was the following:

Catumaxomab (plus paracentesis) improved puncture-free survival in comparison to solely paracentesis in the pivotal study. While theoretically a delay in build-up of fluid could be considered a favourable effect, true clinical benefit of catumaxomab cannot be determined on the basis of the data provided. Due to its important design limitations, the study does not allow assessment of the effect of catumaxomab in isolation from the procedural differences between the treatment arms. Importantly, it is unclear whether the multiple punctures (i.e., drainage to dryness) that were required before administration of catumaxomab arm (but not performed in the control arm) lead to more efficient drainage of fluid and thereby potentially prolonged time to next puncture in the catumaxomab arm. In addition, in an open-label setting, the assessment of the endpoint "time to next puncture" may be biased due to the lack of objective criteria in the protocol to define the need for the next paracentesis. Furthermore, limited information on need of and time to subsequent punctures hamper any conclusions on whether the claimed effect is preserved over time (i.e., life-time number of punctures).

Paracentesis currently represents the primary treatment of malignant ascites, but the number of punctions needed is highly variable, depending on the patient's condition. For patients requiring infrequent paracentesis, the benefit of catumaxomab is not obvious. On the other hand, a permanent catheter can be offered to patients who need frequent paracentesis, allowing fluid draining at home. Therefore, prolonging the time to next puncture might have limited clinical relevance in these patients. Due to all these reasons, the true benefit of catumaxomab cannot be determined.

The uncertain benefit needs to be weighed against the risks associated with catumaxomab treatment, such as gastro-intestinal disorders and symptoms of cytokine release, as well as the (prolonged) hospitalization needed for treatment. The latter is particularly relevant given the current management of ascites in the proposed treatment setting (i.e., last phase of disease where no active systemic treatment options are available) and considering that paracentesis can be performed in an outpatient setting.

In conclusion, the benefits of catumaxomab are unclear, whereas toxicity and impact on patient's quality of life are substantial. Therefore, we consider the benefit-risk balance to be negative.

Antonio Gómez-Outes – ES

Sol Ruiz – ES

Outi Mäki-Ikola – FI

Peter Mol - NL