14 September 2017
EMA/CHMP/552293/2017
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Human IGG1 monoclonal antibody specific for human interleukin-1 alpha XBiotech

International non-proprietary name: human IgG1 monoclonal antibody specific for human interleukin-1 alpha

Procedure No. EMEA/H/C/004388/0000

Note

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

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5520
Send a question via our website www.ema.europa.eu/contact

Table of contents

List of abbreviations

AE	Adverse Event
BMI	Body Mass Index
BSC	Best supportive care
CRC	Colorectal cancer
CRP	C-reactive protein
CRR (ORR)	Clinical response rate (Objective response rate)
CSR	Clinical study report
CT	Computed Tomography
DEXA	Dual Energy X-Ray Absorptiometry
DLT	Dose limiting toxicities
ECOG	Eastern Cooperative Oncology Group
ELISA	Enzyme-linked immunosorbent assay
EORTC-QLQ	European Organization for Research and Treatment of Cancer – Quality of Life Questionnaire
IL-1 α	Interleukin-1 α
IL-1β	Interleukin-1 β
IL-1 RA	Interleukin-1 receptor antagonist
IL-1R1	Interleukin-1 Receptor 1
IL-6	Interleukin-6
LBM	Lean Body Mass
MAA	Marketing authorisation application
mCRC	Metastatic colorectal cancer
MID	Minimal important difference
MRI	Magnetic resonance imaging
MTD	Maximal tolerated dose
ORR (CRR)	Objective response rate (Clinical response rate)
OS	Overall survival
PD	Pharmacodynamics
PD	Progression of disease
PFS	Progression free survival

PK	Pharmacokinetics
PRO	Patient reported outcomes
PS	Performance score
RP2D	Recommended Phase 2 Dose
SAE	Serious Adverse Event
SCS	Summary of Clinical Safety

1. Background information on the procedure

1.1. Submission of the dossier

The applicant XBiotech Germany GmbH submitted on 6 March 2016 an application for marketing authorisation to the European Medicines Agency (EMA) for Human IgG1 monoclonal antibody specific for human interleukin-1 alpha XBiotech, through the centralised procedure falling within the Article 3(1) and point 3 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 28 January 2016.

The applicant applied for the following indication:

Human IgG1 monoclonal antibody specific for human interleukin-1 alpha XBiotech is indicated for the treatment of metastatic colorectal cancer as a single agent in patients who have failed oxaliplatin- and irinotecan-based chemotherapy.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application. The applicant indicated that Human IgG1 monoclonal antibody specific for human interleukin-1 alpha was considered to be a new active substance.

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).

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision CW/1/2011 on the granting of a class waiver.

Information relating to orphan market exclusivity

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.

Applicant's request for consideration

New active Substance status

The applicant requested the active substance Human IgG1 monoclonal antibody specific for human interleukin-1 alpha contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

Scientific Advice

The applicant received Scientific Advice from the CHMP on 25 April 2014. The Scientific Advice pertained to

clinical aspects of the dossier.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Bjorg Bolstad Co-Rapporteur: Eleftheria Nikolaidi

- The application was received by the EMA on 6 March 2016.
- Accelerated Assessment procedure was agreed-upon by CHMP on 1 April 2016.
- The procedure started on 24 March 2016.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 10 June 2016. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 13 June 2016. The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on 24 June 2016. In accordance with Article 6(3) of Regulation (EC) No 726/2004, the Rapporteur and Co-Rapporteur declared that they had completed their assessment report in less than 80 days.
- During the meeting on 8 July 2016, the PRAC agreed on the PRAC Assessment Overview and Advice to CHMP.
- During the meeting on 21 July 2016, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. Furthermore, the CHMP agreed to revert the accelerated assessment to a standard timetable.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 18 October 2016.
- The following GMP, GCP inspections were requested by the CHMP and their outcome taken into consideration as part of the Quality/Safety/Efficacy assessment of the product:
  - A GCP inspection at one investigator site (between 13 June 2016 to 17 June 2016) and the CRO site located in Poland (between 20 June 2016 to 24 June 2016). The outcome of the inspection carried out was issued on 12 August 2016.
  - A GMP inspection at one site responsible for manufacture of the active substance and the finished product, located in the United States of America, between June 6 and June 10, 2016. The outcome of the inspection carried out was issued on June 24, 2016.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 21 November 2016.
- During the PRAC meeting on 1 December 2016, the PRAC agreed on the PRAC Assessment Overview and Advice to CHMP.
- During the CHMP meeting on 15 December 2016, the CHMP agreed on a list of outstanding issues to be sent to the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 22 March 2017.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 6 April 2017.
- During the CHMP meeting on 21 April 2017, outstanding issues were addressed by the applicant during an

oral explanation before the CHMP.

- During the meeting on 18 May 2017, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a negative opinion for granting a marketing authorisation to Human IgG1 monoclonal antibody specific for human interleukin-1 alpha XBiotech .

1.3. Steps taken for the re-examination procedure

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

Rapporteur: Alexandre Moreau Co-Rapporteur: Jorge Camarero

- The applicant submitted written notice to the EMA on 2 June 2017 to request a re-examination of Human IGG1 monoclonal antibody specific for human interleukin-1 alpha XBiotech CHMP opinion of 18 May 2017.
- During its meeting on 27 July 2017, the CHMP appointed Alexandre Moreau as Rapporteur and Jorge Camarero as Co-Rapporteur.
- The applicant submitted the detailed grounds for the re-examination on 18 July 2017 (Appendix 2 of Final Opinion). The re-examination procedure started on 19 July 2017.
- The joint rapporteur's re-examination assessment report was circulated to all CHMP members on 17 August 2017.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's detailed grounds for re-examination to all CHMP members on 6 September 2017.
- During the CHMP meeting on 13 September 2017, the detailed grounds for re-examination were addressed by the applicant during an oral explanation before the CHMP.
- During the meeting on 14 September 2017, the CHMP, in the light of the scientific data available and the scientific discussion within the Committee, re-examined its initial opinion and in its final opinion concluded that the application did not satisfy the criteria for authorisation and did not recommend the granting of the marketing authorisation.

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Metastatic colorectal cancer is a highly invalidating and life threatening condition with a poor prognosis. Unintentional weight loss associated with cancer is a well-known phenomenon, which is commonly known as "cancer cachexia".

2.1.2. Epidemiology

Approximately half of all patients with cancer experience cachexia with the prevalence rising as high as 86 % in the last 1–2 weeks of life. Around 45 % of cancer patients lose more than 10 % of their original body weight during disease progression (Vaughan *et al* 2013).

2.1.3. Biologic features

Cancer cachexia is defined as a complex condition of tissue wasting, which develops as a secondary disorder in cancer patients and leads to progressive functional impairment (Fearon et al 2011). This condition is characterised by systemic inflammation, negative protein and energy balance and involuntary loss of Lean Body Mass (LBM), with or without wasting of adipose tissue.

2.1.4. Clinical presentation, diagnosis and stage / prognosis

Clinically, cachexia is represented by significant weight loss in adults, accompanied by alterations in body composition and disturbed balance of biological systems. Generally, an unintentional weight loss of >5% from historical weight is associated with cachexia as a clinically relevant metabolic symptom, except patients with a body mass index of <20 kg/m2. Death usually occurs once weight loss has reached 30% of the patients' historical stable body weight, with cachexia being directly attributable for 20% of cancer deaths (Vaughan *et al* 2013).

2.1.5. Management

Corticosteroids could in theory be an option for the target population however these drugs are frequently used in palliative care of patients with advanced cancer, the benefit/risk balance is poorly documented (Cochrane 2013). Megesterol acetate, a synthetic derivative of progesterone, has been found to improve appetite and cause a weight gain and also an improvement of Quality of Life (QoL) in cancer patients compared to placebo. However, the exact mechanism behind this weight gain and whether the drug actually increases muscle mass is unclear.

Currently, there are no approved therapies that can effectively reverse cancer related cachexia and other tumour-related symptoms, and all available treatment options are considered palliative. There is therefore still an unmet need for treatment of advanced Colorectal Cancer (CRC) patients.

About the product

Human IgG1 monoclonal antibody specific for human interleukin-1 alpha XBiotech (also referred to as Xilonix or Hutruo in this assessment report) is a recombinant human IgG1 monoclonal antibody specific for human interleukin-1α (IL-1α) (MABp1). The entire MABp1 heavy and light chain sequences are identical to those found in naturally-occurring human IgG1α, with the light and heavy chain variable regions being identical to those originally expressed by a peripheral blood B lymphocyte that was obtained from a healthy individual.

Neutralizing IL-1α activity with Human IgG1 monoclonal antibody specific for human interleukin-1 alpha may have broad antineoplastic activity. Depending on the site of action, IL-1α mediates a number of crucial physiological processes related to response to injury (e.g. tumour growth). At the site of injury (such as in the microenvironment of the growing tumour) IL-1α induces the expression of vascular growth factors including vascular endothelial growth factor (VEGF), thereby mediating growth and angiogenesis. IL-1α also induces expression of matrix metalloproteinases that in turn have pleiotropic activities including tissue matrix breakdown, regulation of FAS mediated apoptosis and inflammation.

Through its role on platelets, IL-1α also regulates interactions between endothelial cells and leukocytes, driving activation of vascular endothelial cells and transendothelial migration of inflammatory cells into the tumour microenvironment. Similarly, tumour-platelet microemboli formed between platelets and circulating tumour cells provides tumour cells with enhanced ability to migrate from the vasculature into the tissues, forming new

metastasis. Finally, IL-1 α links these tumour processes to metabolic dysregulation, by signalling an injury response through IL-1 receptors on POMC neurons that interdigitate the endothelial microvasculature of the hypothalamus.

The Applicant claimed indication:
MABp1 is indicated for the treatment of metastatic colorectal cancer as a single agent in patients who have failed oxaliplatin- and irinotecan-based chemotherapy.

Subsequently revised proposed indication:

MABp1 is indicated for the control or relief of debilitating symptoms associated with advanced colorectal cancer.

Posology:
The dose of MABp1 is 7.5 mg/kg administered intravenously every two weeks until disease progression or unacceptable toxicity.

Method of administration:
MABp1 should be administered as an intravenous infusion over a 1-hour period (60 ± 15 minutes). It should not be administered as an intravenous bolus or push.

Type of Application and aspects on development

- Accelerated procedure

The CHMP agreed to the applicant's request for an accelerated assessment as the product was considered to be of major public health interest. This was based on promising data on symptom control that may have a beneficial impact on QoL of the mCRC patients, and could also potentially improve survival in a patient population with high unmet medical need.

However, during assessment the CHMP concluded that it was no longer appropriate to pursue accelerated assessment, as several Major Objections not resolvable under accelerated assessment have been raised on aspects related to quality, non-clinical, clinical pharmacology but also clinical efficacy and safety.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as a concentrate for solution for infusion containing 50 mg/ml of the active substance human IgG1 monoclonal antibody against human IL-1a. Other ingredients are disodium phosphate heptahydrate, citric acid monohydrate, trehalose dihydrate, polysorbate 80, water for injection, phosphoric acid (for pH-adjustment) and sodium hydroxide (for pH-adjustment).

The product is available in a 10 mL Type I glass vial with a chlorobutyl rubber stopper and metal seal with flip off cap. Each vial contains 6 mL of concentrate solution for infusion containing 300 mg of the active substance.

2.2.2. Active Substance

General Information

The active substance, hereafter referred to as MABp1, is an anti-IL-1α monoclonal IgG1κ antibody. The common name of the active substance is human IgG1 monoclonal antibody against human IL-1a (no INN is currently available).

The genetic sequences for the heavy and light chains were isolated from a healthy individual naturally expressing anti-human IL-1α antibodies. The antibody is expressed in and secreted from a Chinese hamster ovary (CHO) cell line, and purified by standard techniques for purifying monoclonal antibodies.

The mechanism of action of MABp1 is stated to be by steric blockade, preventing IL-1α from binding to its receptors.

The structure is shown in Figure 1 below.

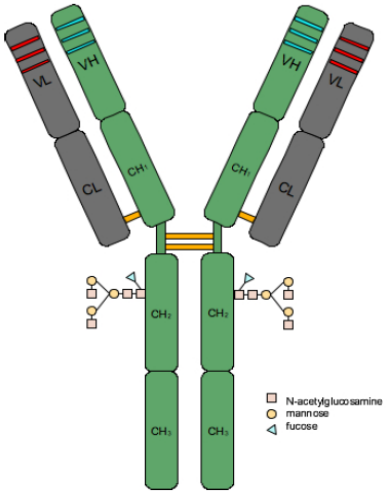


Figure 1: Structural schematic of MABp1

The amino acid sequences for the heavy (452 amino acids) and light (214 amino acids) chains have been provided. The heavy and light chain sequences correspond to human IgG1κ. Post-translational modifications include pyroglutamic acid at the heavy chain amino terminal glutamine (Q) residue and heavy chain C-terminal truncation by cleavage of the terminal lysine (K) residue. There is a single glycosylation site per heavy chain and the majority of the glycan species are G0F type (i.e. as shown in figure 1, asialo-, agalacto-, core-fucosylated bi-antennary complex-type N-glycan).

The MABp1 primary glycoform has a molecular weight of approximately 148.1 kilodaltons.

MABp1 binds to human IL-1α with a dissociation equilibrium (affinity) constant (KD) stated to be in the 22 to 260 picomolar range, which is regarded as high affinity.

Manufacture, characterisation and process controls

Description of manufacturing process and process controls

MABp1 active substance is secreted from cells expanded from a vial of a qualified WCB, through shake flasks and a 25 L bioreactor to seed a 500 L production bioreactor. The yield has been defined. The culture is clarified by

depth filtration, and bioburden control is maintained through a 0.2/0.1 µm filtration. Process controls have been defined.

The purification follows a process which is considered typical for monoclonal antibodies, using chromatography steps and viral inactivation/removal steps.

Control of materials

No animal derived products are used in the process, except for the CHO production cells and materials used in the construction of filters used for clarification of the production cell cultures and the UF/DF cartridges. The filters are certified to be in compliance with EU Guideline EMEA/410/01 and are therefore considered to pose negligible TSE (Transmissible Spongiform Encephalopathies) risk.

Raw materials and product-contacting materials used in active substance manufacturing process have been listed with their purpose, grade and manufacturer. Compliance with Ph.Eur. has been confirmed for the majority of materials. Water for injection used for preparation of buffers is listed as USP grade.

The parental cell line is a Chinese hamster ovary cell line. Variable Heavy Chain (HC) and Light Chain (LC) amino acid sequences were identified from a healthy human donor with reactivity against human IL1-alpha. The nucleotide sequences encoding the heavy and light chains were inserted into an *E.coli* plasmid for amplification and transfected into the parental cell line. An adequate description of the genetic manipulations to generate the production cell line has been provided. A clone (1005C2) was selected and amplified to create the Master Cell Bank (MCB). A Working Cell Bank (WCB) was generated from a vial of the MCB. Sufficient information is provided regarding the testing of the MCB and WCB.

Two end of production (EOP) cell banks have been generated. These have been characterised and have been shown to contain the expected A-type and C-type virus like particles typical of a CHO cell line. The genetic stability has been sufficiently demonstrated.

Control of critical steps and intermediates

Control parameters and tests have been described. Critical steps have been identified for the active substance manufacturing process.

In-process testing is performed during all phases of production to monitor process performance and contamination control.

Process validation

An evaluation of data for the processing of 14 upstream batches at full scale, including lots made using growth media from a previous supplier, was provided, to establish critical process parameters, in process controls and critical process controls.

Subsequently a process qualification was carried out using three full scale lots representing consecutive batches. The results indicate that the process consistency is adequate.

Manufacturing process development

Manufacturing process development during clinical development included a change in the cell line and a change in growth medium which resulted in changes in the proportions of dimers and of acidic species.

Characterisation

The active substance has been sufficiently characterised by physicochemical and biological state-of-the-art methods revealing that the active substance has the expected structure of a monoclonal IgG1κ antibody.

Peptide mapping by LC-MS has been carried out on finished product batches to confirm the primary amino acid sequence. Secondary and higher order structure has been reported.

Glycan characterisation has been carried out using capillary electrophoresis and cleaved glycans analysis by MALDI-TOF mass spectrometry.

Non-reduced and reduced SDS-CE electropherograms of active substance lots have been presented.

High molecular weight species have also been characterised by sedimentation velocity analytical ultra-centrifugation and SEC-HPLC with static light scattering detection. The applicant has identified that MABp1 may form dimers to an extent which has been qualified by analysis of quantities present in clinical lots.

A wide range of binding affinity to human IL-1α (22 to 260pM) has been claimed.

The following effector functions for anti-IL-1α antibody MABp1 have been assessed: complement-dependant cytotoxicity (CDC) using normal human serum on CHO-IL1α cells, C1q binding by direct ELISA using biotinylated human C1q full-length protein, Antibody Dependent Cellular Cytotoxicity (ADCC) using CHO-IL-1α cells as target and Jurkat cells with luciferase reporter as effector cells, ADCC using CHO-IL1α target cells and NK92.CD16 as effector cells and measurement of released lactate dehydrogenase, FcγIIIa receptor binding by competition with fluorescently labelled human IgG for binding to fluorescent donor labelled FcγRIIIa on HEK293 cells and FcRn receptor binding by measuring affinity (expressed as a dissociation constant, K_D) for immobilised recombinant human FcRn.

Results from biological activity characterisation show no evidence for ADCC above background, nor evidence for CDC above background.

The effects of physicochemical attribute variation on IL-1α and Fc receptor binding kinetics have been incompletely characterised.

Specification

The proposed specification for MABp1 active substance includes tests for appearance, pH, concentration, purity, identity, binding kinetics, charge heterogeneity, carbohydrate profile, impurities and sterility.

As outlined above, changes in the cell line and growth medium resulted in changes in the proportions of dimers and of acidic species. The mechanism of aggregation is not known and has not been demonstrated to be under adequate control to provide assurance of safety throughout the shelf life. Although most attributes are maintained within clinically justified limits, this is not the case for glycation (which the company has linked to aggregation) or for the amounts of basic/neutral/acidic species. At the time of opinion, this represented an outstanding major objection.

Analytical methods

The descriptions of the analytical procedures, their controls and their validation have been provided and are generally acceptable.

Binding Kinetics analysis (Octet) of the interaction between MABp1 and IL-1α is the bioassay for the active substance and this assay is also used (in parallel with a cell based potency assay) for the finished product.

Batch analysis

Batch analysis data from 25 lots, 17 of which were at the scale of the proposed commercial process, indicate a reasonable level of consistency for the active substance.

Reference materials

Please refer to the finished product section. The use of finished product as reference for active substance testing (applies only to the binding kinetics analysis) has been justified.

Stability

All material specifications for the stability containers, including product contact material, are identical to those of the full size active substance container closure system. Stability sample containers are filled at a much higher surface area to volume ratio than is used for the full scale active substance storage and should therefore represent worse case storage conditions.

12 months long term stability data from 6 representative batches of active substance stored at 2-8°C has been provided. These data demonstrate that active substance material held at 2-8°C is stable through 12 months with no significant trends in concentration, purity, or potency observed.

In addition, data from active substance stability samples held under accelerated conditions (thermally stressed: stored at 25°C and mechanically stressed: 5°C on shaker) have been provided. The data shows that active substance held at 25°C is stable through 6 months.

The data from samples stored at 25°C studies also indicate that SEC-HPLC, SDS-CE, Binding Kinetics (KD%), and cIEF main peak percent and acidic peaks percentage are stability indicating assays for the active substance.

Photostability studies have not been carried out. In the absence of photostability data the storage instructions for the active substance and the finished product include protection for light exposure.

Based on the available data the proposed expiration period for active substance is considered acceptable.

2.2.3. Finished Medicinal Product

Description of the product and Pharmaceutical Development

The finished product is presented as a concentrate for solution for infusion containing 50 mg/ml of the active substance human IgG1 monoclonal antibody against human IL-1a. Other ingredients are disodium phosphate heptahydrate, citric acid monohydrate, trehalose dihydrate, polysorbate 80, water for injection, phosphoric acid (for pH-adjustment) and sodium hydroxide (for pH-adjustment).

The product is available in a 10 mL Type I glass vial with a chlorobutyl rubber stopper and metal seal with flip off cap. Each vial contains 6 mL of concentrate solution for infusion containing 300 mg of the active substance.

There is an overfill of 0.5 mL to allow withdrawal of 6mL. This is considered acceptable.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur standards. There are no novel excipients used in the finished product formulation.

The finished product container closure complies with Ph.Eur requirements.

The finished product formulation buffer was designed for stabilization of MABp1 against chemical, thermal and mechanical degradation. Initial formulation development work was performed with three different candidate

formulation buffers (Buffers A, B and C using different concentrations of each component). These buffers were tested for their ability to stabilize samples against short-term thermal degradation at 50°C. Buffer B was selected for the formulated bulk used to manufacture the product and has been used throughout non-clinical and clinical development. The non-clinical studies as well as the clinical study protocol 2009-PT004 used finished product at 15mg/mL concentration. However, all finished product used in the pivotal clinical trial used finished product at the 50mg/mL concentration.

Manufacture of the product and process controls

The finished product manufacturing process consists of formulation of the active substance material, followed by transfer to the aseptic fill suite for initiation of the filling process. The formulated bulk is sterile filtered within a laminar flow hood into a single use bag specific for the fill machine used for aseptic filling. This bag is then installed into the filling machine and the fill process commences.

Control parameters and tests have been described. Critical steps have been identified for the finished product manufacturing process.

Actions taken in case steps designated as critical deviate from their acceptance range have been described.

Validation for asepsis has been presented. An evaluation of 21 lots has been provided to establish critical process parameters, in process controls and critical process controls, with a subsequent qualification of the process, using 3 lots.

Acceptable shipping validation data has been provided.

Product specification

The proposed specification for MABp1 finished product includes tests for appearance, clarity/opalescence, pH, concentration, osmolality, purity, identity, potency, binding kinetics, charge heterogeneity, fill volume, particulate matter, container-closure integrity and sterility.

The tests proposed are in general appropriate. However, the control of the finished product requires further justification. As already discussed in the active substance section, most quality attributes are maintained within clinically justified limits. However, this is not the case for glycation (which the company has linked to aggregation) and for the amounts of basic/neutral/acidic species. A control strategy that would ensure consistent manufacture of product with characteristics that are equivalent to the product used in pivotal clinical studies has not been provided. At the time of opinion, this represented an outstanding major objection.

Analytical Methods

The descriptions of the analytical procedures, their controls and their validation have been provided and are generally acceptable.

Batch Analysis

Data for 25 batches show reasonable consistency from batch to batch. However, as outlined above there are remaining concerns regarding the control of glycation and basic/neutral/acidic species

Reference materials

The reference standard is used both for the active substance and finished product testing and is made from a representative lot of finished product or formulated bulk. The procedure for qualifying new reference standards has been described and found acceptable.

Stability of the product

The proposed expiration period for finished product stored at 2-8°C is 12 months. Samples placed in the finished product stability program are stored in a container closure system identical to the one proposed for commercial supply.

Long term stability data from samples stored at 2-8°C is available for 20 batches for up to 36 months (36 months for 4 batches, 30 months for 3 batches, 24 months for 5 batches, 18 months for 3 batches and 12 months for 5 batches).

Data for up to 6 months is available for samples stored in the inverted position (stored at 2-8°C), mechanically stressed samples (stored at 2-8°C) and thermally accelerated samples (stored at 25°C, 30°C and 40°C respectively).

Simulated in-use stability data has been supplied for three finished product lots diluted in saline for intravenous administration to support the proposed in-use shelf life of 12 hours at 15 °C - 25 °C.

The data show an increasing trend for soluble oligomer/dimer in the majority of batches manufactured in 2014 and 2015, which was absent from the first 4 or 5 batches produced (dated 2013) and which originates in the active substance. Data also show an increase of acidic species by cIEF and CEX analyses. The structural change causing the increase needs to be further investigated.

No evidence of measurable increase in dimer has been seen when the product is diluted in saline and held for longer than the anticipated requirement for medical use.

Data from mechanically stressed and inverted samples held at 2-8 °C demonstrate similar characteristics to finished product held in the upright position. No trends were observed, except for an increase in soluble oligomer species, at approximately the same rate as for vials held in the upright position.

Thermally accelerated samples at all temperatures studied showed a rapid increase in the soluble oligomer. Thermally stressed samples also demonstrated a decrease in purity by CEX-HPLC and percent of primary isoform by cIEF.

Although the data generally support the proposed shelf life of 12 months at 2-8°C, further information on the nature of structural changes leading to changes in percentages of acidic, main and basic peaks is needed. A specification for dimer content has been justified based on clinical experience.

Adventitious agents

Evidence in the dossier for sterility assurance and bioburden control throughout manufacturing is adequate.

No human or animal derived products are used in the process, except for the CHO production cells and materials used in the construction of filters used for clarification of the production cell cultures and the UF/DF cartridges. The filters are certified to be in compliance with EU Guideline EMEA/410/01 and are therefore considered to pose negligible TSE (Transmissible Spongiform Encephalopathies) risk.

For viral safety the types and number of validated viral clearance steps are sufficient and viral validation data suggest adequate clearance.

A viral clearance study was conducted in which four model viruses (murine minute virus (MVM), xenotropic murine leukemia virus (xMuLV), pseudorabies virus (PRV), and respiratory enteric orphan III (REO-3)) were spiked into scaled down manufacturing processes. Scale down models and process controls used to generate viral clearance data are representative of the manufacturing process applied for.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

The module 3 was generally poorly presented, with much of the expected information missing or presented in the wrong sections. In many instances process and analytical data was presented as qualitative figures without the numerical data that that would allow assessment of inherent variability. It was also apparent that the data presented was often generated with earlier versions of the manufacturing process which were not representative of the proposed commercial manufacturing process.

In the day 120 List of Questions 6 major objections were raised on the quality aspects in addition to a high number of other concerns. The major objections related to the following deficiencies:

Inadequate information on the construction of the production cell line.

- Lack of information to demonstrate that the active substance manufacturing process is adequately validated.
- Lack of information to demonstrate that an adequate control strategy is in place for the active substance manufacturing process.
- Lack of information to demonstrate that an adequate control strategy is in place for the finished product manufacturing process.
- Lack of information to demonstrate that the finished product manufacturing process is adequately validated.
- Lack of evidence that the proposed commercial process for is equivalent to the process used for viral clearance studies.

During the procedure the company provided further data and justifications which led to most of the major objections and other concerns being resolved. However, at the time of opinion one major objection remained in relation to lack of sufficient control of glycated species and acidic/neutral/basic species, which the company has linked to the observed, poorly controlled, aggregation. The company could not demonstrate that the proposed commercial manufacturing process would be sufficiently controlled to ensure that these quality attributes would be within the range of the product used in pivotal clinical studies.

In addition to the major objection, three other concerns remain to be resolved:

- incomplete description of the finished product composition
- incomplete characterization and control of degradation
- lack of justification of approach to verification of sterilising filter integrity before use

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

In conclusion, the application is currently not considered approvable from a quality perspective since a control strategy that would ensure consistent manufacture of product with characteristics that are equivalent to the product used in pivotal clinical studies has not been provided.

2.3. Non-clinical aspects

2.3.1. Introduction

2.3.2. Pharmacology

Four non-GLP *in vitro* primary pharmacology studies were conducted with MABp1. The studies were mainly performed to determine if there were any relevant non-clinical species for further non-clinical investigations.

Primary pharmacodynamic studies

- Study PT-005: The objective was to determine whether the anti-IL-1α antibody MABp1 shows immunoreactivity with normal tissues in human and *Cynomolgus monkey*. Staining was observed on some epidermal cells. Data generated by the applicant indicates that about 0.2% of peripheral blood mononuclear cells (PBMC) in healthy individuals express IL-1α. However, no IL-1α expressing PBMC in primary lymphatic organs were observed.

- Study PT-006: The objective was to determine whether MABp1 showed binding interactions with IL-1α in rat, mouse, porcine and monkey. The binding kinetics was investigated using Surface Plasmon Resonance. There was virtually no association between mouse, porcine or rat IL-1α and MABp1. On the other hand, monkey IL-1α did show interaction with MABp1, however, the dissociation constant was about 20 times higher for monkey than human IL-1α. The monkey IL-1α-MABp1 complex associated slower and dissociated more rapidly compared to the human protein.

- Study PT-007: IL-1α from human and *Cynomolgus monkey* were tested for the ability to interact with IL-1R1 cytokine receptor on human umbilical vein endothelial cells (HUVEC). Contrary to *Cynomolgus* IL-1α, the human IL-1α was able to induce ICAM-1 expression on the HUVECs, thus showing differences between human and *Cynomolgus* IL-1α in their ability to interact with human target cells. In the same study report, a competition assay between human and *Cynomolgus* IL-1α was presented. Chinese Hamster Ovary (CHO) cells were engineered to express human IL-1α. Based on this assay, it was deduced that soluble *Cynomolgus* IL-1α required 188-375 fold molar excess to achieve equivalence with soluble human IL-1α for complete blockade of MABp1 antibody binding to the IL-1R1 receptor.

- Study PT-008: the objective was to examine the interaction of MABp1 with blood cells isolated from mice or *Cynomolgus monkey*. Flow cytometry of mouse whole blood showed no binding of MABp1 to peripheral blood mononuclear cells (PBMC). In addition to MABp1, commercial hamster anti-mouse-IL-1α and mouse anti-human-IL-1α antibodies were used as positive controls. No positive staining of PBMCs were observed with these two antibodies either. Similar results were obtained with flow cytometry of *Cynomolgus* whole blood. No binding of MABp1 to cynomolgus monkey PBMCs was observed.

Reports from additional *in vitro* studies were submitted in response to the D120 LoQ. The applicant presented data indicating different effects by MABp1; including binding of membrane associated IL-1α, binding of soluble IL-1α but not IL-1ra or IL-1β, inhibition of IL-1α mediated upregulation of ICAM-1 and E-selectin on HUVEC cells, and inhibition of transendothelial migration of cells. The inhibition of E-selectin is suggested to possibly have a role *in vivo* by blocking E-selectin on vascular endothelial cells, and thereby inhibiting recruitment of peripheral blood mononuclear cells to sites of inflammation. The applicant also describes an analysis of IL-1α protein sequence alignments for a number of possible models, including dog, monkey, mouse, pig, rabbit, rat and sheep. The two animals with the highest co-linearity between their IL-1α proteins and human were sheep and

monkey. Attempts to isolate sheep IL-1α in order to investigate binding between this protein and MABp1 and the IL-1α proteins were however not successful.

Secondary pharmacodynamic studies

No secondary pharmacodynamic studies have been performed.

Safety pharmacology programme

No safety pharmacology studies have been performed.

Pharmacodynamic drug interactions

No pharmacodynamic drug interactions studies have been performed.

2.3.3. Pharmacokinetics

A standard operating procedure (SOP) describing the ELISA method used to determine the level of MABp1 and endogenous anti-human IL-1α antibody concentration in human and animal plasma/serum samples, has been submitted (report QC030). Report QC030 has been assessed in the clinical part of the assessment.

No absorption, distribution, metabolism, excretion or pharmacokinetic studies have been performed.

2.3.4. Toxicology

Single dose toxicity

No single dose toxicity studies have been performed.

Repeat dose toxicity

One GLP compliant repeat dose toxicity study, including single dose groups, was conducted in mice (PT002).

Ninety-six animals were randomly assigned by weight and sex to four groups that were administered by intraperitoneal (IP) injection with a dose of either 0 mg/kg (vehicle) or 78 mg/kg MABp1 or 156 mg/kg MABp1 or 312 mg/kg MABp1 therapeutic antibody as a single dose on day 0, or repeatedly at study day 0, 7 and 14. There were 24 animals per group divided equally into four subgroups, with blood sampling and necropsy at day 7, day 14 and day 28. For the long term single dose group, blood sampling and necropsy was performed at day 29.

Following MABp1 administration, all animals were observed daily for any changes in activity, gross appearance, food intake, body weight and body temperature. Gross necropsy, blood and tissue collections were processed and subjected to haematology, chemistry, ELISA and histopathological analysis.

All animals appeared normal, except for a non-study drug related illness in one animal. No deaths attributed to test article occurred during the study. There were no macroscopic changes observed with organs and tissues collected at necropsy. Nor did histopathological analysis reveal any drug-related lesions in any organ or tissue examined.

There were no haematology outcomes. Minor, but statistically significant changes in blood urea nitrogen (BUN), BUN/creatinine ratio (B/C), globulin (GLOB) or total serum protein (TP) were observed in some groups. The BUN or B/C effects did not, however, appear to be dose dependent. Elevations in GLOB, or serum antibody, are a natural consequence of MABp1 (globulin) infusion.

Genotoxicity

No genotoxicity studies have been performed.

Carcinogenicity

No carcinogenicity studies have been performed.

Reproduction Toxicity

Reproductive and developmental toxicity studies have not been performed.

Toxicokinetic data

Toxicokinetics showed that the serum MABp1 antibody level correlated with the administered dose of MABp1. Repeated dose administration resulted in a lower plasma level, compared to single dose administration, which may indicate formation of anti-drug antibodies.

Table 1: MABp1 concentration in mice (mg/ml). Data are expressed as mean ± standard deviation

Group	Treatment	Day7	Day14	Day28	Day29
Group 01 (vehicle)	Single dose short term	0.00±0.00 (n=7)			
	Double doses		0.00±0.00 (n=6)		
	Triple doses			0.00±0.00 (n=5)	
	Single dose long term				0.00±0.00 (n=5)
Group 02 (low dose)	Single dose short term	0.47±0.20 (n=6)			
	Double doses		0.29±0.12 (n=5)		
	Triple doses			0.24±0.08 (n=3)	
	Single dose long term				0.03±0.02 (n=6)
Group 03 (median dose)	Single dose short term	1.27±0.28 (n=6)			
	Double doses		0.55±0.08 (n=6)		
	Triple doses			0.53±0.09 (n=4)	
	Single dose long term				0.06±0.03 (n=5)
Group 04 (high dose)	Single dose short term	1.93±0.28 (n=6)			
	Double doses		0.80±0.31 (n=6)		
	Triple doses			0.41±0.07 (n=4)	
	Single dose long term				0.17±0.08 (n=6)

Local Tolerance

No local tolerance studies have been performed.

Other toxicity studies

No antigenicity studies have been performed.

2.3.5. Ecotoxicity / environmental risk assessment

No ecotoxicity/environmental risk assessment studies have been performed.

2.3.6. Discussion on non-clinical aspects

Biological activity and selection of animal species

The applicant argues that monkey is not an appropriate model for non-clinical studies. The argumentation is in part based on the assumption that monkeys will establish an antibody response (ADA) towards MABp1, making it difficult to achieve sufficient antibody exposure during repeat dosing of MABp1. Further, the applicant argues that the monkeys may have to be given immunosuppressive medication to treat infusion reactions, thereby complicating the assessment of the results. However, the applicant has not provided any evidence that MABp1 is particularly potent as an antigen. The immunological reaction towards MABp1 in animals should not be expected to be substantially different from what is observed with other human monoclonal antibodies. Consequently, it should not be taken for granted that ADA responses will appear in the monkeys, at least not in all animals. Recent examples where monkeys have been used in spite of ADA responses are the human monoclonal antibodies alirocumab and evolocumab (see Praluent and Repatha EPAR). For evolocumab, only 2 out of 36 monkeys in the 6-month study developed ADA. As such, the argument not to conduct studies with monkeys due to possible ADA formation is not sufficiently justified and cannot be endorsed.

Further, the applicant is of the opinion that a 20-fold difference in dissociation constant for MABp1 between human and *Cynomolgus monkeys* will make it difficult to achieve adequate exposure levels. It is agreed that such a difference is not optimal. However, similar or even greater differences in affinity have been found with other monoclonal antibodies, such as golimumab and secukinumab (see Simponi and Cosentyx EPAR). Golimumab was shown to have 34-fold less affinity and to be 72-fold less potent in neutralising recombinant *Cynomolgus* TNFα, compared to affinity and neutralisation of human TNFα. Regardless of these differences, *Cynomolgus monkey* was used in the repeat dose toxicity studies. In these studies, golimumab showed similar results as other TNFα blockers. Similarly, secukinumab displayed pharmacological activity in the repeat-dose toxicity studies in monkeys in spite of significant affinity differences for human and *Cynomolgus monkey* IL-17A. It should also be taken into consideration that *in vitro* Kd-studies using recombinant IL-1 α only gives an indication of the affinity experienced in animals, and that the difference in affinity *in vivo* might be quite different.

It has been shown that IL-1α amino acid sequences from different monkeys have in best case, a similarity of 88% with the human IL-1 α version. The investigated monkey species were rhesus, C*ynomolgus*, pigtail macaque and marmoset. It is noted that the whole sequence of IL-1 α has been compared, and not the important area of the sequence, i.e. the antibody epitope. Antibody epitopes are of limited size, often in the range of 5-10 amino acids, which in the case of IL-1 α would render multiple possible binding sites where there are no differences in the amino acid sequence between humans and monkeys. This is further discussed under Repeat dose and reproductive and developmental toxicity below.

The applicant points to that the mentioned problems with monkeys also would be the case with transgenic animals. However, that is not correct, since transgene animals would solve the problem with differences in amino acid sequences and disassociation constant. Interpretation of results from studies with transgenic

animals could be challenging, but transgenic animals are considered a possibility when other options are not present.

To clarify the mechanism of action for MABp1 the applicant has referred to *in vitro* data. Additionally, a series of *in vivo* studies has been performed with IL-1 α vaccination. Mice have been vaccinated with murine IL-1 α to establish an immunological response against IL-1 α. The results showed reduced growth of subcutaneously injected tumours and blood vessels in the tumours. A reduction of tumour growth was also seen when serum was transferred from IL-1 α vaccinated mice to naïve mice injected with tumours. Similar results were observed independently of whether tumour cells expressed IL-1 α or not.

The results from these *in vivo* studies display that an anti-IL-1 α immune response indirectly, and probably directly, lead to growth reduction of tumour. However, the immunological response that is established in mice after vaccination is likely quite different from administration of MABp1. Probably most important is that MABp1 is a monoclonal antibody, while the antibody response after vaccination with IL-1 α will be polyclonal. MABp1 will thus have only one epitope, while the polyclonal antibodies will be directed at many different epitopes on IL-1 α. Additionally, the antibodies may be of different class and subclass than MABp1, and thus have different properties of which secondary responses they trigger. The concentration of antibodies and potential signal substances in serum will also be different. Further, in the part of the experiments where not only serum has been used, the T cell response will also be effective. All these differences make it difficult to relate the results from this *in vivo* study to MABp1. Nevertheless, when taken into consideration this substantial reservation, it seems that anti-IL1a treatment has a growth inhibiting effect on tumours and their blood supply.

MABp1 is less likely to cross-react with human proteins compared to other monoclonal antibodies. The reason is that MABp1 has been cloned directly from an affinity matured human B-cell and has not been further modified (also referred in a tissue cross-reactivity study (study PT0005)). Unfortunately, the validity of study PT0005 is questionable, since no staining was reported from this study, and positive controls were lacking. Further, since MABp1 binds a cytokine, it is more likely that MABp1 binds other soluble cytokines than tissues in a cross-reactivity study. In comparison, secukinumab is a human monoclonal antibody targeted at IL-17. In the MAA for Cosentyx (see EPAR) data from cytokine binding studies were presented (TNFα, IFNγ, TGFβ1, TGFβ2, IL-1β, IL-2, IL-6, IL-8, IL-13, IL-18, IL-19, IL-20, IL-22 and IL-23). Similar studies with investigations of cytokine binding other than IL-1α, IL-1ra and IL-1β are recommended for MABp1, but are not considered essential.

A study to investigate binding affinity to FcRn, C1q complex and FcγRIIIa, and potential CDC and ADCC reactions, was performed. Binding to the C1q complex was observed, but potential relevance of this finding is yet unknown.

Secondary pharmacology

The justification for the absence of secondary pharmacodynamic studies is that MABp1 is a true human therapeutic antibody, i.e. the antibody was cloned directly from a human peripheral B lymphocyte. According to ICH S7A, secondary pharmacodynamic studies are defined as studies on the mode of action and/or effects of a substance not related to its desired therapeutic target. Whether or not MABp1 is a true human therapeutic antibody is considered irrelevant when discussing secondary pharmacological properties.

Safety pharmacology

No separate safety pharmacology studies or toxicity studies with safety pharmacology endpoints have been performed. The applicant is of the opinion that safety pharmacology is not necessary to investigate since MABp1 is highly specific, expression of IL-1a is limited to monocytes, platelets, tumours and necrotic cells, and that

widespread presence of natural anti-IL-1α antibody in healthy individuals suggests that MABp1 is not associated with any toxicity. Taken into account the provided clinical data on safety and the fact that no further non-clinical toxicity studies are required, it is considered unnecessary to conduct safety pharmacology studies.

Pharmacodynamic drug interaction

Pharmacodynamic drug interaction studies were not performed. The lack of studies is justified by the fact that monoclonal antibodies, in general, are at low risk for drug interactions, as they do not undergo hepatic or renal metabolism. The applicant apparently mixes up pharmacodynamic and pharmacokinetic drug interaction in their justification of the lack of studies. Nonetheless, for an antibody with expected selective binding characteristics, the risk for direct pharmacodynamic interaction is considered to be low (see clinical part of the assessment report for further discussion).

Pharmacokinetics

The lack of regular absorption and distribution studies is considered acceptable.

Studies to investigate metabolism and excretion are not considered necessary. It is generally recognised that the excretion of antibodies occurs by degradation into peptides and amino acids.

The lack of pharmacokinetic drug interaction studies is acceptable, since MABp1 is a protein and its metabolism is therefore not expected to be influenced by other drugs, and vice versa.

Repeat dose and reproductive and developmental toxicity

The toxicology program for MABp1 is very limited. Limitations are not considered to be due to the nature of the active substance but due to the absence of the implementation of a thorough non-clinical program. The applicant describes MABp1 as a true human therapeutic antibody generated by a natural human immune response and cloned directly from a human peripheral B lymphocyte. No *in vitro* affinity maturation or modifications have been made. Further, it is emphasised that some individuals have a natural anti-IL-1α antibody response, which is not associated with toxicological effects. Based on this, the applicant does not expect any toxic effects caused by MABp1.

The applicant is of the opinion that a relevant species for a repeat dose toxicity study does not exist. This assumption is based on the expectation that ADA reactions will make it difficult to achieve sufficient MABp1 exposure in the animals, and the appearance of infusion reactions and formation of immune complexes. Further, it is argued that such reactions have to be treated with immunosuppressive medications. As discussed above, based on experience with other human monoclonal antibodies, it is not certain that ADA reactions will appear, at least not in all animals. The risk for ADA reactions will be the same for MABp1 as for other human monoclonal antibodies. There are many examples of repeat dose toxicity studies performed in monkeys without significant problems or need for immunosuppressive medication, such as alirocumab, evolocumab, daratumumab, necitumumab and nivolumab. The applicant also points to the fact that there are substantial sequence differences for IL-1a between human and the investigated monkey species. It is agreed that there are differences, but since epitope mapping has not been performed it is unknown whether the sequence differences actually appear in parts of the sequence where MABp1 does not bind. It is also shown that MABp1 binds with significantly lower affinity to *Cynomolgus monkey* IL-1a than human IL-1a. However, similar or even higher differences in affinity have not prevented repeat dose toxicity studies with other similar monoclonal antibodies (see EPAR for Simponi and Cosentyx). Hence, the applicant's conclusion that a relevant specie to use for non-clinical studies does not exist is not supported. Taking into consideration the available clinical safety data for MABp1, it was considered that requesting further non-clinical toxicity studies would be unethical and inappropriate.

An embryo-foetal developmental toxicity study has not been performed. The applicant argues that the patients have an average age and history of treatment making it less likely for them to get pregnant. Further, animals lacking IL-1a have normal gestation, birth and growth of offspring. The applicant is of the opinion that since MABp1 has not been studied in pregnancy, and there is no relevant non-clinical reproductive data, MABp1 should be contraindicated during pregnancy. It is not agreed that there are any compelling reasons to contraindicate the use of MABp1 during pregnancy. A contraindication is also not in line with the principles outlined in the Guideline on risk assessment of medicinal products on human reproduction and lactation: From data to labelling (EMEA/CHMP/203927/2005). It is instead recommended not to use MABp1 during pregnancy and in women of childbearing potential not using contraception. In addition to the arguments presented by the applicant, it is shown that placental transfer of IgG1 during organogenesis is relatively low (1-10% of maternal plasma concentration) (Bowman et al, 2013). The argumentation for not doing embryo-foetal developmental toxicity study is considered as sufficient, and in line with guideline ICH S9. However the recommendations regarding pregnancy as proposed in the SmPC are currently not acceptable.

Genotoxicity, carcinogenicity and other toxicity studies

No genotoxicity, carcinogenicity, local tolerance or antigenicity studies have been performed. The IgG1 molecule itself does not represent a carcinogenic risk. This is acceptable, and in line with relevant guidelines for monoclonal antibodies (ICH S6).

Ecotoxicity/environmental risk assessment

According to the Guideline on the Environmental Risk Assessment (ERA) of Medicinal Products for Human Use (EMEA/CHMP/SWP/4447/00), proteins, such as monoclonal antibodies, are exempted from conducting of ERA studies because they are unlikely to result in significant risk to the environment. The Applicant's justification for not submitting ERA studies is therefore considered acceptable. MABp1 is not expected to pose a risk to the environment.

2.3.7. Conclusion on the non-clinical aspects

The limitations related to the non-clinical data submitted within this application are not further pursued in light of the clinical data available.

2.4. Clinical aspects

2.4.1. Introduction

GCP

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.

- Tabular overview of clinical studies

Study ID	No. of study centres / locations	Design	Study Posology	Study Objective	Subjs by arm entered / compl.	Duration	Gender M/F Median Age	Diagnosis Incl. criteria	Primary Endpoint
2014-PT026	42 centres Europe (35) Russia (4) Georgia (3)	Phase III randomised double blind placebo-controlled	MABp1 7.5 mg/kg once every 2 weeks, IV, a total of 4 doses + BSC* Placebo (IV) + BSC*	Efficacy, safety	222/207 111/102	8 weeks 8 weeks	128/79 64 yrs 59/43 63 yrs	CRC (metastatitor unresectable) refractory to standard therapies, and with metabolic and functional symptoms	ORR[a]
2009-PT004 (open, but not recruiting)	1 centre USA	Phase I/II, open label, uncontrolled	MABp1 mg/kg[b] once every 3 weeks, IV, a total of 3 doses + BSC*	Safety, tolerability, PK	52/52	n/a[c]	24/28 61 yrs	Solid organ tumours (18 types)	Tumour response LBM QoL OS
Colorectal cohort					14/14				mCRC refractory to standard therapies
2010-PT015	1 centre USA	Phase I, open label	MABp1 2.5, 3.75, and 7.5 mg/kg of IV every 2 weeks, IV, a total of 2 doses	Safety, tolerability, PK	14			Advanced hematologic malignancies	
2017-PT041		Phase I, open label	MABp1 7.5 mg/kg, IV, 1 dose	Safety, tolerability, PK	6			Healthy patients	

* BSC included mainly psychological support, dietary advice, exercise advice, antibiotics, anti-emetics, and analgesics.

[a] ORR is a composite measure, including change in lean body mass (LBM) and change in quality of life.

[b] The dose and frequency in the dose escalation included: 0.25 mg/kg, 0.75 mg/kg 1.25 mg/kg and 3.75 mg/kg every 3 weeks, and 3.75 mg/kg every two weeks. Subjects enrolled in the expansion cohort received MABp1 at the recommended phase 2 dose.

[c] Duration of treatment: until progression of disease or toxicity

2.4.2. Pharmacokinetics

The applicant has presented four PK studies (Study 2009-PT004, 2010-PT015, 2014-PT026 and 2017-PT041) including one study performed in healthy subjects (study 2017-PT041).

Study 2009-PT004, was performed in a first-in-human, Phase I/II trial of MABp1 in patients with refractory solid tumours [Hong, 2014]. A total of 52 patients with 18 different malignancies were enrolled and treated. Three patients were treated at each of the first three dose escalation levels (0.25 mg/kg, 0.75 mg/kg, 1.25 mg/kg every 3 weeks), 27 were treated at 3.75 mg/kg every 3 weeks, and 16 were treated at 3.75 mg/kg every 2 weeks.

Clinical study, 2010-PT015, was a phase I study of MABp1 in subjects with advanced haematologic malignancies. Fourteen subjects with advanced haematologic malignancies were treated as part of a dose escalation. All subjects had relapsed or refractory leukaemias, for which no standard therapies were anticipated

to result in a durable remission. Patients were dosed with 2.5, 3.75, and 7.5 mg/kg of intravenous MABp1 every two weeks.

In the phase III clinical study, 2014-PT026, patients were treated with 7.5 mg/kg of MABp1 in the treatment arm and samples were collected for pharmacokinetic assessment.

Examination of the sample concentration collected after infusion shows a mean plasma concentration of 151 mcg/ml. The mean plasma concentration of the trough values (pre-dose every two weeks) was 17 mcg/ml.

Additional PK data have been generated to further support the proposed dose in this application. The study 2017-PT041, was initiated on 20 February 2017 and the last patient last visit was on 7 March 2017. This was a dedicated PK study of MABp1 performed in healthy individuals using a single dose of 7.5 mg/kg (N=6). PK samples were collected at pre-infusion (T=0), and post-infusion time points of 0.5 hr, 1 hr, 1.5 hr, 2 hr, 3 hr, 4 hr, 5 hr, 6 hr, 12 hr, 24 hr (day 1), 48 hr (day 2), 96 hr (day 4), 192 hr (day 8), and 336 hr (day 14) for a total of 15 time points per patient. These data were used to generate the PK curve. PK parameters were calculated and evaluated using an appropriate model.

Table 2: Summary of all Results from MABp1 Clinical Studies

	Dose (mg/kg)	Dose Interval (weeks)	Number of Cycles	Number of MABp1-treated Patients with PK results	Elimination Rate Constant (day^{-1})	Half Life (days)	AUC of Each Cycle (ug•day/ml)	Cumulative AUC* (ug•day/ml)	Cmax (ug/ml)	Accumulation Ratio	Volume of Distribution (L)	Clearance (L/day)
Phase I PT004 Cohort I	0.25	3	3	3	0.1969±0.0416	3.7±1.0	26.8±4.0	116.5±5.1	4.61±0.67	1.14±0.21	4.1±0.8	0.80±0.17
Phase I PT004 Cohort II	0.75	3	3	3	0.2996±0.0694	2.4±0.6	94.2±28.9	418.5±174.9	20.86±5.60	1.07±0.13	2.9±0.4	0.83±0.14
Phase I PT004 Cohort III	1.25	3	3	3	0.2280±0.0510	3.2±0.9	137.6±41.8	452.0±66.5	26.84±5.06	1.04±0.18	3.1±0.9	0.72±0.28
Phase I PT004 Cohort IV	3.75	3	3	27	0.1954±0.0694	4.0±1.5	406.4±124.7	1717.8±609.0	77.87±16.69	1.09±0.15	3.3±0.9	0.68±0.39
Phase I PT004 Cohort IV	3.75	2	3	16	0.2395±0.0883	3.2±1.0	351.4±67.4	1709.9±494.3	82.31±13.97	1.17±0.10	3.3±0.8	0.76±0.25
Phase I PT015 Cohort I	2.5	2	2	6	0.2490±0.0606	3.0±0.9	217.5±93.9	431.4±196.7	40.52±9.05	1.05±0.08	4.5±1.6	1.11±0.59
Phase I PT015 Cohort II	3.75	2	2	5	0.1693±0.0494	4.4±1.4	303.5±91.7	477.6±227.4	57.49±12.95	1.28**	5.1±1.0	1.02±0.39
Phase I PT015 Cohort III	7.5	2	2	3	0.2432±0.0105	2.9±0.1	604.1±207.9	754.7**	139.08±31.41	1.03±0.00	4.2±0.3	1.04±0.11
Phase III PT026	7.5	2	4	207	0.1760±0.0442	4.2±0.9	1183.4±308.9***	3099.2±1188.7	153.2±39.1	1.09±0.25	3.8±1.0	0.66±0.26
Phase I PT041	7.5	NA	1	6	0.2572±0.0734	2.9±1.0	754.8±124.5	NA	182.8±23.9	NA	2.8±0.8	0.71±0.31

Results are reported as Average ± Standard Deviation for each parameter. * Cumulative AUC have high variation because the number of cycles finished by patients could vary from 1, 2, 3 or 4 in various studies. The 3.75 mg/kg dose in PT004 has different value compared with 3.75 mg/kg in PT015 because the number of cycles were different for these two studies. The same applies with 7.5 mg/kg in PT015 vs. PT026.
** Data is only available from one patient. Standard deviation is not available.
*** AUC of each cycle for PT026 is overestimated because only two data points were available. PK curve is linear compared to exponential decay exhibited in other studies when more data points were available.

Absorption

MABp1 is a monoclonal antibody delivered by intravenous infusion.

The concentrations determined in patients at the proposed dose (7.5 mg/kg) resulted in plasma MABp1 concentrations of approximately (mean ± SD) 150 ± 40 µg/mL with plasma MABp1 concentrations reported as high as 298 µg/mL.

Distribution

The distribution of MABp1 is confirmed to be mainly in the vascular system. Volume of distribution ranged from 2.8 to 5.1L on average.

Elimination

As a monoclonal antibody, MABp1 is expected to be catabolised by proteolysis intracellularly. No renal elimination is expected to be relevant. Similarly, hepatic impairment is not expected to influence the clearance of MABp1. No studies have been performed in patients with hepatic impairment.

Half-life of MABp1 ranged from 2.9 to 4.4 days on average.

Dose proportionality and time dependencies

The data from the PK studies suggest that the post-dose plasma/serum concentrations of MABp1 are linear and dose-dependent. Data suggest that consistent plasma/serum concentrations are attained following each cycle with an accumulation ration of 1.10.

Special populations

No studies to determine PK in patients with renal or hepatic impairment have been performed.

The applicant has investigated the potential effect of weight, sex, age and disease burden on the pharmacokinetics of MABp1, with weight and the interaction of sex and weight being a significant covariate on post-dose (peak) MABp1 concentrations and volume of distribution.

Pharmacokinetic interaction studies

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

2.4.3. Pharmacodynamics

Mechanism of action

No mechanism of action studies have been conducted.

Primary and Secondary pharmacology

Pharmacodynamics analyses were performed in a first-in-human, Phase I/II trial of MABp1 in patients with refractory solid tumours [study 2009-PT004/Hong, 2014].

Analysis of serum cytokine levels revealed a reduction in IL-6 levels after treatment with MABp1. Of the 52 subjects treated, 43 had data available from screening and at week 8.

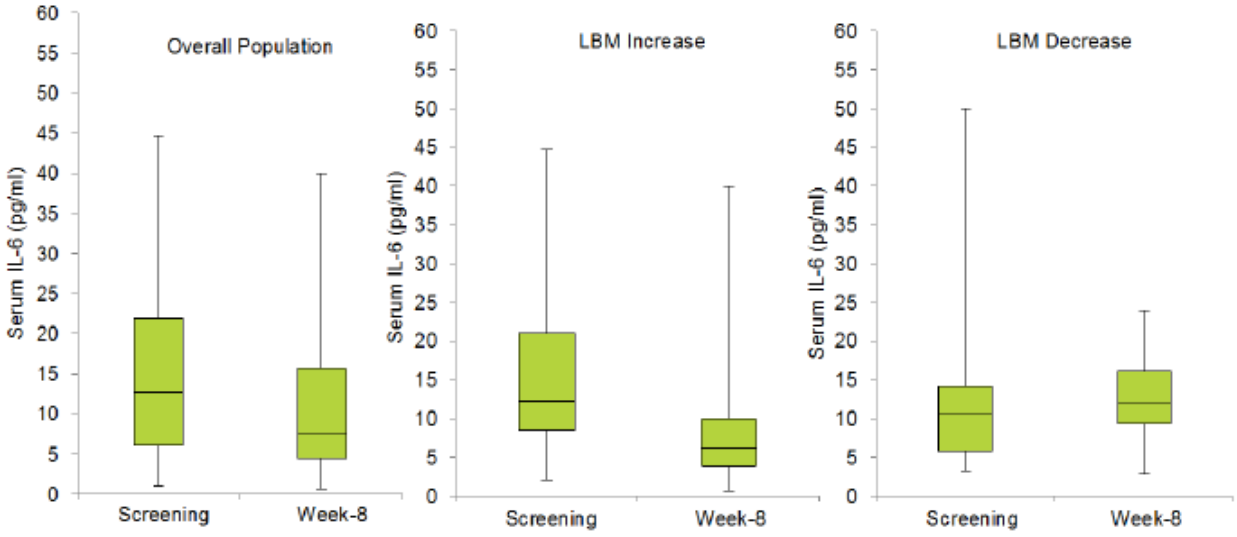


Figure 2: Plasma IL-6 levels as measured by ELISA

IL-1α is expressed on the surface of platelets, thus platelet numbers were analysed across dose cohorts. Platelet counts presented are differences between those measured prior to treatment and at week 8 (after three doses of antibody therapy). The 3.75mg/kg dose cohort was initially provided every three weeks. This dosing was increased in frequency to every two weeks (2 week).

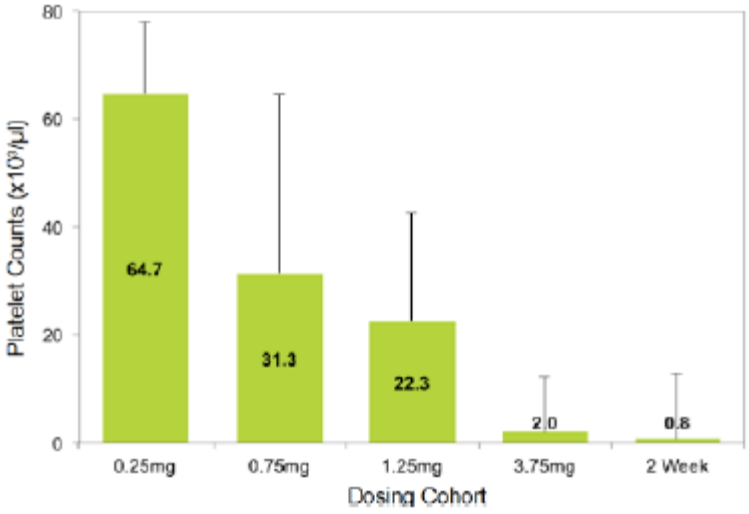


Figure 3: Dose-Dependent Correction of Thrombocytosis

Flow cytometry was also used to examine IL-1α expression on CD14+CD16+ monocytes.

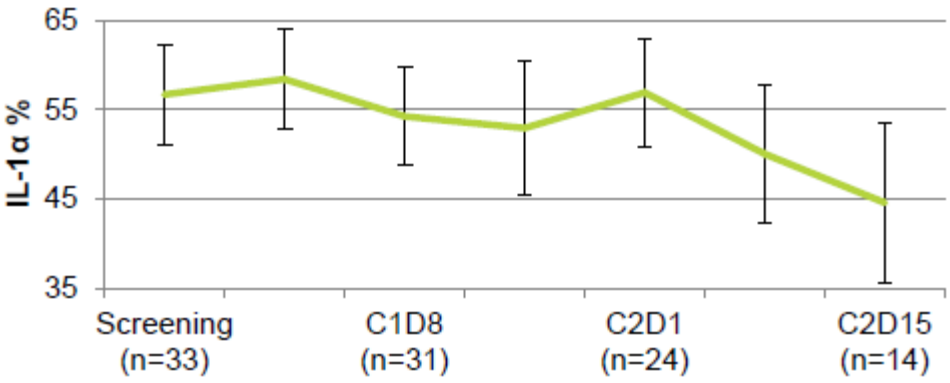


Figure 4: IL-1α expressing monocytes present in peripheral blood as percentage of CD14+CD16+ monocytes

2.4.4. Discussion on clinical pharmacology

The presented PK data is based on a limited dataset in a limited number of patients, especially at the dose intended to be licensed. This has been supplemented by PK data (as requested) in healthy subjects (n=6) [2017-PT041]. PK data from another patient study [2010-PT015] has also been provided. Further details regarding the design and conduct of studies 2010-PT015 and 2017-PT041 are required.

The data submitted show that relatively consistent results are observed across all clinical studies regarding pharmacokinetic parameter for MABp1 however there are differences between healthy subjects and patients that have not been sufficiently explained.

Presented PK analyses should be confirmed with non-compartmental analysis and covariate analysis could be confirmed with a population PK analysis. The range of values obtained with the 2017-PT041 PK study and the range of values from the analyses of previous studies (with bare minimum of points) present differences which were not adequately explained. The available PK data provide a characterisation of the selected dose of 7.5 mg/kg, but do not support it. Due to the fact that the 2017-PT041 study was a single dose PK study, it can be concluded that there is insufficient PK data to support the proposed dose of 7.5 mg/kg MABp1 administered intravenously every two weeks until disease progression or unacceptable toxicity.

No excretion, metabolism or interconversion studies are required for a monoclonal antibody. Being an immunoglobulin, it is catabolised by ubiquitous proteolytic enzymes, not restricted to hepatic tissue. As the target for MABp1 is a soluble cytokine, target-mediated degradation is not expected.

The applicant has not fully investigated the potential for cytokine-mediated DDIs. The possible effect on P450s requires further consideration.

The claimed mechanism of action of lowering inflammation reactions in advanced cancer patients by inhibiting IL-1α, has not been clearly shown. There is a lack of evidence linking inhibition of IL-1α to the decrease in mononuclear monocytes and blood plate counts. From the submitted documentation, it is unclear how the monocytes from patient sera expressing IL-1α have been detected. It is still unclear how IL-1α on blood plates was identified. The applicant should have provided further data on spotting of IL-1α on monocytes and platelets, supporting a selection of IL-1α positive monocytes and blood platelets in patient sera that can confirm the claimed mechanism of action. This issue remains unclear.

The observations made in the Phase 1 2009-PT004 study were only trends, overall there were no statistically significant reductions in neither IL-1α positive monocytes, nor blood plate counts from patients sera presumably

expressing IL-1α. The amount of blood platelets at the two highest dose levels (3.75 mg/kg every 3 and 2 weeks respectively) remained stable and was presumably statistically significant. At the other dose levels the platelet count decreased.

The reduction in IL-6 in the overall population was not significant; however, a declining trend was observed that was more pronounced in patients with increasing LBM. The basis for making any firm conclusions in this very small population is, however, at best very limited.

No QT prolongation study has been conducted by the Applicant. The Applicant has provided a summary of the available QT-data from several studies, across multiple dose levels and disease indications, including the pivotal study (2014 PT026) and study 2012PT023 (V3), which investigated the applied doses. The latter study is still ongoing and blinded. Additionally, the presentation of the result seems to be contradictory and difficult to interpret. The submitted data does not allow for a thorough assessment of a potential QT prolongation. This should be clearly reflected in the SmPC. The Applicant indicated that the QT/QTc data from study 2012-PT023 (V3) would be submitted as soon as available when unblinded.

2.4.5. Conclusions on clinical pharmacology

The presented PK data is based on a limited dataset in a limited number of patients, especially at the dose intended to be licensed. This has been supplemented by PK data (as requested) in healthy subjects (n=6) [2017-PT041]. PK data from another patient study [2010-PT015] has also been provided. Further details regarding the design and conduct of studies 2010-PT015 and 2017-PT041 are required. Presented PK analyses should be confirmed with non-compartmental analysis and covariate analysis could be confirmed with a population PK analysis. The range of values obtained with the 2017-PT041 PK study and the range of values from the analyses of previous studies (with bare minimum of points) present differences which require clarification and discussion. The available PK data provide a characterisation of the selected dose of 7.5 mg/kg, but do not support it. Due to the fact that the 2017-PT041 study was a single dose PK study, the issue of absence of PK data and use of absolute minimum points for estimating PK parameters can be considered partially resolved. The applicant should also further discuss the potential for cytokine-mediated DDIs.

The claimed mechanism of action of inhibiting of IL-1α and thereby the inflammation process in advanced cancer has not been properly demonstrated. Only preliminary clinical PD-studies have been performed and the submitted data have still not shown any statistically significant correlation of dose levels with effect on the chosen PD measures.

2.5. Clinical efficacy

2.5.1. Dose response study

The 2009-PT004 study was an open label, first-in-man, phase I trial of MABp1 in patients with advanced cancers. The study was conducted at the M.D. Anderson Cancer Centre in Houston, Texas.

The study population consisted of patients with advanced malignancy that were refractory to standard therapy or for which no standard therapy existed. This study utilised a standard 3+3 design and dose escalation proceeded as described in table below. The MABp1 therapeutic antibody was administered at four different dose levels in the dose escalation part of the trial.

The mean serum levels at the highest clinical dose (3.75 mg/kg once every two weeks) tested in this study were approximately 77 µg/ml and 87 µg/ml following the first and third cycles, respectively (Table 3).

Table 3 Serum concentration of MABp1 in patients by dose level

Dose Level (mg/kg IV)	C1D1 – Serum Concentration (µg/ml)			C3D1 - Serum Concentration (µg/ml)		
	Mean	CV %	Individual Max	Mean	CV %	Individual Max
0.25 mg/kg (n=3)	4.42	20.13	5.40	4.95	15.63	5.65
0.75 mg/kg (n=3)	20.47	33.51	24.79	21.34	25.45	25.68
1.25 mg/kg (n=3)	26.71	27.95	35.07	26.21	18.59	29.65
3.75 mg/kg (3wk, n=27)	72.88	20.06	113.17	82.69	24.37	120.67
3.75 mg/kg (2wk, n=16)	77.23	14.35	101.25	86.97	14.50	108.46

The dose-escalation phase of the study seems acceptable with a common design. However, a maximum tolerated dose was never estimated. Dose-limiting toxicity was not seen in any of the chosen dose cohorts.

Considering that an MTD was not determined, an optimal therapeutic dose of MABp1 has not been found. Nevertheless, a higher dose (7.5 mg/kg every other week) was selected for the pivotal trial based on these data.

2.5.2. Main study

Study 2014-PT026: a double blind, placebo controlled pivotal Phase III study evaluating MABp1 in symptomatic colorectal cancer patients refractory to standard therapy

Methods

The pivotal study **2014-PT026** was a randomised, double blind, placebo controlled, multicenter, parallel-group Phase III trial in subjects with symptomatic, advanced colorectal cancer that is resistant to standard of care therapies.

Patients were randomized 2:1 to receive an intravenously administered regimen once every 2 weeks (one cycle) for a total of 4 IV infusions. The treatment period consisted of 4 cycles. Subjects randomised to treatment arm received 7.5 mg/kg MABp1 at each cycle while subjects randomised to control arm received IV placebo.

The duration of study was 8 weeks. After Week 8 assessment, subjects from both arms could receive MABp1 in an open label extension, in which other subsequent anti-cancer therapies were also allowed.

Study Participants

The **main inclusion criteria** were as follows:

1. Subjects with pathologically confirmed colorectal carcinoma that is metastatic or unresectable and which is refractory to standard therapy. To be considered refractory, a subject must have failed both an oxaliplatin (oxaliplatin may have been in the adjuvant setting) and an irinotecan based regimen.

2. Symptomatic Disease: One symptom from each domain (metabolic and functional) must be present.

a) Evidence of metabolic dysfunction, defined as the presence of one or more of the following:

- Any degree (up to 20%) of unintentional total body weight loss in the previous 6 months

- Serum Interleukin 6 levels ≥10 pg/ml

b) Evidence of reduced function or presence of cancer related symptoms as determined by EORTC QLQ-C30.

- Appetite reduction, with a score of >10

- Presence of fatigue, with a score of >10

- Presence of pain, with a score of >10

- Decreased Role, Emotional and Social function, with a score of < 90.

3. Eastern Cooperative Oncology Group (ECOG) performance status 1 or 2.

4. In the Investigator's judgement, a life expectancy of at least three (3) months.

The **main exclusion criteria** were as follows:

1. >20% total body weight loss in the previous 6 months.

2. Serious uncontrolled medical disorder, or active infection, that would impair the ability of the patient to receive protocol therapy.

3. Subjects who have not recovered from the adverse effects of prior therapy at the time of enrolment to ≤ grade 1; excluding alopecia and grade 2 neuropathy.

4. Women who are pregnant or breastfeeding.

5. History of progressive multifocal leukoencephalopathy or other demyelinating disease.

6. Subjects on immunosuppressive therapy, including transplant patients.

7. Subjects with known brain metastases.

Treatments

Subjects randomised to the treatment arm received 7.5 mg/kg MABp1 via intravenous (IV) injection once every 2 weeks (one cycle) for a total of 4 infusions (four cycles). Subjects randomised to the control arm received IV placebo at 7.5 mg/kg via intravenous (IV) injection once every 2 weeks (one cycle) for a total of 4 infusions (four cycles).

Best supportive care (BSC) is defined as those measures intended to provide palliation of symptoms and improve Quality of Life (QoL). This included, but was not limited to, psychological support, dietary advice, exercise advice, antibiotics, anti-emetics, and analgesics.

Concomitant treatment

The following treatments were restricted until the completion of Week 8 assessment:

- Chemotherapy, radiotherapy, immunotherapy or hormonal therapy, or biologic agents
- Treatment with cancer related fatigue with corticosteroids (except for patients with COPD and asthma), megestrol acetate, dronabinol, stimulants.
- Live virus vaccines.

The concomitant use of any investigational agents, immunosuppressive agents and TNF- or IL-1 inhibitors were prohibited during the study period.

Outcomes/endpoints

The **primary efficacy endpoint** was the objective response rate (ORR), a composite measure assessing of change in lean body mass (LBM) and change in QoL in terms of the symptoms of fatigue, pain, and appetite from baseline to week 8. Objective response was defined as:

1) Improvement or stabilization (≥0 kg change) of LBM as assessed by Dual-energy X-ray Absorptiometry (DEXA) scan from baseline to week 8; and

2) Improvement or no worsening (≥0 score point change) on any two of the three symptoms scale measures (fatigue, pain, appetite) of EORTC QLQ-C30 from baseline to week 8.

In order to be considered a responder, a subject had to meet both individual components of the composite endpoint.

Dual-energy X-ray absorptiometry was utilised to determine the LBM. DEXA scans were performed at screening and at Week 8 to assess changes in body composition. The analysis of DEXA images was performed by a central imaging vendor.

The applicant proposed the change in LBM as a new prognostic outcome measure, i.e. a primary endpoint for the assessment of antineoplastic effects of MABp1. By using DEXA to measure LBM as a primary endpoint, the applicant intended to provide both a direct measure of clinical benefit, and a surrogate measure for survival in the target advanced cancer population.

Quality of life was assessed using the EORTC QLQ-C30 questionnaire (version 3) at screening, Week 8 or Early Termination visit if the subject is discontinued prior to Week 8.

Secondary efficacy variables included the following pharmacodynamic measures: (1) reduction in serum IL-6; and (2) stabilisation of platelet count at 8 week compared to screening. In addition, change in functional scales and global QoL scale were evaluated as assessed by the EORTC QLQ-C30 questionnaire at screening and 8 week follow-up.

Tumour response was not an endpoint of the pivotal trial, however radiographic assessment of tumour size at baseline and Week 8 was to be collected and evaluated on an exploratory basis. Tumour assessments could be done using a Computed Tomography (CT) or a Magnetic Resonance Imaging (MRI), and the same modality had to be used at the initial vs. Week 8 tumour assessments.

Sample size

The trial was designed to have 80% power to detect 20% effect (assuming 55% and 35% response rate in the treatment and placebo groups respectively) with one-sided alpha of 0.0125 and 2:1 allocation ratio. The alpha level was set to 0.0125 in order to account for the two-component composite endpoint.

Initially, the required sample size was estimated to be 276 which factored in a 5% drop-off rate. During the planned interim review at 50% enrolment the DMC suggested to increase the oversampling to 20% to account for the higher than the projected number of patients missing the endpoint data. They further recommended adding another 10 subjects to cover the mistakenly randomised patients, who will not be in the analysis dataset. Thus the modified sample size was estimated to be approximately 339.

Randomisation

A central randomisation scheme with Interactive Web Response System (IWRS) was employed to facilitate effective randomisation and allocation concealment. The scheme used a block randomisation technique, randomly assigning participants within blocks (block size 6) based on a 2:1 allocation ratio to MABp1+BSC or Placebo+BSC arm respectively.

Blinding (masking)

A Central randomisation sequence was generated using Oracle Clinical Remote Data Capture (OCRDC) application and stored in a secured back-end table of the clinical database. After confirmation of eligibility, participants were assigned the treatment allocation. Study coordinators at the clinical site completed the randomisation electronic Case Report Form (eCRF) indicating the patient has met inclusion criteria and ready to be randomised. Investigator and Clinical Research Organisation (CRO) or Sponsor personnel involved in the management of the study did not have access to unblinded information until after the final database lock on December 04, 2015.

CRO personnel responsible for the submission of SUSARs had privileges in the electronic database that allowed for unblinding of individual patients for the purpose of regulatory reporting.

Statistical methods

As per the SAP the intent-to-treat (ITT) population was defined as all randomised patients who received at least one infusion of the study drug. Which in fact was a modified ITT population and for the purpose of this report we will refer this as mITT population. mITT population was the primary analysis population for efficacy evaluation.

For the purpose of primary efficacy analysis:

1. Patients missing follow-up DEXA and or EORTC assessments were considered to have progressed with respect to the primary endpoint.

2. Patients who received treatment for worsening symptoms, such as steroids or stimulants, were considered to have progressed with respect to the primary endpoint.

3. Patients randomised to placebo arm but who receive test article were considered to have progressed with respect to the primary endpoint.

The primary endpoint was compared between the MABp1 and placebo group using Pearson chi-square test. Relative risk and unadjusted odds ratio estimates are presented with 95% confidence intervals (95% CI). Accounting for the two components of the composite endpoint, 1-tailed type I error of 0.0125 was used for determining statistical significance of the primary outcome.

The following secondary efficacy analyses were conducted:

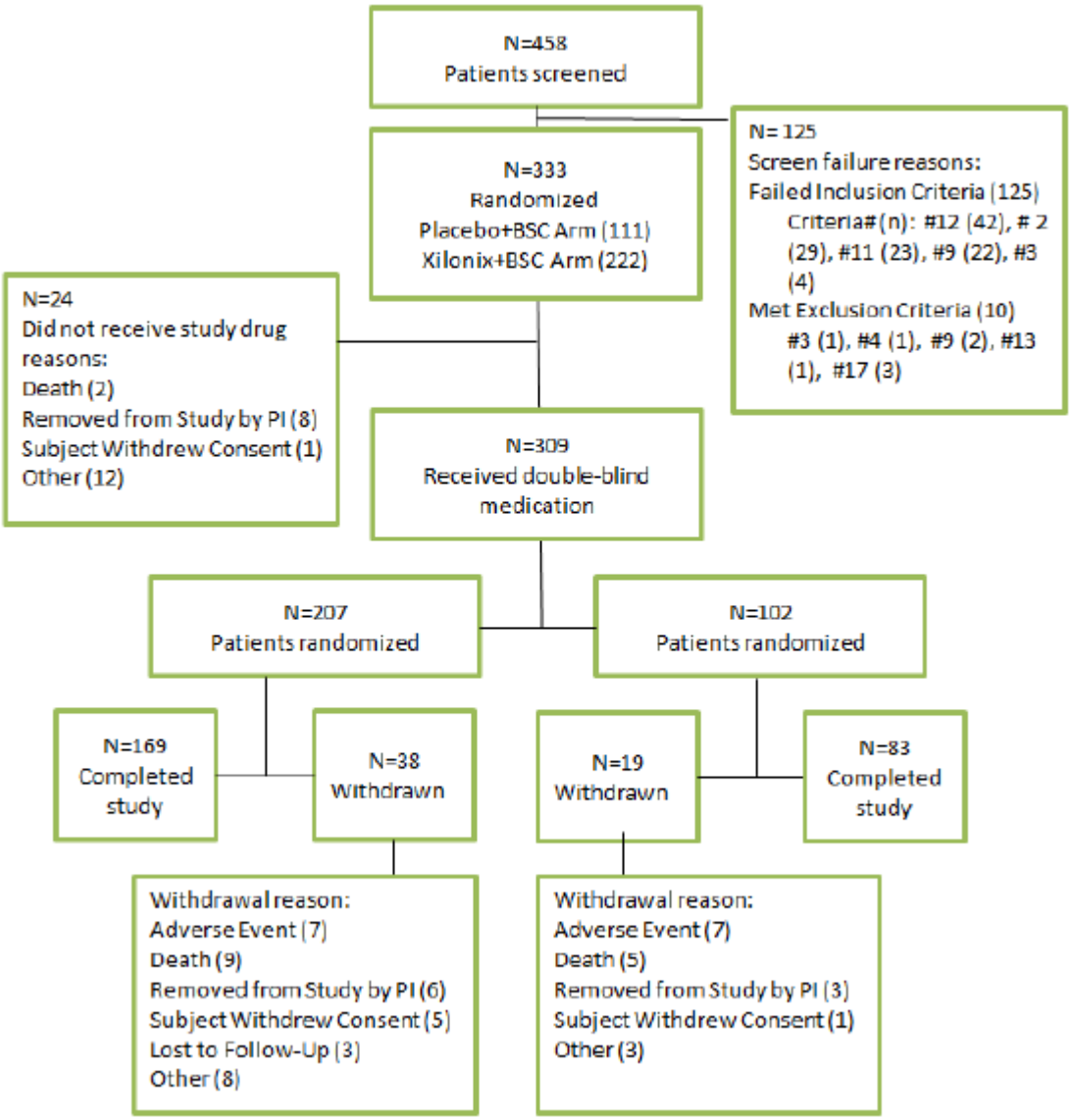
Change at follow-up assessment (visits C3 onward carried forward) on LBM, EORTC QLQC30 Score, platelet count and serum IL-6 level were assessed using analysis of covariance model (SAS GLM procedure), with treatment groups as factor and baseline value as covariate. The difference in least-square means and 2-sided P values derived from analysis of covariance model for comparison. Significance was tested at 2-sided p of 0.05.

Planned subgroup analyses of primary and secondary endpoints were performed with stratification variables-baseline ECOG performance status, gender and KRAS mutation status. Within each subgroup factor, the

outcomes were compared using chi-square test. Adjusted odds ratio and 95% CI were calculated using multivariable logistic models. The covariates fitted in to the model were ECOG status, gender and KRAS status.

Results

Participant flow



Recruitment

The pivotal study was performed at 35 centres (including 7 countries in Europe, 3 in Georgia and 4 in Russia). Most of patients were recruited in the European centres (including Bulgaria, Czech Republic, France, Germany, Hungary, Poland and UK).

The pivotal study was initiated in May 20th 2014 and ended November 3rd 2015 (study period was 1.5 years).

Conduct of the study

There have been 7 protocol amendments (2 global and 5 country-specific). The Statistical Analysis Plan was amended once (Version 1.1, 20 Nov 2015).

A total of 132 patients (60%) in MABp1 arm and 77 patients (69%) were reported to violate the study protocol. The important protocol deviations in the pivotal study are shown in Table 4. The most frequently reported important protocol deviations were “out of window visit”.

Table 4 Important Protocol Deviations by Study Arm (All randomized patients)

Type of Protocol Deviation	Xilonix+BSC (n=222)	Placebo+BSC (111)
Out of window visit, n(%)	80 (36%)	50 (45%)
Outcome assessment not done or done out of window, n(%)	22 (10%)	11 (10%)
Subject entered study and did not satisfy entry criteria, n(%)	10 (5%)	4 (4%)
Subject received wrong treatment or incorrect dose, n(%)	20 (9%)	12 (11%)

Baseline data

The demographic parameters and baseline characteristics for the ITT population are shown in Table 12. Note that enrolment of subjects was stratified by baseline ECOG status, gender and KRAS mutation.

The median (range) body mass index (BMI) of the patients at baseline was 25.8 (22.8-28.7) kg/m2 in the MABp1 arm and 25.8 (22.8-29.2) kg/m2 in the placebo arm, while the median LBM at baseline were 43.7 (36.3-49.7) kg and 44.6 (37.8-50.3) kg, respectively.

Table 5 Demographic and Baseline Characteristics (ITT)

	Treatment Group		Total (N= 309)
	Xilonix+BSC (N= 207)	Placebo+BSC (N=102)	
Age, year			
Mean	63±10	63±9	63±10
Median	64	63	63
Min-Max	31-83	38-84	31-84
Age distribution, n(%)			
<65 years	112 (54%)	60 (59%)	172 (56%)
≥65 to <75 years	72 (35%)	32 (31%)	104 (34%)
>75 years	23 (11%)	10 (10%)	33 (11%)
Sex, n(%)			
Female	79 (38)	43 (42)	122 (39)
*Race, n(%)			
White	202 (98)	101 (99)	303 (98)
Asian	2 (1)	0	2 (1)
Geographic Region , n(%)			
EU	176 (85)	91 (89)	267 (86)
Georgia	15 (7)	4 (4)	19 (6)
Russia	16 (8)	7 (7)	23 (7)
*KRAS Mutation Status, n(%)			
KRAS Mutation	85 (41%)	37 (36)	122 (39)
KRAS wild-type	91 (44%)	56 (55)	147 (48)
Test Not Done	30 (14%)	9 (9)	39 (13)
ECOG Performance Status			
1	170 (82%)	80 (78)	250 (81)
2	37 (18%)	22 (22)	59 (19)
Baseline Weight, kg			
Mean	74±20	76±16	75±18
Median	72	75	74
Min-Max	36-172	43-154	36-172
Histology, n(%)			
Adenocarcinoma	204 (99%)	100 (98)	304 (98)
Adenocarcinoma in situ	1 (0%)	1 (1)	2 (1)
Other	2 (1%)	1 (1)	3 (1)
Number of prior chemotherapy regimens, n(%)			
1	9 (4)	8 (8)	17 (6)
2	51 (25)	26 (25)	75 (24)
3	53 (26)	30 (29)	81 (26)
4	41 (20)	20 (20)	59 (19)
5	22 (11)	7 (7)	29 (9)
≥6	27 (13)	11 (11)	37 (12)

Abbreviation: ECOG= Eastern Cooperative Oncology Group

* Race was missing for 4 patients and KRAS Mutation Status was missing for one patient.

Numbers analysed

Table 6: Patient disposition

	Treatment Group		Total N=333
	Xilonix+BSC (N= 222)** n (%)	Placebo+BSC (111) n (%)	
Randomized	222	111	333
Never treated	15 (7)	9 (8)	24 (7)
Intent to Treat Population (ITT)*	207 (93)	102 (92)	309 (93)
Discontinued from study	38 (17)	19 (17)	57 (17)
Reason for discontinuation			
Adverse Event	7 (3)	7 (6)	14 (4)
Death	9 (4)	5 (5)	14 (4)
Lost to Follow-Up	3 (1)	0 (0)	3 (1)
Other	8 (4)	3 (3)	11 (3)
Removed from Study by PI	6 (3)	3 (3)	9 (3)
Subject Withdrew Consent	5 (2)	1 (1)	6 (2)

*ITT: All patients who were randomized and received at least one infusion of study drug

**Percentages are based on all randomized patients

A total of 24 subjects who were randomized but did not receive any dose of the study drugs were excluded from the primary analysis.

Outcomes and estimation

The primary efficacy analyses of composite ORR were performed in the ITT and PP populations, which consisted of 309 subjects (207 subjects in MABp1 arm and 102 patients in placebo arm) and 292 subjects (207 subjects in MABp1 arm and 85 patients in placebo arm), respectively. Main efficacy results for the primary endpoint of composite ORR (for the mITT and PP populations) are presented in Table 7.

The primary efficacy analysis on the ITT population (which actually corresponds to mITT population) showed that the ORR was 33% (68/207) for the MABp1 arm and 19% (19/102) for placebo arm, resulting in a difference in effect size of 14%, which was statistically significant based on a one-sided test (p=0.004).

Table 7: Clinical Response Rate (study 2014-PT026)

	Hutruo+BSC	Placebo+BSC
N	207	102
Clinical Response, n (%)	68 (33%)	19 (19%)
P value from Pearson Chi-Square test (one-tailed)	0.0045	
Unadjusted Odds Ratio (95% CI)	1.76 (1.12, 2.77)	

Analysis of individual components of the composite endpoint

In Table 8, Table 9 and Table 10 results for the analysis of individual components of the primary endpoint are shown by both clinical response rate and magnitude of change between the study arms.

Change in LBM: There were no significant differences in the LBM change from baseline between the MABp1 and the placebo arms at Week 8. Besides, the magnitude of the mean LBM increase (change from baseline, LS mean±SE) in the placebo arm (0.60 ±0.32 kg) was slightly higher than that in the MABp1 arm (0.53±0.22 kg) (Table 8).

Change in QoL domains: Descriptive statistics for the QoL domains of the EORTC QLQ C30 Questionnaire (i.e. mean scores at baseline vs Week 8, and change LS mean) suggest that there were no statistically significant changes in each arms at Week 8 compare to baseline in the QoL scales (global QoL, role function, physical, emotional or social) or disease-related QoL symptoms (pain, appetite and fatigue). Besides, there are no statistically significant differences between the study arms. The observed differences ("change LS mean±SE" scores) in all QoL scales were, however, below the minimal important difference (MID) of 10 mean score (Table 10).

Outcomes (responder rates) by individual components of the primary composite endpoint indicate only small (≤7%) differences between the study arms in terms of individual endpoints of LBM, Pain and Appetite while no difference was seen for Fatigue (**Error! Reference source not found.**).

Table 8: Change in Objective Measures By Treatment Arm (mITT)

	LS Mean±Standard Error		P (LS mean difference)
	Placebo+BSC	Xilonix+BSC	
Change in LBM, kg	0.60±0.32	0.53±0.22	0.87

Table 9: Response by Individual Components of Clinical Response Endpoint (mITT)

Components of Clinical Response	Xilonix+BSC (N=207)	Placebo+BSC (N=102)	Difference (effect size)	P value (1-sided Pearson Chi-Square test)	Relative Risk (95% CI)
	Objective Response, n (%)	Objective Response, n (%)			
LBM Response	105 (51%)	46 (45%)	6%	0.18	1.13 (0.87, 1.45)
Pain	93 (45%)	45 (44%)	1%	0.45	1.02 (0.78, 1.33)
Fatigue	94 (45%)	46 (45%)	0%	0.48	1.01 (0.78, 1.31)
Appetite	114 (55%)	49 (48%)	7%	0.12	1.15 (0.91, 1.45)

Table 10: Change in Patient Reported Measures By Treatment Arm (mITT)

	Placebo+BSC (n= 102)			Xilonix+BSC (n= 207)			P (LS mean diff)
	Baseline Mean (95% CI)	Week 8 Mean (95% CI)	Change LS Mean ±SE	Baseline Mean (95% CI)	Week 8 Mean (95% CI)	Change LS Mean ±SE	
Global QOL Score	50.6 (47.2 to 54.0)	47.1 (42.4 to 51.7)	-4.03±2.27	48.8 (46.1 to 51.5)	48.0 (44.6 to 51.4)	-2.36± 1.58	0.52
Role Function Score	64.7 (59.8 to 69.6)	59.7 (53.1 to 66.3)	-7.83±3.02	66.4 (62.4 to 70.3)	60.8 (56.1 to 65.4)	-6.83± 2.12	0.79
Physical Function Score	72.0 (67.4 to 76.6)	68.4 (63.2 to 73.5)	-3.38±2.19	70.7 (67.7 to 73.7)	66.0 (62.5 to 69.5)	-5.11± 1.53	0.52
Emotional Function Score	64.3 (59.8 to 68.8)	67.8 (62.5 to 73.0)	1.37±2.34	67.2 (63.9 to 70.5)	69.3 (65.7 to 72.9)	2.50± 1.64	0.69
Social Function Score	64.4 (59.2 to 69.5)	64.8 (58.0 to 71.6)	0.00±3.06	64.3 (60.6 to 67.9)	63.5 (59.0 to 68.0)	-0.89± 2.14	0.81
Fatigue Score	47.6 (43.1 to 52.1)	49.6 (43.8 to 55.3)	3.58±2.72	49.2 (46.0 to 52.5)	51.7 (47.5 to 55.8)	4.05± 1.90	0.89
Pain Score	38.4 (33.2 to 43.6)	38.4 (32.1 to 44.8)	3.45±3.16	36.6 (32.7 to 40.4)	41.1 (36.2 to 46.0)	5.91± 2.19	0.52
Appetite Score	31.0 (25.1 to 36.9)	38.8 (30.9 to 46.7)	9.51±3.50	37.0 (32.9 to 41.1)	37.6 (32.6 to 42.6)	3.82± 2.43	0.19

Secondary efficacy analysis

Results for secondary efficacy analysis of change in IL-6 levels and change in platelet count are shown in Table below.

Table 11: Results of secondary endpoints analysis (ITT)

	LS Mean±Standard Error		P value (LS mean difference)
	Placebo+BSC	Xilonix+BSC	
*IL-6 Change, pg/mL	9.9±2.7	1.6±1.9	0.012
Change in Platelet Count, 1000/cu mm	39.53±7.56	13.45±5.33	0.0052

*Four outliers were excluded from the analysis.

As shown in Table 17, no significant differences were observed in the EORTC functional scales or global QoL score between the MABp1 and placebo arms.

Exploratory Analysis of Tumour Response

Disease progression was assessed in the pivotal study using conventional approaches. A CT imaging at baseline and Week 8 (or early termination) was used to evaluate patients with respect to RECIST criteria for disease progression. Analysis of tumour response data showed that 17% (35/207) of patients in the MABp1 arm vs 12% (12/102) of patients in the Placebo arm had stable disease at Week 8.

Sensitivity analysis

In order to investigate the impact on the primary outcome, a sensitivity analysis was conducted when only subjects who actually had an increase in LBM were included in the analysis set (excluding those that maintained pre-existing LBM). Results are presented in Table 12.

When the primary endpoint was re-defined as: ≥1 kg LBM change and stabilisation or improvement in 2 of 3 symptoms, a statistically significant difference in CRR was observed (20% for the MABp1 arm vs 9% for the placebo arm, i.e. +11% difference in favour of MABp1, mITT population, one-tailed p=0.0068). However, the difference was not statistically significant when a cut-off value of ≥1.25 kg was used (i.e. +7% difference in effect size in favour of MABp1, mITT population, one-tailed p=0.034).

Table 12 Primary Endpoint using Different LBM Cut-off Values

	mITT Population, n=309			
LBM Cut-off Value (kg)	MABp1 (n=207)	Placebo (n=102)	Effect Size	P (1-tail)
	Met Primary Endpoint, n (%)	Met Primary Endpoint, n (%)		
≥0.0	68 (33%)	19 (19%)	14%	0.0045
≥0.5	50 (24%)	16 (16%)	8%	0.044
≥0.75	46 (22%)	12 (12%)	10%	0.013
≥1.0	41 (20%)	9 (9%)	11%	0.0068
≥1.25	29 (14%)	7 (7%)	7%	0.034
Assessing Individual Endpoints (LBM and EORTC) separately				

The magnitude of LBM gain (mean±SD) observed for the patients that met the endpoint of the sensitivity analysis was similar between the arms, i.e. 2.24±0.39 kg in the MABp1 arm vs. 1.83±1.08 kg in the placebo arm for the mITT population.

Summary of main efficacy results

The following table summarises 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 13 Summary of efficacy for trial 2014-PT026

Title: A Double Blind, Placebo Controlled Pivotal Phase III Study Evaluating MABp1 in Symptomatic Colorectal Cancer Patients Refractory to Standard Therapy		
Study identifier	2014-PT026	
Design	Randomized, double blind, placebo controlled, multicentre Phase III trial in patients with symptomatic, advanced colorectal cancer that is refractory to standard therapies of at least oxaliplatin- and irinotecan-based regimens	
	Duration of main phase:	8 weeks

	Duration of Run-in phase: Duration of Extension phase:		14 days Indefinite period of time (i.e. until progression or toxicity), subjects from both arms could receive MABp1 in an open label extension
Hypothesis	Superiority		
Treatments groups	MABp1 arm		7.5 mg/kg IV once every 2 weeks (one cycle) for a total of 4 infusions (four cycles) plus BSC*, ITT: 222 patients
	Placebo arm		IV infusions following the same schedule described for MABp1, plus BSC*, ITT: 111 patients
Endpoints and definitions	Primary endpoint	ORR	A composite endpoint, including change in lean body mass (LBM) and change in quality of life (including symptom scales for fatigue, appetite and pain) using the EORTC-QLQ-C30 Questionnaire, as determined from screening to week 8.
	Secondary endpoints	IL-6 and platelet count	Reduction in serum IL-6 levels and stabilization of platelet count investigated at 8 week compared to baseline.
	Secondary endpoints	Change in functional scales and global QoL	Assessed using the EORTC-QLQ-C30 Questionnaire
Database lock	No information given in the CSR		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	**mITT** (at Week 8)		
Descriptive statistics and estimate variability	Treatment group	MABp1 arm	Placebo arm
	Number of subject	207	102

	ORR % of subjects (n)	33% (68)	19% (19)
	Difference (effect size, %)	14%	
Effect estimate per comparison	ORR	Comparison groups	MABp1 vs Placebo
		Unadjusted Odds Ratio	2.14 (1.21, 3.78)
		P-value (one-tailed)	0.004
Analysis population and time point description	**PP** (at Week 8)		
Descriptive statistics and estimate variability	Treatment group	MABp1 arm	Placebo arm
	Number of subject	169	83
	ORR % of subjects (n)	40% (68)	23% (19)
	Difference (effect size, %)	17%	
Effect estimate per comparison	ORR	Comparison groups	MABp1 vs Placebo
		Unadjusted Odds Ratio	2,27 (1,25-4,12)
		P-value (one-tailed)	0.003
Notes	An updated PP analysis has now been provided in response to the D120 LoQ. However, a total of 5 responders in the placebo arm were excluded from the PP analysis as these patients were among the 17 placebo patients that received erroneously MABp1, and hence were considered non-responders. This hampers the reliability of PP analysis results.		

* BSC included, but was not limited to, psychological support, dietary advice, exercise advice, antibiotics, anti-emetics, and analgesics.

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

N/A

Clinical studies in special populations

No studies have been performed in special populations and none has been warranted. The numbers of older patients included in study 2014-PT026 and 2009-PT004 are stated below in the table according to different age categories.

Table 14: Number of patients recruited by age group in the clinical efficacy trials

	Age 65-75 (Older subjects number/ total number)	Age >75 (Older subjects number/ total number)	Age 85+ (Older subjects number/ total number)
2014-PT026	72/207	23/207	not specified
2009-PT004	10/52	7/52	not specified

* ITT population receiving MABp1

Supportive study

Exploratory study 2009-PT004

This was an open label, Phase I study of MABp1 in patients with advanced cancers and was designed to assess the safety and tolerability of MABp1, as well as provide preliminary evidence of efficacy in patients with different types of solid tumours that are refractory to standard chemotherapy regimens. This study is currently open but not recruiting patients and the results provided concern the interim analysis (n=52, at data cut-off: 31st October 2013). Eligible patients were at least 18 years of age; had an ECOG score of 0, 1, or 2. A washout period of 4 weeks since the last dose of chemotherapy, biological or targeted therapy, radiation therapy, or surgery was required before receiving the study drug.

The study utilised a standard 3+3 dose escalation, investigating the doses of MABp1 of 0.25 mg/kg, 0.75 mg/kg, 1.25 mg/kg, and 3.75 mg/kg. Patients received intravenous infusion of MABp1 once every 3 weeks. One cycle of therapy consisted of 3 weeks (21 days).

Main outcome measures investigated in this study at baseline vs 8 weeks after the first dose concern the following: (i) LBM assessment using DEXA, (ii) Tumour response using the RECIST criteria (version 1.1), (iii) changes in serum concentration of IL-6 were measured as a biomarker for antii-IL-1α activity, (iv) CRP as a surrogate marker of inflammation, and (v) patient wellbeing was assessed on day 1 of each cycle using the EORTC-QLQ C30 questionnaire (version 3.0).

Tumour responses

According to the applicant, of the 24 patients that were evaluated according to RECIST criteria, an overall response rate of 37% (9/24) was achieved (defined as stable disease or better for ≥ 3 months).

Lean Body Mass

Out of the 34 patients who were evaluated according to standard criteria, 30 complied as scheduled both at screening and at the 8-week follow-up assessment. Analysis of baseline and follow-up DEXA scans showed that 70% (21/30) had increases in lean body mass (LBM). Responders showed an average LBM improvement of

1.9±2.0 kg (95% CI 1.08 to 2.77 kg, p<0.001) compared to their baseline values, while the average change for the entire cohort was 1.0 kg (p=0.02).

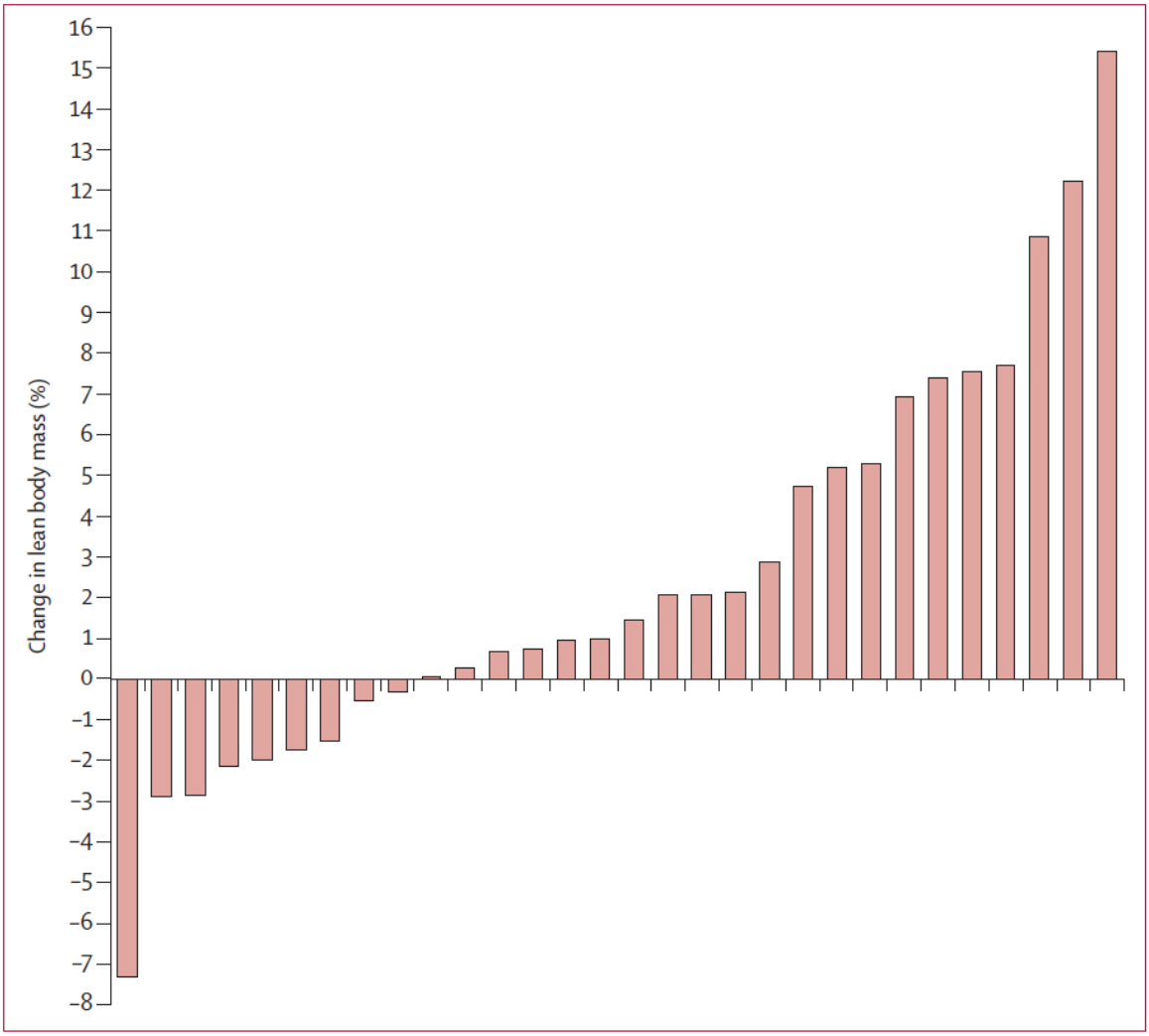


Figure 5. Most patients (21/30 or 70%) showed increase in lean body mass (LBM) of 1.9±2.0 kg after three infusions of antibody therapy (p<0.001). Patients were evaluated with DEXA (dual energy X-ray absorptiometry) more than 2 weeks prior to the start of treatment. Each bar represents the change in LBM for a single patient. Lean body mass change is expressed as a percentage of total body weight from baseline.

Analysis of the patients with CRC

The majority of patients enrolled and treated in this pilot trial had refractory metastatic colorectal cancer (14 out of 52). Five of these CRC patients (36%) responded with an increase in LBM, and the average increase was 4.6%. Among the 14 subjects with colorectal carcinoma, the median overall survival was 6.7 months for the ITT population (which included three patients enrolled with waivers) and 8.7 months for the per protocol population.

The applicant states that median survival duration correlated with increases in LBM. For those with an increase in LBM from baseline to week 8, the median survival duration was 19.3 months. This was in contrast to a median OS of 6.6 months seen in those with no evidence of LBM increase (log-rank p 0.098).

2.5.3. Discussion on clinical efficacy

This MAA concerns a monoclonal antibody MABp1, with activity against interleukin-1α, which is intended for the control or relief of debilitating symptoms associated with advanced colorectal cancer.

The proposed dose is 7.5 mg/kg MABp1 administered intravenously every two weeks until disease progression or unacceptable toxicity.

This application is mainly based on one single pivotal study (2014-PT026) in symptomatic CRC patients who are refractory to standard therapy. In addition, an open label Phase I dose escalation study (2009-PT004) with a Phase II expansion cohort of 14 patients with CRC is submitted as a supportive study.

In the dose escalating study, a dose range of 0.25 mg/kg to 3.75 mg/kg was tested (the latter as once every two or three week regimen), and no maximum tolerated dose was determined. However, a higher dose (7.5 mg/kg every other week) was selected for the pivotal trial.

Design and conduct of clinical studies

Study 2014-PT026 was a randomised, double blind, placebo-controlled, multicentre, parallel-group Phase III trial in subjects with symptomatic, advanced colorectal cancer that is resistant to standard of care therapies. Patients were randomised 2:1 to receive an IV regimen of MABp1 or placebo in addition to BSC once every 2 weeks (one cycle) for a total of 4 IV infusions. The treatment period consisted of 4 cycles. BSC included, among others, psychological support, dietary advice, exercise advice, antibiotics, anti-emetics and analgesia.

The duration of study was 8 weeks. After this period, subjects from both arms could receive MABp1 until disease progression or unacceptable toxicity in an open label extension, in which other subsequent anti-cancer therapies were also allowed. Consequently, these data will be subject to bias, hampering the interpretability of these data.

Inclusion/exclusion criteria

The patient population comprised patients with metastatic or unresectable CRC, which is refractory to standard therapies of oxaliplatin- and irinotecan-based treatment regimens (i.e. patients failed at least to two lines of previous treatment). Besides, patients had to have a symptomatic disease, which was evaluated by means of the following criteria: (i) evidence of metabolic dysfunction (either unintentional loss in bodyweight (any degree, up to 20%) in the previous 6 months or serum IL-6 levels ≥10 pg/ml), and (ii) evidence of reduced function or presence of cancer related symptoms (appetite, fatigue, pain) as determined by EORTC QLC-C30 Questionnaire. Patients had to have one symptom from each of the above-mentioned domains.

The inclusion criteria concerning unintentional weight loss at baseline is considered critical to identify relevant patient population. In general, a weight loss of <5% from the historical weight in last 6 months is not considered clinically relevant. According to Vaughan et al 2013, approximately 50% of cancer patients experience a weight loss due to metabolic dysregulation which is progressive and irreversible condition (i.e. cancer related cachexia). Consequently, inclusion of patients with “any degree” of weight loss is questioned. The applicant has not collected any information regarding the degree of prior weight loss at baseline (i.e. the number of patients with weight loss of ≥5% vs <5% at baseline and the distribution of patients with different degree of weight loss to the study arms is unknown). This is considered a major shortcoming which has not been resolved.

Due to the fact that approximately half of all cancer patients is expected to experience cachexia, the inclusion based on only the IL-6 threshold of >10 pg/ml has not been justified. In some clinical studies the prognostic value of IL-6 was discussed; however, there is no evidence which support the IL-6 level of >10 pg/ml as a marker of cancer-related cachexia.

Taken together, it can be questioned whether a relevant patient population has been enrolled in the pivotal study.

In general, the exclusion criteria are considered acceptable. Exclusion of patients with >20% total body weight loss in the previous 6 months is also supported, as these patients are usually at the point at which the disease might no longer be responsive to (symptomatic) treatment.

Severe renal or hepatic impairment was an exclusion criterion and hence there is no experience in patients with these conditions. This was reflected in the proposed SmPC. Exclusion of some relevant patient populations such as those with brain metastases was also reflected in the proposed SmPC section 4.4.

Outcomes/endpoints

The primary endpoint was objective response rate (ORR), a composite measure, assessing change in lean body mass (improvement or stabilisation) and change in quality of life (fatigue, appetite and pain) (improvement or no worsening) using the EORTC QLQ-C30 Questionnaire, as determined from screening to Week 8. In order to be considered a responder, a subject had to meet both components of the composite endpoint.

It should be noted that the composite ORR in this pivotal study is not the same as the traditional endpoint of ORR used in assessment of anti-cancer drugs. The latter is based on the tumour response assessment (i.e. proportion of patients in whom a CR or PR was observed).

According to the Guideline on the Evaluation of anticancer medicinal products in man, well-established primary and/or secondary endpoints to assess antineoplastic effects of a new drug in confirmatory trials include cure rate, OS and PFS/DFS. In the pivotal study 2014-PT026, none of the above-mentioned endpoints were employed.

Lean body mass as a surrogate for survival

The applicant proposed LBM as a new prognostic outcome measure in the pivotal study. A dual-energy X-ray absorptiometry (DEXA) method was used for estimation of LBM. By using DEXA, the applicant intended to provide both a direct measure of clinical benefit, and a surrogate for survival in the target advanced cancer population.

The evidence on the relationship between LBM and OS is based on the exploratory study (2009-PT004, n=52 at data cut-off for interim analysis). According to the applicant, advanced cancer patients with solid tumours treated with MABp1 unexpectedly recovered from key disease symptoms during therapy. In the colon cohort (n=14), the median survival for 36% (5/14) of patients who had increase in LBM from baseline to Week 8 was observed to be longer than those who showed reduction in LBM (19.3 months vs 6.6 months, respectively). However, these findings are based on a very limited data set, and small numbers of each tumour types treated and different inclusion criteria and dose regimens/schedules investigated hampers a sound interpretation of the data. Importantly, unintentional weight loss in previous 6 months was not an inclusion criterion in study 2009-PT004, and only 6 of 30 patients with LBM data seem to have a weight loss of >5% for an undefined period of time at pre-screening. Besides, several potential sources of bias with regards to LBM estimations by DEXA have not been addressed, e.g. concomitant medications such as corticosteroids and NSAIDs etc. Of note, tumour response was not evaluated in colon cohort patients. As a result, data from the exploratory study do not provide strong evidence in support of the causal relationship between the LBM and the anti-tumour effects of MABp1 (i.e. OS or tumour stabilisation), and hence the validity of LBM as a surrogate for survival is questioned.

Lean body mass as component of the composite endpoint for symptom control

In principle, LBM is considered to be a relevant parameter for demonstration of symptom control in advanced cancer patients. However, as stated above, inclusion of patients who have an unintentional weight loss of >5% in previous 6 months is a prerequisite when considering the validity of LBM as a primary endpoint in the pivotal study.

There are several concerns regarding the reliability of the LBM data obtained by DEXA as this method is subject to inherent inaccuracies. These include mainly the following: (i) DEXA cannot distinguish lean soft tissue from water, which could confound estimate of muscle mass. Consequently, the magnitude of LBM estimates can be impacted by the hydration status of the patients, (ii) As patients with advanced cancer may likely have water retention (oedema) due to some concomitant medications such as corticosteroids and NSAIDs, and other reasons (e.g. nutritional support or parenteral hydration in palliative care), or may be dehydrated due to reduced oral intake, nausea, and vomiting following anticancer treatment, potential bias in the LBM estimates cannot be excluded. Since the objective measure in the pivotal study was based on DEXA assessments, fluid and food consumption should have been standardised prior to these assessments.

Taken together, the LBM estimates based on the DEXA scans might have been subject to several sources of bias.

Assessment of QoL-cancer related symptoms as component of the composite endpoint

Quality of life was assessed using the EORTC QLQ-C30 questionnaire (version 3) at screening, Week 8 or Early Termination visit. Among the cancer related symptoms of fatigue, appetite and pain as determined by the questionnaire, appetite and fatigue are considered as clinically relevant symptoms for the target population. However, the evaluation of pain *per se* is questioned as part of the co-primary endpoint. As this parameter is potentially subject to bias due to the types/amount of analgesic drugs used by the patients, it is not considered to be a sensitive outcome measure.

Secondary endpoints included the following PD measures: (1) reduction in serum IL-6; and (2) stabilisation of platelet count at 8 week compared to screening. In addition, change in functional scales and global QoL scale were evaluated as assessed by the EORTC QLQ-C30 questionnaire at screening and 8 week follow-up. The PD parameters of serum IL-6 and platelet counts were selected as secondary endpoints based on the findings from the exploratory study 2009-PT004, in which a reduction in both parameters was observed following the treatment with MABp1. However, these findings are based on very limited data as discussed above and are considered preliminary.

Tumour response was assessed on an exploratory basis in the pivotal study.

Comparator/ best supportive care / concomitant therapies

For the intended patient population, available treatment options are currently limited, and there are no widely used treatment options for patients who failed two lines of standard treatment in the EU. As the pivotal study is designed to demonstrate symptom control in advanced cancer patients, placebo plus BSC is considered acceptable as comparator in a palliative setting.

The concomitant use of several anti-cancer therapies and other drugs for symptomatic treatment such as corticosteroids, megesterol etc were restricted during the study. The use of supportive palliative measures, including relevant concomitant medication can be warranted as part of the BSC of the individual patients and this was generally balanced between the treatment arms.

Baseline characteristics

In general, the demographic parameters and baseline characteristics in the ITT population seem to be balanced between the study arms. A total of 122 patients (39%) had KRAS mutation which is in accordance with the expected prevalence. However, no information was collected concerning the BRAF mutation status at baseline, which is also indicative of poor prognosis in CRC patients. No patients received immunotherapy prior to enrolment.

Statistical analysis and conduct of the pivotal study

The applicant has in its response to the Day 120 LoQ described the protocol deviations in more detail. Overall the out of window visits appear to be of minor importance although it must be considered a weakness of the study protocol that it had no specified window for post-infusion vitals. A more serious issue is the inclusion of two patients who did not meet one of the inclusion/exclusion criteria, and four violations occurring due to improper washout timelines which indicates unclear protocol and routines during the study. This adds to the uncertainty regarding the conduct of the pivotal study and hence the validity of the study results.

The applicant stated that the number of patients with missing endpoint data for no obvious reason is low (n=12, 4%) and that they were effectively replaced by the oversampling. Still, this can be an indicator of poor study conduct it has not been possible to find an explanation for why these patients are lacking endpoint data. The occurrence of incorrect calculation resulting in dosing errors in 32 patients implies unclear routines during the study conduct. An even more critical point is that no less than 17 patients in the placebo arm received MABp1 erroneously and this was claimed to be detected during de-identified PK analysis. Taken together all these protocol violations strengthen the impression of a rather unclear study protocol resulting in poor study conduct. Particularly, the proportion of placebo patients received active treatment is considered too high, hampering the quality of data produced in the pivotal study.

The detailed description of blinding, masking and randomisation procedures indicate that these very important issues were handled correctly in the pivotal study.

Efficacy data and additional analyses

A total of 333 patients were randomised to pivotal study (ITT-all randomised); of whose 207 patients received MABp1 and 102 patients received placebo treatment. Twenty-four patients discontinued the study prematurely without having received any dose of study drugs.

The primary analysis population for efficacy evaluation was the ITT population (corresponds to mITT, i.e. subjects who received at least one infusion of study drugs), which consisted of 309 subjects (207 subjects in MABp1 arm and 102 patients in placebo arm). The updated primary analysis in the PP population included 252 subjects (169 subjects in MABp1 arm and 83 patients in placebo arm, respectively).

Analysis of the composite endpoint ORR

The primary efficacy analysis on the ITT population (which actually corresponds to mITT population) showed that the ORR was 33% (68/207) for the MABp1 arm and 19% (19/102) for placebo arm, resulting in a difference in effect size of 14%, which was statistically significant based on a one-sided test (p=0.004). The use of a one-sided test has not been prospectively defined. To convert from two-sided to one-sided test, the applicant reduced the p value for significance to 0.0125 (instead of 0.05), which is considered rather conservative.

Analysis of individual components of the composite endpoint

The analysis of the individual components (i.e. change in LBM and change in disease-related QoL symptoms of pain, fatigue and appetite) did not result in any clinically meaningful or statistically significant differences between the study arms.

LBM endpoint: There were no significant differences in the LBM change from baseline between the MABp1 and the placebo arms at Week 8. Besides, the magnitude of the mean LBM increase (change from baseline, LS mean±SE, mITT population) in the placebo arm (0.60 ±0.32 kg) was slightly higher than that in the MABp1 arm (0.53±0.22 kg) (p=0.87).

QoL domains: Descriptive statistics for the QoL domains of the EORTC QLQ C30 Questionnaire (i.e. mean scores at baseline vs Week 8, and change LS mean) suggest that there were no statistically significant changes in each arms at Week 8 compare to baseline in the QoL scales (global QoL, role function, physical, emotional or social) or disease-related QoL symptoms (pain, appetite and fatigue). Besides, there were no statistically significant differences between the study arms. The observed differences ("change LS mean±SE" scores) in all QoL scales were, however, below the threshold of 10 mean scores, which is usually accepted as clinically relevant difference, i.e. minimal important difference (MID) to distinguish those who have had a true HRQOL benefit from those who have not.

Outcomes (responder rates, %) by individual components of the composite endpoint indicated only small (≤7%) and statistically not significant differences between the study arms in terms of individual endpoints of LBM, Pain, Appetite and Fatigue.

Sensitivity analysis

In order to investigate the impact on the primary outcome, a sensitivity analysis was conducted when only subjects who had an increase in LBM were included in the analysis set (excluding those that maintained pre-existing LBM). When the primary endpoint was re-defined as: ≥1 kg LBM change and stabilization or improvement in 2 of 3 QoL symptoms of fatigue, appetite and pain, a statistically significant difference was observed in CRR (20% for the MABp1 arm vs 9% for the placebo arm, i.e. +11% difference in favour of MABp1, mITT population, one-tailed p=0.0068). However, differences were not statistically significant when cut-off values of ≥0.5 kg, ≥0.75 kg and ≥1.25 kg were used (i.e. +8%, +10% and +7% difference in effect size in favour of MABp1, mITT population, one-tailed p=0.044, p=0.013 and p=0.034, respectively).

Secondary endpoints

Baseline IL-6 levels were well balanced between the study arms in the pivotal study. The applicant stated that IL-6 levels remained stable in the MABp1 arm after 8 weeks of therapy with a mean change of 1.6±1.9 pcg/ml while it increased by an average of 9.90±2.71 pcg/ml in the placebo arm (p=0.012, excluding four outliers from the MABp1 arm). However, the difference was not statistically significant when the outliers were included in the analysis. This suggests that these data were not robust enough to support the efficacy of MABp1. In addition, it should be noted that the mean values of IL-6 were still >10 pg/ml in both study arms both at baseline and at Week 8. This does not seem to indicate any favourable pharmacodynamic effect of MABp1 considering the applicants arguments that an IL-6 level of >10 pg/ml is associated with poor survival in cancer patients compared to that of <10 pg/ml. Consequently, the robustness and clinical relevance of these data remain still uncertain.

For platelet counts, a statistically significant difference between the study arms was shown based on LS mean change. It should be noted that the presented mean platelet counts in both arms (i.e. ranging from 232-260x 10^3/mm) are still within the normal range for the healthy subjects (i.e. 150–450 x 10^3/mm) both at baseline vs

Week 8. Usually, a lower platelet count <150x10^3/mm or a higher count of >450x10^3/mm may be of concern in cancer patients, although there might be some differences regarding the reference values. Consequently, the applicant's claim that MABp1-treatment is related to stabilising the platelet counts is not substantiated. The applicant's hypothesis was based on the exploratory study PT004. However, the presented data from the pivotal study suggest no clinically relevant differences between the study arms. In addition, high standard deviation values for these platelet counts hamper drawing any firm conclusions.

Of note, tumour response was assessed on exploratory basis in the pivotal study. The observed difference between the proportion of the patients with stable disease was 12% in the placebo vs 17% in the MABp1 arms, when compared at baseline vs Week 8. The clinical relevance of this small difference is considered questionable. In addition, objective response rate cannot be assessed as no information has been provided regarding the progression of disease. Further, no data are presented to address partial or complete response in the study population.

Supportive trial 2009-PT004

Of the nine patients achieving response according to the RECIST criteria, one had a partial response and the rest stable disease. However, since no more data have been included in the study report, it is impossible to draw any firm conclusions regarding the tumour responses.

The single arm design of the trial does not enable to conclude that the increase in LBM was the result of a drug effect, even if the applicant claims that the increase seen in LBM in this advanced CRC population may correlate with inhibition of IL-1α.

The small patient population makes it impossible to draw any firm conclusions regarding tumour response and benefit in this heterogeneous population.

Proposed Indication

The applicant claims that the pivotal study supports anti-neoplastic efficacy of MABp1 in terms of conventional outcomes. However, no conventional endpoints were employed in this study, except that the tumour response was assessed on an exploratory basis. According to the latter, the observed difference between the proportions of subjects with stable disease in the placebo patients (12%) vs MABp1 patients (17%), is not considered clinically relevant. It should be emphasised that the presented OS data comparing all responders vs. all non-responders in the study regardless of the study arms is neither relevant for the evaluation of efficacy nor for the wording of indication. Importantly, OS data analysed per treatment arm in the pivotal study did not indicate any survival benefit for MABp1 compared with placebo (6.1 months versus 6.3 months, respectively, log-rank p=0.25).

The applicant argued that the EMA guidance explicitly encourage the use of novel primary endpoints based upon symptoms, stating: "In patients with tumour-related symptoms at baseline, symptom control, if related to anti-tumour effects, is a valid measure of therapeutic activity and may serve as primary endpoint in late line therapy studies, provided that sources of possible bias can be minimised". However, it should be emphasised that it is the applicant's responsibility to design a robust pivotal study to address the intended indication. In this case LBM was used as a surrogate for survival based on an exploratory study which did not provide any robust evidence for this purpose. Of note, the applicant did still not provide further data to justify the validity of LBM as a surrogate for survival. The advice given by the CHMP did not indicate that LBM could be a surrogate for OS, either (please refer to final CHMP SA report, April 2014 - EMEA/H/SA/2676/1/2013/II CORRIGENDUM). The CHMP advised the applicant to include QoL as a co-primary endpoint, as LBM has limited clinical significance on its own in demonstrating the efficacy of MABp1 in control of cancer-related symptoms. Regarding the

prerequisite for a prior weight loss of 5% at baseline (considering only 50% of cancer patients experience such a metabolic dysregulation) or the shortcomings of the DEXA in estimation of LBM, the applicant should have made a thorough analysis on these crucial methodological issues prior to initiating the pivotal study.

Nonetheless, the applicant has subsequently proposed the following indication: "*Human IgG1 monoclonal antibody specific for human interleukin-1 alpha XBiotech is indicated for the control or relief of debilitating symptoms associated with advanced colorectal cancer*".

2.5.4. Conclusions on the clinical efficacy

Based on the presented data derived from one pivotal trial, the claimed efficacy in terms of the primary composite endpoint CRR (i.e. +14% difference in favour of MABp1, mITT) is questioned as it is not possible to ascertain how individual components of this endpoint might have contributed to the efficacy. Due to the lack of a clear evidence in support of beneficial effects of MABp1 on both components of the composite endpoint, efficacy cannot be established based on the primary analysis. In addition, in the lack of important baseline data regarding the degree of patients' prior weight loss as well as due to the inclusion of substantial number of patients only based on the IL-6 threshold, it is difficult to evaluate the clinical relevance of the observed efficacy in a sufficient context. Taking also into consideration the lack of correlation to any meaningful changes for the QoL of the MABp1-treated patients, clinical relevance of the observed limited efficacy is unclear.

2.6. Clinical safety

The safety data presented are currently based on two clinical trials; a phase I/II study 2009-PT004 and a Phase III study 2014-PT026.

Patient exposure

Study 2009-PT004:

For the phase I/II study, exposure duration is calculated based on weeks between last infusion date and Cycle 1 infusion date. Different doses up to 3.75 mg/kg every two weeks are given in this study. The following Table 15 and Table 16 present the exposure duration across study groups.

Table 15: Exposure duration by population subgroups in study 2009-PT004

Study Population	Exposure Duration (weeks)	
	N	Median (IQR)
All Subjects	52	6 (3-11)
Gender		
Female	28	6 (3-13)
Male	24	6 (0.1-9)
Race		
Asian	3	2 (0.1-13)
African American	4	6 (3-10)
Hispanic	5	3 (3-8)
White	40	6 (3-11)
Age Group		
Age group <65yr	35	6 (2-10)
Age group 65-75yr	10	6 (3-13)
Age group >75yr	7	4 (3-10)

IQR: interquartile range

Table 16: Distribution of Exposure Duration (weeks) in study 2009-PT004

Number of Weeks	Patients Exposed, n (%)
<2 weeks	10 (19%)
2 to 4 weeks	10 (19%)
>4 to 8 weeks	16 (31%)
>8 to 12 weeks	6 (12%)
>12 weeks	10 (19%)

Study 2014-PT026:

For the phase III study, exposure duration was calculated as Last infusion date – C1D1 infusion date. The dose given is 7.5 mg/kg every 2 weeks. The following tables present the exposure duration across study groups and between arms.

Table 17: Exposure Duration by Population Subgroups (ITT) in study 2014-PT026

	Xilonix+BSC (N=207)			Placebo+BSC (N=102)		
	N	Mean±SD	Median (IQR)	N	Mean±SD	Median (IQR)
All Subjects	207	39±11	43(42-43)	102	38±13	43(42-43)
Female	79	40±11	43(42-43)	43	36±14	43(29-43)
Male	128	38±12	43(42-43)	59	40±11	43(43-43)
Age group=<65yr	112	40±11	43(42-43)	60	37±14	43(41.5-43)
Age group=65-75yr	72	37±12	43(35-43)	32	39±10	43(42.5-44)
Age group=>75yr	23	38±12	43(42-44)	10	37±14	43(41.5-43)

IQR: interquartile range

Table 18: Exposure in Study Arms by Days in study 2014-PT026

Number of Exposure Days	Xilonix+BSC, n (%)	Placebo+BSC, n (%)
≤15 days	20 (10%)	11 (11%)
16 to 30 days	20 (10%)	8 (8%)
31 to 45 days	155 (74%)	77 (75%)
>45 days	12 (6%)	6 (6%)

Adverse events

Study 2009-PT004

In study 2009-PT004, all patients with refractory solid tumours, who received MABp1 were included in the safety analysis. The maximal tolerated dose (MTD) was undefined due to no observed dose limiting toxicities (DLTs), and the highest dose administered was considered the Recommended Phase 2 Dose (RP2D). Over 300 infusions were administered without any infusion reactions. No patients required dose reductions or delays for toxicity, no patients discontinued therapy for toxicity, and there were no treatment related deaths.

Of the 52 patients enrolled in the study, 46 experienced at least one AE and 19 patients had at least one SAE.

The most common AEs reported (≥10%) were: fatigue, proteinuria, anorexia, nausea, constipation, dyspnoea, hyperkalaemia, hypoalbuminemia and vomiting. With regard to SOCs, AEs were most frequently reported in Metabolism and nutritional disorders (50%, driven by anorexia, hyperkalaemia and hypoalbuminemia), Gastrointestinal disorders (46.2%, driven by nausea, vomiting and constipation), and General disorders and administration site conditions (44.2%, driven by fatigue and oedema peripheral).

The most common “possibly related” adverse events were proteinuria 22% (11/52), nausea 13% (7/52) and fatigue 13% (7/52). The most frequent grade 3-4 adverse events were fatigue 3.8% (2/52 patients grade 3) and 1.9% (1/52 grade 4), shortness of breath 3.8% (2/52), and headache 3.8% (2/52). There was one serious adverse event (SAE) listed as possibly drug related: one case of pneumonia in a patient with NSCLC. In all, 3 deaths occurred in the study; two (3.8%) patients had grade 5 events (death due to disease progression), and one patient died due to worsening of respiratory function, which all were considered unrelated to therapy.

A summary of all AEs in subjects treated with MABp1 in Study 2009-PT004 is provided in Table 19.

Table 19: 2009-PT004 AEs (regardless of posited relationship to drug) (N = 52)

Adverse Event	Grade 1-2	Grade 3	Grade 4	Grade 5
Fatigue	12 (23.1%)	2 (3.8%)	1 (1.9%)	
Proteinuria*	12 (23.1%)			
Anorexia	9 (17.3%)			
Nausea	9 (17.3%)	1 (1.9%)		
Constipation	6 (11.5%)	1 (1.9%)		
Dyspnea	5 (9.6%)	2 (3.8%)		
Hyperkalemia	5 (9.6%)			
Hypoalbuminemia	5 (9.6%)			
Vomiting	5 (9.6%)			
Acute kidney injury	1 (1.9%)	1 (1.9%)		
Anemia	3 (5.8%)	1 (1.9%)		
Aspartate aminotransferase increased	1 (1.9%)	1 (1.9%)		
Baseline Thrombocytopenia		1 (1.9%)		
Focal Seizure of the Tongue		1 (1.9%)		
Generalized weakness		1 (1.9%)		
Headache	2 (3.8%)	1 (1.9%)	1 (1.9%)	
Intractable Pain		1 (1.9%)		
Lymphopenia	2 (3.8%)	1 (1.9%)		
Problem awakening from sedation for MRI		1 (1.9%)		
Uncontrolled pain		1 (1.9%)		
Cramps Leg			1 (1.9%)	
Diarrhea	3 (5.8%)		1 (1.9%)	
Disease progression leading to death			1 (1.9%)	
Ear irritation			1 (1.9%)	
Muscle Cramp			1 (1.9%)	
Progression of disease leading to death				2 (3.8%)

*11/52 patients had proteinuria (as measured by urine dipstick) that was "possibly" related to MABp1; 4 of these patients had grade 2 proteinuria. The remaining 7 patients with possibly related proteinuria had grade 1, which correlates poorly with true albuminuria as measured by 24 hour collection36.

Table 20 shows all AEs assessed as possibly related to treatment by the reporting investigators and which occurred in more than 1 patient.

Table 20: Drug-related Adverse Events in study 2009-PT004

Adverse Event (Preferred Term)	No of Subjects	Percent
Proteinuria	11	21.2%
Nausea	7	13.5%
Fatique	6	11.5%
Constipation	2	3.8%
Thrombocytopenia	2	3.8%
Diarrhea	2	3.8%

SAEs were experienced by 19/52 patients in this study. SAEs occurring in at least two subjects were: disesase progression (PD, 2 pts), pain (2 pts) and dyspnoea (3 pts). With regard to SOCs, the most frequent (≥2 patients) SAEs occurred in Gastrointestinal disorders (5 pts), Respiratory, thoracic and mediastinal disorders (5 pts), General disorders and administration site conditions (5 pts) and Nervous system disorders (2 pts).

Study 2014-PT026

In this trial, according to the applicant, over 1200 doses of MABp1 were administered at 7.5 mg/kg to refractory, metastatic CRC patients with cancer-associated symptoms at baseline and ECOG performance status 1 and 2.

The protocol defined the ITT population to consist of all randomised patients who received at least one infusion of MABp1. Therefore, the 24 patients who discontinued prior to receiving a single dose of MABp1 were excluded from the analysis dataset. The analysis dataset consisted of 309 (207 MABp1 and 102 placebo) patients.

Safety Data

All untoward events occurring between Cycle 1 Day 1 and 30 days following the last administration of the study drug were recorded on the eCRF, regardless of whether they were considered related to study drug or not. All AEs were graded according to the CTCAE version 4.0.

Assessment of haematology and chemistry labs was performed by a central diagnostic lab, per the study lab manual and core lab specifications document.

Safety Data Monitoring

Blinded lab data and adverse event data were reviewed at regular intervals by the XBiotech Medical Safety Officer. An independent data monitoring committee (IDMC) reviewed unblinded safety data at 50% of total patient accrual.

A total of 159 (77%) patients in the MABp1 arm and 79 (77%) in Placebo arm had at least one adverse event. Serious adverse events (SAE) were reported in 44 (28%) of patients who received MABp1 and 26 (33%) of patients who received placebo.

Serious infections were observed in patients receiving MABp1 at the 7.5 mg/kg dose including urosepsis, pyonephrosis, upper respiratory infection, peritonitis, and bronchopneumonia. All but one of these events appeared to be secondary to disease progression due to the patients' underlying colorectal cancer. More urinary tract infections (grade 1-2) occurred in the MABp1 group (10 of 159) versus placebo (3 of 79). No opportunistic infections were reported in either group.

In patients that received MABp1 at 7.5 mg/kg for metastatic colorectal cancer, the most common AEs reported (>10%) were abdominal pain, peripheral oedema, fatigue, anaemia, constipation, decrease in weight, asthenia, decreased appetite, and nausea. The majority of these events were grade 1 or 2, and appeared to be related to the underlying CRC. The prevalence of these events was similar in the MABp1 and placebo groups.

Disposition of patients and reasons for discontinuation from study are presented in Table 21.

Table 21: Patient Population and Disposition (ITT) for study 2014-PT026

	Treatment Group		
	Xilonix+BSC (N= 222)** n (%)	Placebo+BSC (111) n (%)	Total N=333
Randomized	222	111	333
Never treated	15 (7)	9 (8)	24 (7)
Intent to Treat Population (ITT)*	207 (93)	102 (92)	309 (93)
Discontinued from study	38 (17)	19 (17)	57 (17)
Reason for discontinuation			
Adverse Event	7 (3)	7 (6)	14 (4)
Death	9 (4)	5 (5)	14 (4)
Lost to Follow-Up	3 (1)	0 (0)	3 (1)
Other	8 (4)	3 (3)	11 (3)
Removed from Study by PI	6 (3)	3 (3)	9 (3)
Subject Withdrew Consent	5 (2)	1 (1)	6 (2)

*ITT: All patients who were randomized and received at least one infusion of study drug
**Percentages are based on all randomized patients

Display of Adverse Events

The following tables show AEs by PT occurring in >3% in the MABp1 and Placebo arms in study 2014-PT026.

Table 22: AEs by preferred term occurring in >3% in study 2014-PT026

MedDRA Preferred Term	Number of patients by Preferred Term (% of total patients with AE)		
	Placebo+BSC (n= 79)	Xilonix+BSC (n= 159)	Total (n= 238)
Abdominal pain	12 (15.19%)	36 (22.64%)	48 (20.17%)
Fatigue	13 (16.46%)	27 (16.98%)	40 (16.81%)
Edema peripheral	7 (8.86%)	28 (17.61%)	35 (14.71%)
Nausea	12 (15.19%)	18 (11.32%)	30 (12.61%)
Anemia	8 (10.13%)	21 (13.21%)	29 (12.18%)
Asthenia	10 (12.66%)	19 (11.95%)	29 (12.18%)
Weight decreased	8 (10.13%)	21 (13.21%)	29 (12.18%)
Constipation	6 (7.59%)	21 (13.21%)	27 (11.34%)
Decreased appetite	8 (10.13%)	18 (11.32%)	26 (10.92%)
Ascites	7 (8.86%)	12 (7.55%)	19 (7.98%)
Vomiting	6 (7.59%)	12 (7.55%)	18 (7.56%)
Dyspnea	5 (6.33%)	12 (7.55%)	17 (7.14%)
Abdominal pain upper	4 (5.06%)	12 (7.55%)	16 (6.72%)
Aspartate aminotransferase increased	5 (6.33%)	10 (6.29%)	15 (6.30%)
Blood alkaline phosphatase increased	3 (3.80%)	11 (6.92%)	14 (5.88%)
Disease progression	5 (6.33%)	9 (5.66%)	14 (5.88%)
Pyrexia	4 (5.06%)	9 (5.66%)	13 (5.46%)
Urinary tract infection	3 (3.80%)	10 (6.29%)	13 (5.46%)
Blood bilirubin increased	3 (3.80%)	9 (5.66%)	12 (5.04%)
Diarrhea	2 (2.53%)	9 (5.66%)	11 (4.62%)
Back pain	2 (2.53%)	8 (5.03%)	10 (4.20%)
Anxiety	3 (3.80%)	4 (2.52%)	7 (2.94%)
Arthralgia	4 (5.06%)	3 (1.89%)	7 (2.94%)
Chest pain	3 (3.80%)	4 (2.52%)	7 (2.94%)
Cough	3 (3.80%)	4 (2.52%)	7 (2.94%)

Twenty-six (26) patients experienced treatment-related AEs, of which the majority were grade 1/2, and only few of grade 3. None were of grade 4 or grade 5. Treatment-related AEs occurring in ≥ 1% (more than 2 pts) were pheripheral oedema (5 or 7 pts), nausea (4 pts) and possibly anaemia (unclear this if appeared in 2 or 3 pts in the latter case).

In contrast, 153 patients experienced AEs that were not considered related.

Infections

There were more infections in the MABp1 group compared to placebo:

Table 23: Infections observed in study 2014-PT026

	Xilonix +BSC	Placebo +BSC
N	207	102
AE	24 (11.6%)	8 (7.8%)
SAE	5 (2.4%)	0

The majority of these events were not serious and none of the events were deemed to be associated with MABp1 therapy. These were bronchitis, bronchopneumonia, cystitis, influenza, lower respiratory tract infection, nasopharyngitis, oesophageal candidiasis, pyonephrosis, sputum purulent, upper respiratory infection, upper respiratory tract infection bacterial, viral infection, urosepsis (1 patient each), upper respiratory tract infection (2 pts), oral candidiasis (2 pts) and urinary tract infection (10 pts).

All 5 of the infection SAEs in the MABp1 treatment arm were considered as “not related” by both the investigator and the sponsor, see Serious Adverse Events. All of the adverse events of infection in the MABp1 treatment arm were also assessed as “not related”. Four of the 5 SAEs recovered. One SAE of peritonitis resulted in death. In all, 4/5 of the SAEs were considered severe and one was a mild SAE consisting of and Upper Respiratory Tract Infection, which resolved with antibiotics. Of the four severe SAEs, two were urinary tract infections associated with obstruction from the underlying tumour, one bronchopneumonia in a patient with pulmonary metastases and one report of peritonitis following surgery for a mechanical ileus. There were no reports of opportunistic infections, tuberculosis reactivation, Progressive multifocal leukoencephalopathy (PML) or demyelination.

Updated information received from the Applicant during the procedure:

A closer examination of the SAEs for the 8 week period revealed two additional SAEs of infections that had been previously coded based on their organ system, rather than as infections, The SAEs were a case of “pneumonitis” reported in the MABp1 group, and a patient who developed an infectious gastroenteritis in the placebo group. None of these SAEs were considered to be related to treatment. Updated AE and SAE rates are given to take into account these two reports, see Table below.

Table 24: Infection events after 8 weeks of therapy PT026 (updated)

	Xilonix N=207	**Placebo N=102**	**p-value (Fisher's Exact Test)**
Infection AEs	25 (12.1%)	9 (8.8%)	0.44
Infection SAEs	6 (2.9%)	1 (1%)	0.43

Infection rates in the open label extension compared to the 8 week study are given and the incidence of AEs and SAEs of infections in the open label study was similar to the incidence in the MABp1 of the 8 week study, see Table below.

Table 25: Infection events in open label phase of PT026 compared to 8 week study

	Open Label extension Xilonix N=202	8 week study Xilonix N= 207	8 week study Placebo N=102
Infection AEs	26 (12.9%)	25 (12.1%)	9 (8.8%)
Infection SAEs	7 (3.5%)	6 (2.9%)	1 (1%)

Infection is a common event in CRC patients having received chemotherapy, and the rates observed in this study in the MABp1 arm seem to be lower than the placebo level observed in other studies which the Applicant refers to. However, these studies might have had a longer duration than only 8 weeks, which may contribute to a higher frequency, as well.

The imbalance in infection related AEs and SAEs is present, both during the 8 weeks study period and the extension phase, and in disfavour of patients treated with MABp1 compared with placebo. The number of events was, however, relatively small. There was no imbalance in deaths caused by infections between the treatment arms, although also here numbers are very limited. An increased risk of infection with MABp1 can, however, at present not be dismissed based on the available clinical data and on previous experience with agents that inhibit the IL-1 system.

Infusions reactions

In the 2014-PT026 study 2 infusion reactions occurred (grade 1 and grade 2), which were not severe and these subjects were able to continue on study. There were no SAEs of immunogenicity reactions including infusion reactions.

Immunosuppression

Immunosuppression is considered a theoretical risk of the antibody. According to the applicant's protocol for study 2014-PT026, there is no evidence of immunosuppression or increased susceptibility to infection of any kind in patients treated with MABp1, and there have been no human anti-human antibodies against MABp1 detected. This was claimed at a stage where over 140 patients had been treated with MABp1 and no infusion reactions had been observed.

Thrombocytopenia

Thrombocytopenia developed in 5% of MABp1 patients, versus 2% of placebo. There were no grade 3 or 4 events of thrombocytopenia and no episodes of bleeding associated with thrombocytopenia.

Proteinuria

Proteinuria had previously been identified as a potential side effect of therapy with MABp1. However, an analysis of proteinuria showed that in subjects with no proteinuria at baseline, 14% in the MABp1 group subsequently developed proteinuria, versus 16% in the placebo group. There were no grade 3 or 4 events, and these events were not associated with renal insufficiency.

Serious adverse event/deaths/other significant events

Serious adverse events

Study 2009-PT004:

SAEs were experienced by 19/52 patients in this study. SAEs occurring in at least two subjects were disease progression (PD, 2 pts), pain (2 pts) and dyspnoea (3 pts). With regard to SOCs, the most frequent (≥2 patients)

SAEs occurred in Gastrointestinal disorders (5 pts), Respiratory, thoracic and mediastinal disorders (5 pts), General disorders and administration site conditions (5 pts) and Nervous system disorders (2 pts). There was one SAE listed as possibly drug related—pneumonia in a patient with NSCLC. Two (3.8%) patients had grade 5 events (death due to PD), which were considered unrelated to therapy, and one patient died due to worsening of respiratory function.

Study 2014-PT026

An overview of all SAEs observed in both arms in study 2014-PT026 is given in Table 26.

In the PT026 study, there was a slightly lower incidence of SAEs in the treatment arm compared to placebo. No deaths were related to study drug treatment, and all were consistent with progression of the subjects' underlying tumour.

There were 47 SAEs in MABp1 arm, involving a total of 44 patients. 37 of these events were associated with documented or suspected disease progression. The remaining 10 events were considered unlikely or not related to therapy.

There were 33 SAEs, occurring in 26 patients, in the placebo arm. 24 of these events were associated with documented or suspected disease progression. Of the remaining 9 events none were assessed as related by the Principal Investigator (PI) and Sponsor, and this could be agreed.

According to the Applicant, there were only two SAEs that occurred during the study that were assessed as possibly or probably related to therapy. These are supposedly discussed in the Clinical Study Report (CSR). When looking into the CSR, all SAEs observed were apparently not related to therapy, except for one SUSAR of Right Forearm Deep Venous Thrombosis that was reported in a patient on the MABp1 arm and assessed as "possibly related".

SAEs were most frequently reported in the SOCs General disorders and administration site conditions (14 pts on MABp1 vs. 9 pts on placebo) and Gastrointestinal disorders (7 pts. vs. 5 pts). Of note, in the Infections and infestations SOC there were 5 serious events in MABp1 arm versus 0 in the placebo arm.

The applicant claims that other striking clinical observations, while not prospectively considered as endpoints, were made in the Phase III study. Serious adverse event (SAE) reporting was not a planned secondary analysis and the study was not powered to demonstrate differences in SAEs between treatment and placebo groups. However, the 35% reduction in the risk of SAEs in the treatment arm relative to placebo nonetheless appears to be an extraordinary finding (p=0.062). According to the applicant, this may be the first report, in a placebo controlled clinical study with an anticancer agent, of a reduced incidence of SAEs in a treatment arm.

Table 26: All Serious Adverse Events by CTCAE Grade (2014-PT026)

Body System or Organ Class		Group: Xilonix+BCS; SAEs (N=44) Statistics n (%)					Group: Placebo+BCS; SAEs (N= 26) Statistics n (%)				
	AE Preferred Term	Grade I/II	Grade III	Grade IV	Grade V	Total	Grade I/II	Grade III	Grade IV	Grade V	Total
Blood and lymphatic system disorders		1 (2.3%)	2 (4.5%)			2 (4.5%)		3 (11.5%)		1 (3.8%)	4 (15.4%)
	Anaemia	1 (2.3%)	2 (4.5%)			2 (4.5%)		3 (11.5%)		1 (3.8%)	4 (15.4%)
Cardiac disorders							1 (3.8%)				1 (3.8%)
	Acute myocardial infarction						1 (3.8%)				1 (3.8%)
Gastrointestinal disorders		1 (2.3%)	4 (9.1%)	1 (2.3%)		6 (13.6%)		3 (11.5%)	2 (7.7%)		5 (19.2%)
	Abdominal pain		1 (2.3%)			1 (2.3%)					
	Anal haemorrhage	1 (2.3%)				1 (2.3%)					
	Gastroenteritis							1 (3.8%)			1 (3.8%)
	Ileal stenosis							1 (3.8%)			1 (3.8%)
	Ileus			1 (2.3%)		1 (2.3%)			2 (7.7%)		2 (7.7%)
	Rectal haemorrhage		1 (2.3%)			1 (2.3%)					
	Subileus		1 (2.3%)			1 (2.3%)					
	Vomiting		1 (2.3%)			1 (2.3%)		1 (3.8%)			1 (3.8%)
General disorders and administration site			3 (6.8%)		12 (27.3%)	15 (34.1%)		5 (19.2%)		4 (15.4%)	9 (34.6%)
	Asthenia							1 (3.8%)			1 (3.8%)
	Condition aggravated		1 (2.3%)		1 (2.3%)	2 (4.5%)		2 (7.7%)			2 (7.7%)
	Death				1 (2.3%)	1 (2.3%)				2 (7.7%)	2 (7.7%)
	Disease progression		1 (2.3%)		8 (18.2%)	9 (20.5%)		1 (3.8%)		1 (3.8%)	2 (7.7%)
	Disease progression/ Death				1 (2.3%)	1 (2.3%)				1 (3.8%)	1 (3.8%)
	Fatigue		1 (2.3%)			1 (2.3%)		1 (3.8%)			1 (3.8%)
	Obstruction				1 (2.3%)	1 (2.3%)					
Hepatobiliary disorders			3 (6.8%)			3 (6.8%)		2 (7.7%)		1 (3.8%)	3 (11.5%)
	Hepatic failure		2 (4.5%)			2 (4.5%)		2 (7.7%)		1 (3.8%)	3 (11.5%)
	jaundice extrahepatic obstructive		1 (2.3%)			1 (2.3%)					
Infections and infestations		1 (2.3%)	3 (6.8%)		1 (2.3%)	5 (11.4%)					
	Bronchopneumonia		1 (2.3%)			1 (2.3%)					
	Peritonitis				1 (2.3%)	1 (2.3%)					
	Pyonephrosis		1 (2.3%)			1 (2.3%)					
	Upper respiratory infection	1 (2.3%)				1 (2.3%)					
	urosepsis		1 (2.3%)			1 (2.3%)					
Injury, poisoning and procedural complications			1 (2.3%)			1 (2.3%)					
	Hip fracture		1 (2.3%)			1 (2.3%)					
Investigations				1 (2.3%)		1 (2.3%)					
	Alanine aminotransferase increased			1 (2.3%)		1 (2.3%)					
Metabolism and nutrition disorders			1 (2.3%)		1 (2.3%)	2 (4.5%)					
	Dehydration		1 (2.3%)		1 (2.3%)	2 (4.5%)					
Neoplasms benign, malignant and unspecified (incl cysts and polyps)					1 (2.3%)	1 (2.3%)	1 (3.8%)				1 (3.8%)
	metastases to central nervous system				1 (2.3%)	1 (2.3%)					
	Metastases to central nervous system						1 (3.8%)				1 (3.8%)
Nervous system disorders		1 (2.3%)	1 (2.3%)			2 (4.5%)	1 (3.8%)	1 (3.8%)			2 (7.7%)
	Cerebrovascular accident	1 (2.3%)				1 (2.3%)					
	Metastases to CNS						1 (3.8%)				1 (3.8%)
	Spinal cord compression							1 (3.8%)			1 (3.8%)
	vertigo/metastases to CNS		1 (2.3%)			1 (2.3%)					
Renal and urinary disorders					1 (2.3%)	1 (2.3%)		2 (7.7%)		1 (3.8%)	3 (11.5%)
	Acute renal failure							1 (3.8%)			1 (3.8%)
	renal failure									1 (3.8%)	1 (3.8%)
	Renal impairment				1 (2.3%)	1 (2.3%)					
	Urinary retention							1 (3.8%)			1 (3.8%)
Respiratory, thoracic and mediastinal disorders		2 (4.5%)	1 (2.3%)	2 (4.5%)	1 (2.3%)	6 (13.6%)				2 (7.7%)	2 (7.7%)
	Cardiopulmonary failure				1 (2.3%)	1 (2.3%)					
	Dyspnoea	1 (2.3%)		1 (2.3%)		2 (4.5%)				1 (3.8%)	1 (3.8%)
	Hypoxia	1 (2.3%)				1 (2.3%)					
	Pneumonitis		1 (2.3%)			1 (2.3%)					
	Respiratory failure			1 (2.3%)		1 (2.3%)				1 (3.8%)	1 (3.8%)
Surgical and medical procedures							1 (3.8%)				1 (3.8%)
	Hospitalization						1 (3.8%)				1 (3.8%)
Vascular disorders		1 (2.3%)	1 (2.3%)			2 (4.5%)					
	Deep vein thrombosis		1 (2.3%)			1 (2.3%)					
	Embolism	1 (2.3%)				1 (2.3%)				1 (3.8%)	1 (3.8%)

There was a lower incidence of SAEs in the MABp1 arm as compared to placebo. SAEs occurred in 26 (25.5%) of 102 placebo patients versus 44 (21.3%) of 207 MABp1 patients.

Selected SAEs from Study 2014-PT026:

The SAEs in this table below are serious infections that occurred in the MABp1 arm, as well as a SUSAR of Right Forearm Deep Venous Thrombosis that was reported in a patient on the MABp1 arm. Brief narratives of these events are provided below. As stated previously, all 5 of the infections SAEs in the MABp1 treatment arm were considered not related by both the investigator and the sponsor.

Table 27: Other Serious Adverse Events

Patient	Treatment	Adverse Event	SOC	Date of Onset	Date of Resolution	CTCAE Grade	Relationship to Study Drug
	Xilonix+BSC	urosepsis	Infections and infestations	9/9/14	9/25/14	3	Not Related
	Xilonix+BSC	pyonephrosis	Infections and infestations	7/8/15	7/10/15	3	Not Related
	Xilonix+BSC	Possible Upper respiratory Infection	Infections and infestations	6/6/15	6/13/15	1	Not Related
	Xilonix+BSC	Right Forearm deep venous thrombosis	Vascular disorders	4/23/15	5/18/15	2	Probably Related
	Xilonix+BSC	peritonitis	Infections and infestations	6/16/15	7/25/15	5	Not Related
	Xilonix+BSC	bronchopneumonia	Infections and infestations	10/4/15	10/9/15	3	Unlikely to be Related

For the serious infections observed, 4 of the 5 appeared to be related to the subject's underlying tumour and 5 of the infections resolved promptly with antibiotic therapy.

Deaths

Study 2009-PT004:

In total three cases of death occurred in this study:

- Two deaths were attributed to progressive disease and were determined to be unrelated to study medication.
- A 56 year old male subject with a history of non-small cell lung cancer. This subject was admitted to the hospital on 12 November 2012 with progressively worsening shortness of breath, which was attributed to COPD exacerbation and klebsiella pneumonia. Because his respiratory status was not improving, the subject was discontinued from therapy and plans for discharge to outpatient hospice were initiated. The subject continued to worsen however, and died in the hospital on 27 November 2012.

All these patients received MABp1 doses at 3.75 mg/kg i.v.

Study 2014-PT026:

In study **2014-PT026**, a total of 18 SAEs resulting in 17 deaths occurred, of which none were considered related to treatment by the investigator. These were: metastases to CNS, disease progression (4 pts), condition aggravated (2 pts), death NOS, renal impairment, obstruction, hepatic failure, ileus/peritonitis, dehydration, respiratory failure, hip fracture, cardiopulmonary failure. Data on one fatal case in the MABp1 arm was apparently not included in the response and should be provided. It is not possible to conclude on whether all of the observed deaths in this study are related to MABp1 or not, because there is missing information with regard to some of the fatalities. However, it is agreed that most of the cases seem to be unrelated to treatment, but due to disease progression.

The events resulting in death for 11 patients randomized to placebo are: anemia/fatigue, PD, dyspnea, renal failure, liver failure/ PD, liver failure/ ileus, respiratory failure, thromboembolism, general health deterioration, (pulmonary) thromboembolic event and sudden death NOS. All these deaths were not considered related to treatment or as not unexpected by investigator and/or sponsor

As such, there is no clustering of events leading to death in the either the MABp1 or the placebo arm, which is reassuring. All deaths are possibly related to disease progression.

Laboratory findings

Study 2009-PT004

Thrombocytopenia

In study **2009-PT004**, there were 4 of 52 patients with an apparent decrease in platelet counts after initiation of treatment. These 4 instances of thrombocytopenia, all appeared to coincide with disease progression.

Proteinuria

The most common AE in study **2009-PT004** was proteinuria, and 4 of 12 events were grade II (2+) as measured by urine dipstick. The observed macro-haematuria in 2 of these patients was probably due to their ureteral stents, and the remaining patients had pre-existing proteinuria prior to MABp1 administration. On urinalysis the presence of blood confounds the reading of protein on the dipstick and may cause falsely elevated results. Also, these subjects had no changes in creatinine levels, so glomerular nephritis was unlikely.

As for the grade I proteinuria, this has been shown to have a poor correlation with true albuminuria as measured by 24 hour collection. Based upon the lack of treatment emergent proteinuria in other trials using MABp1, it is unlikely that this finding is truly related to MABp1 administration.

None of the observed SAEs (a total of 5 SAEs occurring in 2 pts) related to laboratory abnormalities in this study (2009-PT004) were considered related to MABp1 treatment.

Study 2014-PT026

In study **2014-PT026,** 5 clinically significant abnormalities were reported as SAEs (3 cases of anemia, 1 pts each of poor renal function and ALT increased) in 4 patients. None of these events were considered related to MABp1. The SAEs in this table are laboratory abnormalities that were reported as serious adverse events.

According to the applicant, there have been no adverse changes in vital signs, physical findings, or other observations related to safety to report from either the PT004 or PT026 trial.

Table 28: Selected laboratory test abnormalities by study group in 2014-PT026

Laboratory Parameter	Xilonix+BSC (207)			Placebo+BSC		
	CTCAE Grade			CTCAE Grade		
	All (%)	3 (%)	4 (%)	All (%)	3 (%)	4 (%)
Anemia	17	2	0	15	0	0
Thrombocytopenia	5	<1	0	2	0	0
Neutropenia	1	0	0	2	0	0
Lymphopenia	17	1	<1	18	0	0
Leukopenia	3	0	0	2	0	0
Elevated Creatinine	0	0	0	2	2	0
Proteinuria[1]	14	0	0	16	0	0

1Proteinuria was defined as any patient that had no proteinuria at baseline, and then subsequently developed 1+ or greater proteinuria as measured by urine dipstick at any follow up visit.

Table 29: Individual Clinically Significant Abnormalities in 2014-PT026

Patient	Treatment	Adverse Event	Date of Onset	Date of Resolution	CTCAE Grade	Relationship to Study Drug
	Xilonix+BSC	Anemia	9/21/15	9/28/15	3	Not Related
	Xilonix+BSC	Anemia	9/21/15	10/12/15	3	Unlikely to be Related
	Xilonix+BSC	Anemia	10/26/15	11/3/15	2	Unlikely to be Related
	Xilonix+BSC	Poor renal function.	5/19/15	5/21/15	5	Not Related
	Xilonix+BSC	alanine aminotransferase increased	5/11/15	5/25/15	4	Not Related

In conclusion, proteinuria and thrombocytopenia were observed in study **2009-PT004**, as mentioned under adverse events, and some cases were assessed as possibly related to treatment with MABp1. Based upon observations from the **2014-PT026** study though, there does not appear to be an increased risk of either thrombocytopenia or proteinuria with MABp1 therapy. Still, the total numbers of events is rather small and no firm conclusions can be drawn.

Safety in special populations

Patients with moderate to severe hepatic impairment

Only patients with adequate hepatic function (total bilirubin ≤1.5 times the upper limit of normal, ALT ≤2 times the upper limit of normal, or ≤3 times the upper limit of normal for patients with known liver metastases) have been investigated to date.

Patients with severe renal impairment

Only patients with adequate renal function (serum creatinine ≤1.5 times the upper limit of normal) have been investigated to date.

Elderly, children, and pregnant and breast-feeding women

According to the applicant, no differences have been observed in the safety profile between patients under the age of 65 and those 65 and older.

MABp1 has not been studied in pregnant or breast-feeding women and not in children.

Immunological events

In study 2009-PT004, over 300 infusions were administered without any infusion reactions. In the pivotal study 2014-PT026 over 1200 doses were given, according to the applicant, and 2 infusion reactions were observed. These infusion reactions were not severe (grade 1 and grade 2) and subjects were able to continue on study. There were no SAEs of immunogenicity reactions including infusion reactions.

The Applicant provided an adequate of overview of validation results for the anti-drug-antibody assays and updated results on immunogenicity testing for Anti-MABp1 antibody levels following MABp1 treatment. No significant level of immunogenicity was observed although ~ 3% (6/204) of patients displayed IgG4 values above LLOQ. These Ab's were not MABp1 specific, and hence not likely to be the result of MABp1 exposure. Results for other Ig subtypes remained below LLOQ.

Infections, infusion reactions and immunosuppression are discussed under Adverse Events heading of this AR.

Safety related to drug-drug interactions and other interactions

Drug interactions are discussed in Section 3.4.1, Pharmacokinetics.

Discontinuation due to adverse events

There is no section in the dossier describing discontinuations due to AEs in detail.

For study **2009-PT004** it is stated that no patients required dose reductions or delays for toxicity and that no patients discontinued therapy due to toxicity. However, no reasons for discontinuations are given.

For the pivotal study, **2014-PT026**, similar proportions (17%) in each arm discontinued treatment – 38 pts on MABp1 and 19 pts on placebo. Reasons for discontinuation were primarily due to AEs (7 pts in each arm; which constitute 3% on MABp1 and 6% on placebo). Similar proportions were due to "Deaths" (9 pts on MABp1, 5 on placebo), "Removed from study by principal investigator" (6 pts vs. 3 pts) and "Other" (8 pts vs. 3 pts), without specifying causes or specific AEs.

2.6.1. Discussion on clinical safety

The present application for MABp1 is intended for the control or relief of debilitating symptoms associated with advanced colorectal cancer.

Safety databases and patient exposure

Two studies were performed in advanced cancer patients.

Briefly, Study **2009-PT004** was an open label, phase I/II dose escalation and expansion cohort in patients (N=52) with refractory solid tumours of great diversity (in all 18 different tumour types), of which 14 (27%) had colorectal cancer.

The pivotal study **2014-PT026** is a phase III registration study (double-blind, randomized, placebo-controlled) comparing MABp1 + BSC (N=207), with placebo + BSC (N=102) in refractory patients with mCRC exhibiting significant cancer-related symptoms.

Study 2009-PT004

Of the 52 patients in the study, 46 experienced at least one AE and 19 patients had at least one SAE. The most common AEs reported *(≥10%)* were: fatigue, proteinuria, anorexia, nausea, constipation, dyspnea, hyperkalemia, hypoalbuminemia and vomiting. The most common (≥10%) drug-related AEs were proteinuria, nausea and fatigue. The most frequent grade 3-4 AEs were fatigue (2 pts), shortness of breath (2 or 3 pts), and headache (2 pts).

SAEs occurring in at least two subjects were disease progression (PD, 2 pts), pain (2 pts) and dyspnoea (3 pts). There was one SAE listed as possibly drug related: pneumonia in a patient with NSCLC. Two (3.8%) patients had grade 5 events (death due to PD), which were considered unrelated to therapy, and one patient died due to worsening of respiratory function.

No patients required dose reductions or delays for toxicity, and no patients discontinued therapy for toxicity, however, the doses administered in this study were much lower than the intended dose for clinical use.

Pivotal study 2014-PT026

Adverse events

Common AEs: In study 2014-PT026, 238 pts experienced at least one AE, of which 79/102 (77%) in the placebo arm and 159/207 (77%) in the MABp1 arm. The most common AEs reported *(≥10%, based on N=238)* were abdominal pain, fatigue, peripheral edema, nausea, anemia, asthenia, constipation, decrease in weight, and decreased appetite. Of the most common AEs, abdominal pain and oedema pheripheral were more frequently reported in the MABp1 arm (23% and 18% vs. 15% and 9%, again based on N=238). The majority of these events were grade 1 or 2.

The grade 3 AEs in MABp1-treated patients occurring in more than 1% (2 pts) were: abdominal pain (5 pts), oedema pheripheral (4 pts), fatigue (6 pts), anaemia (8 pts), ascites (5 pts), 'blood alkaline phosphatase increased' (8 pts), 'aspartate aminotransferase increased' (6 pts), 'blood bilirubin increased' (4 pts), and jaundice (3 pts).

Very few of the AEs observed in this study were deemed to be related to MABp1 treatment by the investigators. Twenty-six (26) patients experienced treatment-related AEs, of which the majority were grade 1/2, and only few of grade 3. None were of grade 4 or grade 5. Treatment-related AEs occurring in ≥ 1% (more than 2 pts) were pheripheral oedema (5 or 7 pts), nausea (4 pts) and possibly anaemia (unclear this if appeared in 2 or 3 pts in the latter case). A properly presented overview and discussion of AEs with regards to severity, both for the MABp1 arm and the placebo arm are lacking.

Infections: There were more infections in the MABp1 group compared with placebo: 12.1% (25 of 207) versus 8.8% (9 of 102), respectively. Seven of these infections were considered to be serious and six of these occurred in the MABp1 arm, and serious infections is considered to be an important identified risk with this medicinal product. Four of these SAEs recovered and one SAE of peritonitis resulted in death. None of these events (AEs or SAEs) were deemed to be associated with MABp1 therapy according to the applicant. The observed increases in infections and severe infections in the MABp1 arm compared with the placebo arm in study PT026 are of concern. Such increases might be caused by an immunosuppressive effect of MABp1. The imbalance in infection related AEs and SAEs is present, both during the 8 weeks study period and the extension phase, and in disfavour of patients treated with MABp1 compared with placebo. The number of events was, however, relatively small. There was no imbalance in deaths caused by infections between the treatment arms, although also here numbers are very limited. An increased risk of infection with MABp1 can, however, at present not be dismissed based on the available, limited clinical data and on previous human experience with agents that inhibit the IL-1 system.

Infusion reactions: 2 infusion reactions occurred (grade 1 and grade 2) in patients receiving MABp1, which were not severe and these subjects were able to continue on study. There were no SAEs of immunogenicity reactions, including infusion reactions.

Proteinuria and thrombocytopenia: Thrombocytopenia developed in 5% of MABp1 treated patients, versus 2% on placebo, and thrombocytopenia is classified as an important potential risk. There were no grade 3 or 4 events of thrombocytopenia, and no episodes of bleeding associated with thrombocytopenia. In this study, 14% in the MABp1 group developed proteinuria, versus 16% in the placebo group. There were no grade 3 or 4 events, and the events observed were not associated with renal insufficiency.

Deaths and serious adverse events

Deaths:

In study **2009-PT009**, three deaths occurred on study, two of which were considered unrelated to study treatment by the investigator, and probably the last case, as well, although a lung infection was diagnosed.

In study **2014-PT026**, a total of 18 SAEs resulting in 17 deaths occurred, of which none were considered related to treatment by the investigator. These were: metastases to CNS, disease progression (4 pts), condition aggravated (2 pts), death NOS, renal impairment, obstruction, hepatic failure, ileus/peritonitis, dehydration, respiratory failure, hip fracture, cardiopulmonary failure. Data on one fatal case on the MABp1 arm, however, it is apparently not included in the response and should be provided. Based on the currently presented data it could be agreed that most of them seem to be unrelated to treatment. The events resulting in death for 11 patients randomized to placebo are: anemia/fatigue, PD, dyspnea, renal failure, liver failure/ PD, liver failure/ ileus, respiratory failure, thromboembolism, general health deterioration, (pulmonary) thromboembolic event and sudden death NOS. All these deaths were not considered related to treatment or as not unexpected by investigator and/or sponsor

As such, there is no clustering of events leading to death in the either the MABp1 or the placebo arm, which is reassuring. All deaths are possibly related to disease progression.

SAEs:

There was a lower incidence of SAEs in the MABp1 arm as compared to placebo. SAEs occurred in 26 (25.5%) of 102 placebo patients versus 44 (21.3%) of 207 MABp1 patients.

There are 44 patients in the MABp1 arm experiencing 47 SAEs in study 2014-PT026, and it seems that no SAE is considered related to the treatment. However, the applicant states there were two serious adverse events that occurred during the study that were assessed as possibly or probably related to the therapy.

SAEs were most frequently reported in the SOCs General disorders and administration site conditions (14 pts on MABp1 vs. 9 pts on placebo) and Gastrointestinal disorders (7 pts. vs. 5 pts). As stated above, in the Infections and infestations SOC there were 5 serious events in MABp1 arm versus 0 in the placebo arm.

Discontinuation:

In the pivotal study, 2014-PT026, similar proportions (17%) in each arm discontinued treatment – 38 pts on MABp1 and 19 pts on placebo. Reasons for discontinuation were primarily due to AEs (7 pts in each arm; which constitute 3% on MABp1 and 6% on placebo). Similar proportions were due to “Deaths” (9 pts on MABp1, 5 on placebo), “Removed from study by principal investigator” (6 pts vs. 3 pts) and “Other” (8 pts vs. 3 pts). .

Laboratory findings and vital signs:

Five clinically significant abnormalities were reported as SAEs (anemia, poor renal function and ALT increased); however, none were considered related to MABp1.

There have been no adverse changes in vital signs, physical findings, or other observations related to safety to report from either the PT004 or PT026 trial.

2.6.2. Conclusions on the clinical safety

Based on an assessment of the currently submitted data, there were no commonly observed adverse events that appear to be definitively related to treatment with MABp1. The majority of the reported adverse events appear

mostly to be related to patients' underlying cancer. Safety data was, however, rather poorly presented in the MAA and difficult to assess/interpret. The observed imbalance of (severe) infections in disfavour of the MABp1 arm in the pivotal study PT026 is of concern, also considering the frailty of patients and the palliative care setting in which MABp1 will be used.

Updated safety information from several clinical studies, in which patients were treated with MABp1, have been submitted in an abbreviated form. These clinical studies include various indications, at different doses and administration forms, different durations and with generally very few patients included. In conclusion, the safety database is still scarce and this hampers the overall safety evaluation. However, no strong safety signals have been observed at present, except for the imbalance in (serious) infections, and hence, serious infections is considered an important identified risk.

2.7. Risk Management Plan

Safety concerns

Summary of safety concerns	
Important identified risks	Serious infections
Important potential risks	Immunosuppression Immunogenicity reactions including infusion reactions Thrombocytopenia Interactions with TNF inhibitors
Missing information	Use in patients with hepatic impairment Use in patients with renal impairment

Pharmacovigilance plan

Not applicable as there are no ongoing and planned additional pharmacovigilance studies/activities in the pharmacovigilance plan.

Risk minimisation measures

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
Important identified risk		
Serious infections	See relevant sections of the SmPC.	None
Important potential risk		
Immunosuppression	See relevant sections of the SmPC.	None
Immunogenicity reactions including infusion reactions (Potential risk)	See relevant sections of the SmPC.	None
Thrombocytopenia (potential risk)	See relevant sections of the SmPC.	None
Interaction with TNF inhibitors	See relevant sections of the SmPC.	None.

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
Missing information		
Use in patients with hepatic impairment	See relevant sections of the SmPC.	None.
Use in patients with renal impairment	See relevant sections of the SmPC.	None.

Conclusion

The CHMP and PRAC, having considered the data submitted in the application was of the opinion that due to the concerns identified with this application, the risk management plan cannot be agreed at this stage.

2.8. Pharmacovigilance

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.

2.9. New Active Substance

The applicant declared that Human IgG1 monoclonal antibody specific for human interleukin-1 alpha has not been previously authorised in a medicinal product in the European Union.

The CHMP, based on the available data, considers Human IgG1 monoclonal antibody specific for human interleukin-1 alpha to be a new active substance as it is not a constituent of a medicinal product previously authorised within the Union. However, in light of the negative recommendation, new active substance status is not applicable at this stage.

2.10. Product information

Due to the aforementioned concerns a satisfactory summary of product characteristics, labelling and package leaflet cannot be agreed at this stage.

2.10.1. 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.* However, due to the aforementioned concerns a satisfactory package leaflet cannot be agreed at this stage.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

MABp1 is intended for the control or relief of debilitating symptoms associated with advanced colorectal cancer.

The aim of therapy with MABp1b is to achieve reversal of tumour-related symptoms in terms of improvement or stabilisation of lean body mass (LBM), as well as to improve QoL in this advanced cancer population.

Unintentional weight loss associated with cancer is a well-known phenomenon, which is commonly known as "cancer cachexia". Approximately half of all patients with cancer experience cachexia with the prevalence rising as high as 86 % in the last 1–2 weeks of life. Around 45 % of cancer patients lose more than 10 % of their original body weight during disease progression (Vaughan et al 2013). Cancer cachexia is defined as a complex condition of tissue wasting, which develops as a secondary disorder in cancer patients and leads to progressive functional impairment (Fearon et al 2011). This condition is characterised by systemic inflammation, negative protein and energy balance and involuntary loss of LBM, with or without wasting of adipose tissue. Clinically, cachexia is represented by significant weight loss in adults, accompanied by alterations in body composition and disturbed balance of biological systems. Generally, an unintentional weight loss of >5% from historical weight is associated with cachexia as a clinically relevant metabolic symptom, except patients with a body mass index of <20 kg/m^2. Death usually occurs once weight loss has reached 30% of the patients' historical stable body weight, with cachexia being directly attributable for 20% of cancer deaths (Vaughan et al 2013).

3.1.2. Available therapies and unmet medical need

Metastatic colorectal cancer is a highly invalidating and life threatening condition with a poor prognosis. Several anticancer drugs, given alone or in combination regimens, are available in the EU/EEA for the treatment of patients with mCRC, including fluoropyrimidines, oxaliplatin, irinotecan and bevacizumab. In patients with RAS wild type tumours, EGFR inhibitors like panitumumab and cetuximab are being used.

The current standard of care for advanced CRC patients in the EU/EEA includes oxaliplatin- and irinotecan-based combination chemotherapy regimens. For patients who failed these therapies, available treatment options are currently very limited. Although new monoclonal antibodies such as regorafenib (inhibitor of multiple kinases, including targets involved in angiogenesis) have been approved as last line treatment option in recent years and are recommended in ESMO Guidelines.

As the pivotal study attempted to demonstrate symptom control in advanced cancer patients based on the assessments of LBM and QoL, corticosteroids could in theory be an option for the target population. Although these drugs are frequently used in palliative care of patients with advanced cancer, the benefit/risk balance is poorly documented (Cochrane 2013). Megesterol acetate, a synthetic derivative of progesterone, has been found to improve appetite and cause a weight gain and also an improvement of QoL in cancer patients compared to placebo. However, the exact mechanism behind this weight gain and whether the drug actually increases muscle mass is unclear.

Currently, there are no approved therapies that can effectively reverse cancer related cachexia and other tumour-related symptoms, and all available treatment options are considered palliative. There is therefore still an unmet need for treatment of advanced CRC cancer patients.

3.1.3. Main clinical studies

The pivotal study 2014-PT026 was a randomised, double-blind, placebo-controlled multi-centre study conducted in advanced CRC patients with ECOG status 1 or 2, who were refractory to two lines of standard of care therapies and also exhibited symptomatic disease. Patients had to have evidence of metabolic dysfunction (either any degree of unintentional weight loss in previous 6 months at baseline or an interleukin-6 level of >10 pg/ml) and evidence of reduced function or presence of cancer-related symptoms (e.g. pain or fatigue or reduced appetite as assessed by EORTC QLQ-C30 Questionnaire). Eligible patients were randomised (2:1) to

receive 7.5 mg/kg IV MABp1+ best supportive care (BSC), or IV placebo + BSC once every 2 weeks (one cycle) for a total of 4 IV infusions. BSC included mainly psychological support, dietary advice, exercise advice, antibiotics, anti-emetics, and analgesics. Duration of treatment was 8 weeks, during which almost all concomitant anti-cancer or symptomatic/palliative treatments (e.g. corticosteroids, megesterol acetate) were restricted. After this period, all subjects could enter an open label extension phase, in which they could receive MABp1 until progression or unacceptable toxicity; all other anti-cancer therapies were allowed during this phase.

The primary efficacy endpoint was ORR, a composite endpoint, which assessed change in LBM (based on DEXA scans) and change in QoL in terms of fatigue, pain, and appetite (based on EORTC QLQ-C30 Questionnaire) from baseline to week 8. In order to be considered a responder, patients had to show: (i) stabilisation or improvement of LBM and (ii) improvement or no worsening on 2 of 3 QoL-symptom scales.

A total of 458 patients were screened and of these 333 patients were randomised into the study arms. The primary analysis population for efficacy evaluation was the mITT population, which consisted of 309 subjects, i.e., 207 subjects in the MABp1 arm and 102 patients in the Placebo arm.

3.2. Favourable effects

The efficacy analysis of the composite endpoint in mITT population demonstrated a statistically significant difference of 14% between responders in the MABp1 arm (33%) and the placebo arm (19%); unadjusted odds ratio=2.14 (95% CI: 1.21, 3.78); one-sided test p=0.004.

A sensitivity analysis of ORR (excluding pain which is subject to bias) in the mITT population showed a 11% difference between responders in the MABp1 arm (26%) and the placebo arm (15%); unadjusted odds ratio=2.00 (95% CI: 1.06, 3.75; one-sided test p=0.01).

The updated analysis of ORR in the PP population showed a 17% difference between responders in the MABp1 arm (40%) and the placebo arm (23%); unadjusted odds ratio=2.27 (95% CI: 1.25, 4.12; one-sided test p=0.003). A sensitivity analysis of ORR (excluding pain) in the PP population showed a 13% difference between responders in the MABp1 arm (31%) and the placebo arm (18%); unadjusted odds ratio=2.07 (95% CI: 1.08, 3.95; one-sided test p=0.01).

3.3. Uncertainties and limitations about favourable effects

The analysis of the individual components of the composite endpoint did not demonstrate any clinically meaningful differences between the study arms, and hence it is not possible to ascertain how individual components might have contributed to the efficacy of MABp1. Whereas the only objective measure “change in LBM” resulted in no differences between the arms, i.e. mean LBM change was comparable for placebo-treated and MABp1-treated patients, 0.60±0.32 kg vs 0.53±0.22 kg, respectively (p=0.87). Also, the other individual component of the composite endpoint based on patient reported outcomes (i.e. change in the mean EORTC scores for pain, fatigue and appetite scales) showed no clinically or statistically significant changes from baseline and no differences between the arms.

Although any degree of prior weight loss within last 6 months was a part of the main inclusion criteria as an evidence of metabolic dysregulation, no data were collected on the degree of patients’ prior weight loss at baseline. Therefore, distribution of patients with different degrees of weight loss at baseline to the study arms remains unknown. In addition, ~33% of all patients were probably enrolled only based on IL-6 threshold of >10 pg/ml, which is not an acknowledged biomarker of metabolic dysregulation.

A total of 5 responders in the placebo arm were excluded from the PP analysis of the composite endpoint (i.e. being considered non-responders) as these patients were among the 17 placebo patients that received erroneously MABp1. This is not a conservative approach, and raises a question whether the observed difference in effect size of 17% for the PP population is reliable.

Regarding secondary endpoint analyses for change in IL-6 level or platelet count from baseline, the clinical relevance of the observed changes from baseline or any potential clinical benefit for the MABp1-treated patients remain unclear. The reliability of reported IL-6 levels is questionable as handling of outliers was not predefined and the outcome changed significantly when analysing with or without the outliers. Moreover, the mean IL-6 levels (excluding the outliers) were still >10 pg/ml in both arms at Week 8, indicating no clinically significant changes from baseline in the inflammation status. Mean platelet counts at baseline vs Week 8 were within normal range and comparable between the arms.

The analysis of functional and global QoL scales of EORTC QLQ-C30 Questionnaire showed neither statistically significant nor clinically relevant changes from baseline in MABp1-treated patients compared to the placebo patients.

3.4. Unfavourable effects

In the pivotal study, the most common AEs reported *(≥10%, based on N=238)* were abdominal pain, fatigue, peripheral oedema, nausea, anaemia, asthenia, constipation, decrease in weight, and decreased appetite. Of the most common AEs, abdominal pain and peripheral oedema were more frequently reported in the MABp1 arm (23% and 18% vs. 15% and 9%, again based on N=238). The majority of these events were grade 1 or 2.

The grade 3 AEs in MABp1 treated patients occurring in more than 1% of patients were abdominal pain, peripheral oedema, fatigue, anaemia, ascites, 'blood alkaline phosphatase increased', 'aspartate aminotransferase increased', 'blood bilirubin increased', and jaundice.

Infections

There is an imbalance of infections (12.1% MABp1 vs 8.8% placebo) and severe infections (3% MABp1 vs 1% placebo) in disfavour of the MABp1 arm in the pivotal study.

SAEs

There were two reported serious adverse events occurring during the study and assessed as possibly or probably related to therapy. Both cases seemed to be thromboembolic events. There was one case of DVT in the MABp1 arm reported as a SUSAR, and the other SAE is a thromboembolic event of moderate severity.

3.5. Uncertainties and limitations about unfavourable effects

The safety database is currently limited, regarding both total number of patients treated and duration of treatment.

MABp1 was not studied in patients with renal, hepatic or cardiac impairment, patients with ECOG <2 and patients with brain metastases.

3.6. Effects Table

Table 30: Effects Table for MABp1 for the treatment of metastatic colorectal cancer as a single agent in adult patients who have failed oxaliplatin- and irinotecan-based chemotherapy

Effect	Short Description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects						
ORR (Primary endpoint) **mITT** **PP**	Composite measure, including improvement/ stabilisation of LBM and improvement/no worsening of QoL (fatigue, appetite and pain) using EORTC QLQ-C30 Questionnaire, as determined from screening to Week 8	%	MABp1 33% 40%	Placebo 19% 23%	Critical uncertainties regarding the robustness of data due to the following: (i) Unknown whether patients had at least 5% weight loss at baseline. The number of patients included based only on IL-6 threshold is unknown. (ii) Uncertainty regarding the reliability of the LBM estimates by DEXA. (iii) 5 responders in placebo arm were excluded from PP analysis as they erroneously received one dose of MABp1.	2014-PT0026
Unfavourable Effects						
Duration of study	Intended (max. 4 infusions)		Up to 8 weeks	Up to 8 weeks	The majority (ca. 75%) treated for 31-45 days (4-7 weeks) in both arms	
Infections			12.1% (25/207)	8.8% (9/102)	Of which 6 serious infections occurred in the MABp1 arm (3%), versus one observed on placebo (1%)	
SAEs			47 SAEs in 44 pts	33 SAEs in 26 pts	Two SAEs related to treatment according to investigator, one DVT, one reason not given, but should be submitted.	

Abbreviations: DEXA: Dual X-ray absorptiometry, EORTC: European Organisation for Research and Treatment of Cancer, LBM: Lean body mass, QoL: Quality of life, ORR: Objective response rate

Notes: Safety parameters between the two arms in study 2014-PT026 were compared for the 8-week, double blind phase only.

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

From a quality point of view, this application is not approvable due to concerns on the control of the active substance and finished product. A control strategy that would ensure consistent manufacture of a product of acceptable quality and with characteristics that are equivalent to the product used in pivotal clinical studies has not been provided.

The primary efficacy analysis based on the composite endpoint of CRR demonstrated a statistically significant difference between the MABp1 and placebo arms (33% vs 19%, respectively; p<0.01). However, the analysis of the individual components of the composite endpoint did not demonstrate any clinically meaningful differences between the study arms, and hence it is not possible to ascertain how individual components might have contributed to the efficacy of MABp1. Whereas the only objective measure "change in LBM" resulted in no differences between the arms, i.e. mean LBM change was comparable for placebo-treated and MABp1-treated patients, 0.60±0.32 kg vs 0.53±0.22 kg, respectively (p=0.87). Also, the other individual component of the composite endpoint based on patient reported outcomes (i.e. change in the mean EORTC scores for pain, fatigue and appetite scales) showed no clinically or statistically significant changes from baseline and no differences between the arms. Therefore, there is lack of a clear evidence in support of beneficial effects of MABp1 on both components of the composite endpoint, and hence efficacy cannot be established based on the primary analysis.

Despite the fact that the composite endpoint measures clinically relevant disease aspects, patients were considered as having met the efficacy outcome although they might potentially have had a worsening in any one of the 3 QoL symptoms of pain, appetite or fatigue, according to the definition of the primary composite endpoint and the primary analysis. This in itself is considered contradictory from an efficacy point of view. Furthermore, in the absence of positive treatment effects on the components of the composite endpoint when analysed separately, the fact that there is a higher proportion of patients having met a favourable efficacy outcome ('responders') to treatment with MABp1 as measured by the composite endpoint gives rise to the question whether some patients could be detrimentally affected by treatment. However, the possibility of detrimental effects of the treatment has not been fully investigated and cannot be excluded. The lack of information on potential detrimental effects hampers inherently the overall assessment of benefit/risk.

Although any degree of prior weight loss within last 6 months was a part of the main inclusion criteria as an evidence of metabolic dysregulation, no data were collected on the degree of patients' prior weight loss at baseline. Therefore, distribution of patients with different degrees of weight loss at baseline to the study arms remains unknown. In addition, ~33% of all patients were probably enrolled only based on IL-6 threshold of >10 pg/ml, which is not an acknowledged biomarker of metabolic dysregulation. Due to the above-mentioned shortcomings and uncertainties, it is difficult to evaluate the clinical relevance of the observed modest difference in the CRR (i.e. 14% in favour of MABp1) as the magnitude of any potential benefit cannot be put into context appropriately.

Regarding secondary endpoint analyses for change in IL-6 level or platelet count from baseline, the clinical relevance of the observed changes from baseline or any potential clinical benefit for the MABp1-treated patients remain unclear. The reliability of reported IL-6 levels is questionable as handling of outliers was not predefined and the outcome changed significantly when analysing with or without the outliers. Moreover, the mean IL-6 levels (excluding the outliers) were still >10 pg/ml in both arms at Week 8, indicating no clinically significant changes from baseline in the inflammation status. Mean platelet counts at baseline vs Week 8 were within normal range and comparable between the arms. Notably, the analysis of functional and global QoL scales of EORTC QLQ-C30 Questionnaire showed neither statistically significant nor clinically relevant changes from baseline in MABp1-treated patients compared to the placebo patients. Consequently, secondary analyses do not provide any additional evidence in support of efficacy.

The safety database is currently limited, regarding both total number of patients treated and duration of treatment. The observed imbalance of infections (12.1% MABp1 vs 8.8% placebo) and severe infections (3% MABp1 vs 1% placebo) in disfavour of the MABp1 arm in the pivotal study is of concern, particularly in light of the claimed indication. In a palliative care setting for treatment of a frail and heavily pre-treated patient

population, these risks are not considered acceptable, especially when potential risks cannot be outweighed by the questionable efficacy.

3.7.2. Balance of benefits and risks

This application is not approvable from a quality point of view due to concerns on the control of the active substance and finished product.

The submitted data derived from one single pivotal trial do not provide compelling evidence of efficacy. It is also difficult to contextualise the true magnitude of the overall efficacy and benefits for advanced CRC patients due the questionable difference in the ORR (mITT) in favour of MABp1 combined with the lack of any significant differences in LBM and none of the QoL measures. Furthermore, the total safety database is currently limited, both regarding patient population and duration of treatment. An increased number of infections (including serious infections) was observed in MABp1–treated patients compared to placebo. The benefit/risk balance of MABp1 is therefore considered negative**.**

3.7.3. Additional considerations on the benefit-risk balance

N/A

3.8. Conclusions

The overall B/R of Human IgG1 monoclonal antibody specific for human interleukin-1 alpha XBiotech is negative.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy for Human IgG1 monoclonal antibody specific for human interleukin-1 alpha XBiotech in the control or relief of debilitating symptoms associated with advanced colorectal cancer, the CHMP considers by consensus that the quality, safety and efficacy of the above mentioned medicinal product is not sufficiently demonstrated, and, therefore recommends the refusal of the granting of the marketing authorisation for the above mentioned medicinal product.

The CHMP considers that:

- A control strategy that would ensure consistent manufacture of a product with characteristics that are equivalent to the product used in pivotal clinical studies has not yet been provided.
- Robust evidence of therapeutic efficacy is insufficiently substantiated.
  - The robustness and meaningfulness of the observed differences of MABp1 compared to placebo in terms of the primary composite, clinical response rate (CRR), is questioned in the absence of positive treatment effects on symptoms and lean body mass separately. It is not possible to fully evaluate the clinical relevance of the observed potential efficacy in a sufficient context due to the lack of important baseline data regarding the degree of patients' prior weight loss as well as inclusion of substantial number of patients only based on the IL-6 threshold.
  - In the absence of positive treatment effects on the components of the composite endpoint when analysed separately, the fact that there are more patients having met a favourable efficacy outcome

('responders') to treatment with MABp1 as measured by the composite endpoint gives rise to the question whether some patients could be detrimentally affected by treatment. However, the possibility of detrimental effects of the treatment has not been fully investigated and cannot be excluded.

  - Secondary endpoint analyses did not provide any additional evidence of clinically relevant efficacy. Importantly, there were no statistically significant or clinically relevant changes from baseline in the functional and global QoL scales based on EORTC QLQ-C30 assessments in MABp1-treated patients compared to the placebo patients.

- The observed increased risk of infections, including serious infections, is of concern in the context of the claimed indication. These risks, based on small numbers from a limited safety database, are not acceptable in a palliative care setting for treatment of a vulnerable and heavily pre-treated patient population, as these are not outweighed by the observed potential beneficial effects.

Due to the aforementioned concerns a satisfactory summary of product characteristics, labelling, package leaflet, pharmacovigilance system, risk management plan and post-authorisation measures to address other concerns cannot be agreed at this stage.

5. Re-examination of the CHMP opinion of 18 May 2017

Following the CHMP conclusion that Human IgG1 monoclonal antibody specific for human interleukin-1 alpha XBiotech was not approvable (see section 4), the applicant submitted detailed grounds for the re-examination of the grounds for refusal.

Detailed grounds for re-examination submitted by the applicant

The applicant presented in writing and at an oral explanation the following grounds for re-examination:

Ground #1 Quality

A control strategy that would ensure consistent manufacture of a product with characteristics that are equivalent to the product used in pivotal clinical studies has not been provided.

Summary of the Applicant`s position:

The day 210 CHMP assessment report stated that although most specification attributes for the active substance and the finished product are maintained within clinically justified limits, this is not the case for glycation and for the amounts of basic/neutral/acidic species.

The applicant fully agrees that the control strategy has to ensure consistent manufacture of product with characteristics that are equivalent to the product used in pivotal clinical studies. Data analysis for all product manufacturing history provide sufficient evidence that the manufacturing process can and does produce product with consistent characteristics that are equivalent to that used in the Phase III clinical study.

Data analyses and specifications for basic/neutral/acidic species composition were performed routinely and these data have been included in all CMC submissions. All batches of product manufactured and shipped in the Phase III study were within specification. However, since the Applicant submitted manufacturing and quality data based on two different processes (i.e. two different media), the CHMP requested clarification on the specifications and supporting data for the process that would be subject to an MA. These data and specifications were clarified, summarized and were submitted at the Oral Explanation.

No specification for glycation was foreseen in the original CMC package. In the context of further product characterization and process analyses, product glycation was quantified. Glycation data were introduced on day 180, at the Oral Explanation. Since identifying glycation, the Applicant has analysed glycation for several batches manufactured, including 8 batches of product used in the Phase III study (3 batches from growth medium 1, 5 batches from growth medium 2). This analysis showed that the process is in control with respect to reasonable variations in glycation. Based on a statistical analysis of the results, specifications for this parameter have now been set.

The company has furthermore performed a detailed statistical analysis of the existing batch data for the amounts of basic/neutral/acidic species and glycosylation, for active substance (cIEF and carbohydrate profile) and finished product (cIEF and CEX). This is possible without the need to generate further data and based on already submitted information.

The results show that a further amendment of the current acceptance criteria is necessary to ensure that the concerned quality attributes are within the range of the product used in pivotal clinical studies. Therefore the limits will be tightened on the basis of the statistical analysis of actual batch results for the clinical trial material. Based on the existing data (including that prepared for discussion at the Oral Explanation), additional statistical analyses and revised release specifications submitted, the Applicant believes that matters relating to the CMC objections are addressed in their entirety.

The Applicant is asking the agency to reconsider the submitted data, including the suggestions that were made to resolve the CMC topic. This has not been possible until this time since CMC was not further discussed at the Oral Explanation and the Applicant's data and proposals were not otherwise discussed. Therefore, the Applicant asks for a re-assessment of the CHMP conclusion that based on the available data the acceptance criteria for glycation and the amounts of basic/neutral/acidic species cannot be set appropriately. It is the opinion of the company that an appropriate control strategy has been established with the data provided during the assessment period and the additional evaluation provided in the response documentation.

During the oral explanation on 12 September 2017 the applicant presented two new proposals for setting active substance and finished product specifications for charge isoforms, glycosylation and glycation. One option related to the inclusion of all growth medium 2 lots and the other option related to the inclusion of only the growth medium 2 lots used in the pivotal phase 3 study PT026.

In relation to the newly performed glycation analysis, the applicant also commented during the oral explanation that all glycation results were obtained by retrospective testing of long-term stability samples and that their amount are not expected to change during storage.

CHMP assessment

The remaining pharmaceutical D210 major objection was related to the control strategy of the active substance and the finished product as several quality parameters acceptance criteria were not considered clinically justified according to the quality profile of the product used during the pivotal clinical studies (The pivotal clinical study is defined as the 2014-PT026 study).

It is underlined that the cell growth medium supplier changed during the pivotal Phase 3 (2014-PT026), from the original media (growth medium 1) to the current media (growth medium 2) representative of the commercial process. The change of the media impacted attributes such as glycosylation, charge heterogeneity and glycation.

It was not demonstrated that the commercial manufacturing process was appropriately controlled to ensure that these parameters are in the range of those found for the products used during the pivotal clinical studies.

In addition, the impact of the modifications observed for the glycosylation on effector functions, including binding to FcRn, was incompletely characterized: the potential impact was not fully discussed and supported by appropriate data.

For the re-examination, the applicant provided a statistical analysis based on already submitted information for the following quality parameters:

- Charge species determined by cIEF for active substance;
- Carbohydrate profile for active substance which included the determination of the G0F, G1F, G1'F, G2F and total fucosylated glycans levels;
- Charge species determined by cIEF and CEX for the finished product (only the CEX method is considered in the finished product specifications);
- Glycation level in the active substance and finished product: These new data were not provided during the assessment and the oral explanation. Considering that the change in the charge variants induced increase in glycation level for the batches that were manufactured by using the current media, a new HPLC method has been developed to determine the level of glycated species and acceptance criteria were defined.

The batches concerned by the statistical analysis were distributed into five categories, except for the glycation determination:

- All pivotal clinical batches;
- Pivotal batches produced in growth medium 2 which corresponds to the current medium used for the commercial manufacturing process;
- Pivotal batches produced in the growth medium 1 which corresponds to the former medium;
- Process validation active substance batches;
- Post-process validation active substance batches.

The proposed statistical analysis raises several concerns as stated below.

It seems that results clearly confirm a different quality profile between the batches produced using the growth medium 1 and the ones produced using the current growth medium 2 in terms of charge species, glycosylation pattern and glycation level. As the commercial manufacturing process uses the current growth medium 2, only the clinical data provided for the batches produced with growth medium 2 should be used as pivotal clinical data.

In setting the specifications, data from the validation batches should also be considered. However, for most of the studied parameters, it appears that results for process validation and post-validation batches are not included in the ranges of growth medium 2 pivotal clinical batches without any further explanation. Moreover, some discrepancies were observed between tables and figures.

Consequently, the proposed acceptance criteria for each parameter are still not established based on the pivotal clinical batches ranges and validation ranges and are still too wide and considered unjustified.

In addition, no attempt has been made to explain the relatively high variation range obtained for the different charge species, which is also evident when comparing batches produced by different manufacturing processes (see batches with growth medium 2 vs growth medium 1, for example). As no change of the acceptance criteria for the carbohydrate profile is proposed, these acceptance criteria are also considered too wide and not clinically

justified. The newly introduced acceptance criteria for glycation level are neither in accordance with the pivotal clinical batches produced with the growth medium 2 nor with the process validation batches as no data were presented specifically for this parameter. It is thus not possible to conclude on the ability of the commercial batches to control this parameter.

The proposal made by the applicant during the oral explanation regarding the specification limits for charge isoforms, glycosylation and glycation is acknowledged. However, the batches mentioned during the oral explanation were not in line with batches mentioned in the re-examination document, which is confusing. Indeed, it is not fully understood what is meant by “growth medium 2 PT026”, “All growth medium 2” and “PT026” batches, as no detailed explanation has been provided. In the absence of the complete data set for the relevant batches, it is not possible to conclude on the newly proposed acceptance criteria for charge variants, glycosylation and glycation.

In addition, it is not clearly understood if the validation data were also considered and the absence of overlap between the pivotal clinical data and the validation data was still not discussed. Indeed, further data and justifications are required to substantiate the proposal, including the establishment of a clear link to the process validation batches.

Therefore, a final conclusion on the suitability of the control strategy of the active substance and the finished product and its ability to generate product with a quality profile that is representative of product used during the pivotal clinical studies (as well as validation batches) cannot be drawn at this point.

Point not resolved

Ground #2 Clinical efficacy

Robust evidence of therapeutic efficacy is insufficiently substantiated (i).

The robustness and meaningfulness of the observed differences of MABp1 compared to placebo in terms of the primary composite, clinical response rate (CRR), is questioned in the absence of positive treatment effects on symptoms and lean body mass separately. It is difficult to evaluate the clinical relevance of the observed potential efficacy in a sufficient context due to the lack of important baseline data regarding the degree of patients' prior weight loss as well as inclusion of substantial number of patients only based on the IL-6 threshold.

Summary of the Applicant`s position:

The target patient population for MABp1 is mCRC patients who have failed two chemotherapy treatments. This well-defined target population has a clear and unmet need for control of the symptoms of the disease, which cause significant suffering in the last stages of life. MABp1 is the first very well tolerated cancer drug developed specifically to target tumour pathways involved in disease progression and the development of debilitating symptoms associated with the disease.

Conclusions regarding clinical efficacy and relevance thereof can, and must be, drawn directly from the primary endpoint as defined. The remark of the CHMP concerning weight loss prior to baseline is neither compatible with the modality used to assess patient responses nor the indication sought and seems not to recognise the purpose and set-up of the pivotal study. The appearance of general confusion with respect to enrolment criteria is, for example, reinforced by the remark that the number of patients enrolled “only based on the IL-6 threshold” was “substantial”. Actually, no patients were included only based on the IL-6 threshold.

CHMP assessment

Overall, the applicant has based the answer on the argumentation that there is an unmet medical need for this population and that the wording of the claimed indication (control or relief of debilitating symptoms associated with mCRC) was not considered during the assessment. The former is acknowledged, since there are very few options for those patients with advanced mCRC after failure of two lines of standard of care therapies. This fact was already considered in the initial assessment as it was stated very clear in the assessment report (B/R section) that there is still an unmet need for treatment of advanced CRC cancer patients.

The applicant's second argument is the lack of consideration for the new wording of the indication that was proposed during the initial MA procedure. This is not supported by the CHMP. In the discussion of the benefit risk it is stated, "*the pivotal study attempted to demonstrate symptom control in advanced cancer patients based on the assessments of LBM and QoL*", hence it seems reasonable to conclude that the change in the indication was in fact taken into account and that the pivotal trial submitted in this application was designed to answer this hypothesis.

The responses submitted by the applicant do not address the main uncertainties identified in this regard, i.e. the absence of positive treatment effects on symptoms and lean body mass separately and the lack of important baseline data regarding the degree of patients' prior weight loss.

The pivotal study met the primary endpoint, but the analysis of the individual components of the composite endpoint did not demonstrate any clinically meaningful differences between the study arms. Nonetheless, the applicant argues that the approach taken to analyse the data should be reconsidered as it is not based on the primary endpoint. The CHMP considers the lack of sound evidence of efficacy from the individual components of the composite endpoint, precludes the assumption of a clear proof of clinical benefit from MABp1. The efficacy data as already assessed for the individual components confirmed the absence of clinically meaningful results (as shown in the following table – also see tables 15, 16).

Table 31: Efficacy results from the individual components of the composite endpoint

Components of Clinical Response	Xilonix+BSC (N=207)	Placebo+BSC (N=102)	Difference (effect size)	P value (1-sided Pearson Chi-Square test)	Relative Risk (95% CI)
	Objective Response, n (%)	Objective Response, n (%)			
LBM Response	105 (51%)	46 (45%)	6%	0.18	1.13 (0.87, 1.45)
Pain	93 (45%)	45 (44%)	1%	0.45	1.02 (0.78, 1.33)
Fatigue	94 (45%)	46 (45%)	0%	0.48	1.01 (0.78, 1.31)
Appetite	114 (55%)	49 (48%)	7%	0.12	1.15 (0.91, 1.45)

In the grounds for re-examination, the applicant has provided different figures, which are not understood (see below) since the number of patients with stabilization or improvement of LBM in the placebo arm are 46 instead of the 37 included in the Applicant's response (see the tables above and below).

	Stabilization or improvement of LBM n (%)	**Composite Endpoint Response** **n (%)**	Stabilization or improvement of ≥2 EORTC symptoms n (%)
Xilonix	105 (51%)	**68 (33%)**	106 (51%)
Placebo	37 (36%)	**19 (19%)**	40 (30%)

The main rationale when it comes to explaining the absence of difference in the components of the primary endpoint is that individual symptoms may wax and wane and thus clusters of symptoms are more reliable readouts for symptom control. The latter is agreed and in fact, a composite endpoint is preferable so as to capture the whole picture of the benefit from MABp1. However, there is no robust justification for the lack of difference in the individual components, questioning the actual benefit of this treatment. An alignment between the composite endpoint and the components would be expected, and has not been shown in this study. Importantly, besides the absence of statistically significant differences in the LBM and QoL domains, there were neither clinically meaningful differences in LBM (0.60±0.32 kg vs 0.53±0.22 kg) nor in all QoL scales, which were below the threshold of 10 mean scores (i.e. minimal important difference MID).

The post hoc analyses seem to favour the MABp1 arm, however, these analyses should be interpreted cautiously given their exploratory nature, being hypothesis generating, and cannot as such rule out the uncertainties in the assessment of the data.

Consequently, the different analyses comparing the symptom cluster on one hand and the responders in LBM (gain of LBM) or QoL domain on the other hand, cannot solve the uncertainties regarding the lack of effect in the individual components of the composite endpoint (in addition to the exploratory nature of these analyses, the populations analysed in these symptom cluster and LBM responders would not be the same as those analysed in the individual components).

In addition, according to the protocol, patients would be recruited if there was evidence of metabolic dysfunction, defined as the presence of one or more of the following: any degree (up to 20%) of unintentional weight loss in the previous 6 months or Serum Interleukin 6 levels ≥10 pg/ml. However, no data were collected on the degree of patients' prior weight loss at baseline. This uncertainty could directly impact on the clinical relevance of the results, since it is widely accepted that patients with an unintentional weight loss of >5% from historical weight is associated with cachexia as a clinically relevant metabolic symptom. However, the applicant states that MABp1 was not developed and the clinical trial was not designed to seek a label as a treatment for cancer cachexia. It is true that the indication claimed by the applicant is for the control or relief of debilitating symptoms associated with advanced colorectal cancer, and this is not focusing solely on cachexia. Nonetheless, cachexia is one of the most important symptoms of cancer patients and as such it was collected in the LBM component of the composite endpoint. The applicant also argues that the 5% criterion used for cachexia studies relates to overall body weight, and the pivotal study was not related to overall body weight or total body weight, but to LBM. Nevertheless, the proportion of patients with an unintentional LBM loss of >5% from historical records is not known either. Finally, no information is presented to address the concerns regarding the reliability of the LBM data obtained by DEXA as this method is subject to inherent inaccuracies (DEXA cannot distinguish lean soft tissue from water).

Point not resolved

Ground #3 Clinical efficacy

Robust evidence of therapeutic efficacy is insufficiently substantiated (ii).

In the absence of positive treatment effects on the components of the composite endpoint when analysed separately, the fact that there are more patients having met a favourable efficacy outcome ('responders') to treatment with MABp1 as measured by the composite endpoint gives rise to the question whether some patients could be detrimentally affected by treatment. However, the possibility of detrimental effects of the treatment has not been fully investigated and cannot be excluded.

Summary of the Applicant`s position:

The comment seems to be based on a misunderstanding of the rationale of the defined primary endpoint and its clinical relevance. The symptom cluster used as the primary endpoint sought to identify a population that had wide-ranging improvement in clinical performance. Control of multiple debilitating symptoms was expected to be a more robust clinical endpoint and to more likely identify subjects with good prognosis than what could be expected for any single symptom measure 19. It is unclear by what rationale the assessor determined that the very fact that the study met its primary endpoint should "give rise to the question whether some patients could be detrimentally affected by treatment". The Applicant will show (on the basis of data already submitted) that there are no detrimental effects of the treatment as compared to placebo; and that the "possibility of detrimental effects" can indeed be excluded.

The assessment appears to suggest that endpoints containing multiple disease aspects or clusters of symptoms must be rejected as a matter of principle, because (for a cluster containing three symptoms A, B and C) a positive score based on positive findings for symptoms A and B could mask a negative finding for C; and, by implication, that the negative finding for C could be so large that it drowns out the positive findings for A and B. For MABp1, the assessment specifically appears to suggest that the positive results in the composite primary endpoint (LBM + 2 out of 3 key cancer symptoms, i.e. fatigue, pain and appetite) - or a positive result on two out of these three key symptoms - could mask a negative result in the third symptom:

> "…, the fact that there is a higher proportion of patients having met a favourable efficacy outcome ('responders') to treatment with MABp1 as measured by the composite endpoint gives rise to the question whether some patients could be detrimentally affected by treatment.
>
> The lack of information on potential detrimental effects hampers inherently the overall assessment of benefit/risk".
>
> "Despite the fact that the composite endpoint measures clinically relevant disease aspects, patients were considered as having met the efficacy outcome although they might potentially have had a worsening in any one of the 3 QoL symptoms of pain, appetite or fatigue, according to the definition of the primary composite endpoint and the primary analysis. This in itself is considered contradictory from an efficacy point of view" (emphasis added).

In the view of the Applicant these "findings", which played a significant role in the overall assessment, need to be reconsidered and re-assessed for the following nine reasons.

1. Cancer-related symptoms tend to cluster, i.e. they occur together. The emergence of clusters of symptoms in advanced cancer is well documented and understood to be linked to systemic inflammatory responses resulting from tumour progression. The symptom cluster used in the MABp1 pivotal study—pain, fatigue and appetite—is supported by longstanding observations in advanced cancer but also from earlier empirical clinical evidence with MABp1 in patients with mCRC. The approach to use a symptom cluster to measure response to therapy is thus well- founded scientifically and clinically to assess outcomes in patients treated with the anti-inflammatory molecule MABp1.

The Applicant specifically focused on a cluster of three key symptoms: fatigue, pain and appetite. It did so for several reasons; It is generally acknowledged that these are debilitating symptoms of late-stage cancer and specifically mCRC; these symptoms are included in the EORTC-QLQ-30 questionnaire, facilitating data capture using a validated methodology; higher levels of pain and decreased appetite have been associated with higher mortality in large-scale trials, respectively, with p-values <0.0001. Fatigue was incorporated into the symptom cluster because it can be severely debilitating and "virtually every intervention used to treat cancer, as well as

the primary disease itself, may cause or contribute to fatigue". Furthermore, existing treatments for cancer-related fatigue, such as methylphenidate, provide modest benefits and have significant side effects which are counterproductive, including anorexia, insomnia, anxiety and confusion. Fatigue, pain and appetite are thus a crucial combination of clinically relevant symptoms.

The applicant also argued that in the Grounds for refusal, reference is made to LBM and symptoms collectively as "clinically relevant disease aspects".

2. The SAWP agreed that symptom clusters could be measured in a single endpoint and suggested that the Applicant should include one additional symptom control measure in its pivotal study, using the EORTC-QLQ-30 questionnaire (and thus, logically, to combine data captured from multiple questions in that questionnaire). The Applicant complied with this request. However, the CHMP appears to not accept this QoL/QLQ methodology.

As mentioned above, the Scientific Advice agreed with measuring LBM by means of the ORR methodology, but recommended to add "*a study outcome measure* [NB: this term was used in singular form] in order to assess "*directly the impact of therapy on the patient's Quality of Life*". This also clearly points to the clinical relevance of the primary endpoint.

The SAWP also recommended to use a method to capture data for the single outcome measure: "*e.g. HRQoL data, e.g. as captured by EORTC QLQ-C30*".

The Applicant followed these recommendations.

Specifically, the Applicant pre-defined in addition to LBM one single outcome measure that would capture the impact of therapy on the patient, i.e. in terms of responder status for stabilization or improvement of two out of three key symptoms.

In order to capture data on this cluster of key symptoms, the Applicant used the EORTC-QLQ-30 questionnaire, which is well established for its use in clinical trials, to provide data for clinical analysis, and which had been recommended by the SAWP.

3., As a matter of probabilities, it is not reasonable to assume that the fact that terminal cancer patients having stabilized or improved on LBM *and* having stabilized or improved on two out of three key symptoms (fatigue, pain and/or appetite), "would give rise to the question" of a negative score on the third symptom (and *a fortiori* it is not reasonable to allege that a possible negative score on the third symptom would outweigh the positive scores on all the other elements).

4. The SAWP advised to create a second endpoint for a combination of symptoms set out in the QLQ-C30 questionnaire. The reason for that approach is sound and based on a deep understanding of clinical oncology.

It is known in clinical practice that in advanced cancer certain symptoms often occur together, or in clusters, and that occurrence of these symptom clusters represents a substantial impact on QoL, associated with poor survival. Such symptom clusters include pain, fatigue, and anorexia. Symptom clusters, including these key elements, are known to be predictors of patient outcomes, including survival. While cancer- related symptoms tend to cluster, i.e. they occur together, there are variations for which symptoms will occur together based on stage of disease, pre-treatment history, and site of primary and metastatic lesions. Therefore, the pivotal study with MABp1 was designed in a prospective manner to capture at least two of three possible variations in terms of symptom responses to therapy.

The potential response to therapy may vary based on these factors. Thus the combination of symptoms used in the primary endpoint should be considered an appropriate strategy for assessing the QoL of individual patients, since improvement of any combination of symptoms—pain-fatigue, fatigue-appetite, or pain-appetite—

represents a clinically meaningful outcome. Analyses of patients that achieved the endpoint in the clinical study confirm this expectation. Indeed, patients who achieved improvement in any two of the key symptoms were significantly more likely to improve on the third (hence the relevance of a symptom cluster that in fact includes the three symptoms used in the primary endpoint).

5. Patients achieving the ORR had significant improvement not only in the key symptoms measured as part of the primary endpoint, but also improved in ALL QoL measures assessed by the EORTC-QLQ-C30 instrument, including social function, physical function, work function, role function, and global QoL.

Table 32: Responder *vs.* Non-Responder Analysis for mITT Population

	LS Mean±Standard Error		P value
	Non-responder	Responder	
Change in Lean Body Mass, kg	0.072±0.22	1.41±0.30	0.0007
Change in Global QoL Score	-6.98±1.56	4.32±2.08	<0.001
Change in Physical Function (PF)	-9.85±1.49	4.12±1.91	<0.001
Change in Role functioning (RF)	-13.43±2.08	3.87±2.77	<0.001
Change in Emotional functioning (EF)	-2.33±1.61	10.03±2.15	<0.001
Change in Social functioning (SF)	-6.71±2.11	10.16±2.81	<0.001
Change in Platelet Count, 1000/ul	33±5	-2±0.8	<0.001
Change in IL-6, pg/mL	10.284±2.212	-3.372±6.307	0.0007
Change in Fatigue Score	10.81±1.81	-8.35±2.42	<0.001
Change in Pain, Score	13.70±2.07	-10.01±2.75	<0.001
Change in Appetite, Score	14.46±2.33	-9.83±3.11	<0.001

As previously stated by the CHMP there is a lack of clear evidence in support of beneficial effects of MABp1 (and similarly, the statement in the D180 report that “Neither the sensitivity analyses of the individual co-primary endpoints, nor the analyses of secondary or exploratory endpoints provide any supportive evidence for efficacy in favour of MABp1.”

6. The assumption that a negative effect could somehow be “hidden” in the third symptom appears to be incompatible with the positive results obtained in the requested post-hoc analysis presented at the Oral Explanation, for each combination of two symptoms (pain-fatigue, fatigue-appetite, or pain-appetite), all of which showed a statistically significant result over placebo.

7. The Assessment Report suggests that separate clinical endpoints should have been defined for each individual symptom in the EORTC-QLQ-30 questionnaire. The company is of the opinion that this, however, would be contrary to the Scientific Advice obtained and contrary to the concept of a composite endpoint per se. As

discussed elsewhere, the prospectively defined symptom cluster used for the primary endpoint more robustly identifies a patient population that has a favourable clinical performance and prognosis than that which would be possible for an individual symptom. This was the fundamental purpose and logic of the primary endpoint.

8. The applicant wishes to understand how the fact that a higher proportion of patients met a favourable outcome can somehow imply that patients could be detrimentally affected by therapy. Moreover, the data does not suggest any significant treatment-related worsening in any of the individual components of the composite endpoint. As shown above, there was also no worsening observed in any other symptom measures.

If there was evidence that some other measures of symptoms (i.e. those not part of the composite endpoint) were significantly worse in the treatment arm as compared to placebo, such a finding could “give rise” to the notion that the treatment is detrimental outside of the primary endpoint measures - but such scenario is not supported by the data.

9. If one would actually suggest that the non-responders on MABp1 could have been doing worse than non-responders on placebo, the Applicant submitted a table based on data already submitted which shows that the profiles of the non- responders that received MBAp1 are highly similar to the profiles of the non- responders on placebo. The clinically relevant finding, of course, is that the *proportion* of responders on MABp1 was far higher than on placebo.

Based on these considerations the company is of the opinion that the assessment needs to be reconsidered in order to re-assess:

- the clinical relevance related to improvement in two out of three measures in the proposed indication;
- the inherent benefits associated with achieving improvement in any two symptoms; and
- the factual findings of the study, where improvement was seen in all measures for patients achieving the primary endpoint; and where variation in symptom clustering is a recognized aspect of advanced cancer.

CHMP assessment

It is clarified to the applicant that the previous assessment never suggested that endpoints containing multiple disease aspects or clusters of symptoms must be rejected as a matter of principle, because a positive score based on positive findings for symptoms A and B could mask a negative finding for C. It is also reminded that the CHMP did not question the relevance of the selected symptoms. Again, and according to the provided efficacy results, one could reasonably believe that some patients could be detrimentally affected by the treatment. The Applicant was therefore asked to reassure the CHMP and to discuss the possibility of detrimental effects of MABp1.

The Applicant’s answer is mainly focussing on the justification of the symptoms used in the primary endpoints. This was not the aim of the issue, if correctly understood. The Applicant has however (re) submitted a table comparing the profiles of the non-responders that received MBAp1 to that of the non-responders on placebo.

Change / Incidence from Baseline	Progressed (n=222)				Met Primary Endpoint (n=87)			
	MABp1 (n=139)	Placebo (n=83)	P (t-test)	P (Wilcoxon Test)	MABp1 (n=68)	Placebo (n=19)	P (t-test)	P (Wilcoxon Test)
Lean Body Mass, kg	-0.1±3.2	0.4±3.7	0.399	0.626	1.4±1.4	1.1±0.8	0.38	0.77
Role functioning	-15.38±28.01	-10.43± 30.35	0.477	0.228	6.46± 26.62	8.84± 31.60	0.74	0.77
Emotional functioning	-2.41±21.08	-1.36± 25.39	0.798	0.955	10.84± 21.35	15.84± 26.62	0.40	0.89
Social functioning	-7.07±27.66	-6.57± 34.10	0.883	0.806	10.38± 25.58	23.84± 28.41	0.073	0.054
Fatigue Score	13.68±26.77	12.13± 28.03	0.861	0.692	-9.09± 21.98	-17.16± 25.66	0.18	0.40
Pain Score	19.99±32.44	10.14± 31.35	0.077	0.058	-12.04± 24.26	-14.84± 19.85	0.65	0.46
Appetite Score	15.28±36.62	20.58± 33.17	0.263	0.626	-15.21± 28.53	-8.79± 24.55	0.38	0.44
Global QoL Score	-7±23	-8±25	0.679	0.877	5±19	8±19	0.55	1.00
Serum IL-6 Levels	4.1±2.0	11.8± 2.8	0.017	0.172	-3.5± 2.8	3.5± 5.5	0.99	0.44
Platelet Count, 1000/mm^3	23±75	47± 83	0.046	0.052	-4± 56	12± 60	0.30	0.29
Serious Adverse Events	41 (29%)	24 (29%)	1.00*		3 (4%)	2 (11%)	0.30*	
Disease Control RECIST	18 (13%)	8 (10%)	0.52*		17 (25%)	4 (21%)	1.00*	

These data are still difficult to interpret. Results show that there are globally no statistically significant differences between placebo and MAPp1 in the non-responder's population, and no statistically significant differences between placebo and MAPp1 in the responder's population. Results also show that there are no statistically significant differences in serum IL6 levels and platelet counts between placebo and MAPp1 in the responder's population. This questions the impact of MABp1 on these two secondary efficacy endpoints.

Point not resolved

Ground #4 Clinical efficacy

Robust evidence of therapeutic efficacy is insufficiently substantiated (iii).

Secondary endpoint analyses did not provide any additional evidence of clinically relevant efficacy. Importantly, there were no statistically significant or clinically relevant changes from baseline in the functional and global QoL scales based on EORTC QLQ-C30 assessments in MABp1-treated patients compared to the placebo patients.

Summary of the Applicant`s position:

All of the secondary analyses – without exception – provided support for the primary endpoint and conclusions with respect to efficacy. For the changes in the pharmacodynamic secondary endpoints (platelets and IL-6 levels), statistical significance in favour of MABp1 was reached at the level of the treatment arms as a whole (p=0.0052 for changes in platelets level, and p=0.0012 for changes in IL-6). The company points out that, even if the criticisms formulated in the assessment with regard to IL-6 and platelets were correct, those criticisms

could not detract from the fact that the increase in IL-6 and platelet levels was greater in the placebo arm than in the MABp1 arm. That finding supports the understanding of the method of action of MABp1as well as the positive primary findings.

For individual secondary endpoints that were self-reported outcomes (EORTC-QLQC30 functional scales and global QoL), no statistically significant differences were seen between treatment and placebo arms. However, that cannot detract from the positive findings regarding the primary endpoint.

Indeed, individual symptoms may wax and wane. This is precisely why *clusters* of symptoms are more reliable readouts for symptom control. That is also why the Applicant used a combination of self-reported symptoms (fatigue, pain and appetite) together with the objective radiographic measure of LBM, to create a more robust assessment of clinical performance than that which could be achieved using any single symptom measure.

However, when the individual self-reported measures (functional scales and QoL) were analysed with respect to the primary endpoint (i.e. as a cluster), statistically and clinically significant improvement in these outcomes was observed. This provides further confirmation that improvement in the combination of self-reported and objectively measured symptoms that make up the primary endpoint are indeed linked to wider ranging improvement in patient performance.

CHMP assessment

The secondary endpoints do not seem to offer a robust support to the claimed pharmacological effect of MABp1.

If a statistically significant difference between the study arms was shown based on LS mean change for platelet counts, results were more contrasted for IL-6 levels. The applicant stated that IL-6 levels remained stable in the MABp1 arm after 8 weeks of therapy with a mean change of 1.6±1.9 pcg/ml while it increased by an average of 9.90±2.71 pcg/ml in the placebo arm (p=0.012, excluding four outliers). However, the difference was not statistically significant when the outliers were included in the analysis. This suggests that these data were not robust enough to support the efficacy of MABp1.

It has indeed been reported that cancer-associated inflammation is a key determinant of disease progression and survival in colorectal cancer which can contribute to tumour angiogenesis, invasion, and metastatic spread. As an inflammatory cytokine, IL-6 can be theoretically involved in immune regulation, haematopoiesis, and carcinogenesis. However, some analyses have assessed the association between serum interleukin-6 level and risk of CRC, and most of the data were inconsistent or insignificant.

Regarding the platelet counts, despite the statistically significant difference, the clinical meaning of this finding in questionable, since the mean platelet counts in both arms (i.e. ranging from 232-260x 103/mm) were within the normal range for the healthy subjects (i.e. 150–450 x 10^3/mm) both at baseline vs Week 8. No antitumor effect has been seen for MABp1.

The absence of statistically significant or clinically relevant changes from baseline in the functional and global QoL scales based on EORTC QLQ-C30 assessments in MABp1-treated patients compared to the placebo patients, has been discussed in the first question.

Ground #5 Clinical Safety

The observed increased risk of infections, including serious infections, is of concern in the context of the claimed indication. These risks, based on small numbers from a limited safety database, are not acceptable in a palliative care setting for treatment of a vulnerable and heavily pre-treated patient population, as these are not outweighed by the observed potential beneficial effects.

Summary of the Applicant`s position:

MABp1 is a well-tolerated drug. First, there was not a single infusion reaction in 600 patients injected with MABp1 over the course of multiple trials. Second, there was not a single drug-related SAE in the pivotal trial. Third, and most importantly, the total number of SAEs was lower in the MABp1 arm than in the placebo arm:

"In the PT026 study, there was a slightly lower incidence of SAEs in the treatment arm compared to placebo."

In the CHMP Assessment Report, it is stated that "an increased risk of infection with MABp1 can, however, at present not be dismissed". It is the applicant`s view that being unable to dismiss a particular risk cannot justify a final conclusion that an important risk has been identified.

However, the overall difference in infections between the study arms was not statistically significant: The p-value for Infection AEs was p=0.44; the p-value for Infection SAEs was p=0.43.

None of the infection events were deemed by the investigators to be treatment-related.

Further, there was a grand total of only six infection-related SAEs found. The Applicant brought the treating physicians to the Oral Explanation so they could explain that the risk of infections and that their SAEs were not related to MABp1. At the Oral Explanation, however, there was no possibility for the experts to express their testimony.

In overall, the Applicant concludes that the assessment of infections appears not to reflect the data submitted and appears not to be in line with the previous conclusions. The Applicant also is of the opinion that before finally concluding on this, the testimony of the treating physicians could have been made available.

CHMP assessment

There were more infections in the MABp1 group compared to placebo. On the one hand, the observed increased risk of infections could be considered a major concern in such a frail patient population. On the other hand, most of these events were not serious, and none of the events were deemed to be associated with MABp1 therapy. These were bronchitis, bronchopneumonia, cystitis, influenza, lower respiratory tract infection, nasopharyngitis, oesophageal candidiasis, pyonephrosis, sputum purulent, upper respiratory infection, upper respiratory tract infection bacterial, viral infection, urosepsis, upper respiratory tract infection, oral candidiasis, and urinary tract infection. Two additional SAEs of infections that had been previously wrongly coded by the Applicant were added. All seven of the infection SAEs in the MABp1 treatment arm were considered as "not related" by both the investigator and the sponsor.

As a conclusion, there were no commonly observed adverse events that appear to be definitively related to treatment with MABp1. The safety database is considered limited, preventing a thorough assessment of the overall risks associated with MABp1.

Overall conclusion on grounds for re-examination

The CHMP assessed all the detailed grounds for re-examination and argumentations presented by the applicant. The quality of the product is still insufficiently controlled, and the benefits of MABp1 for the control or relief of debilitating symptoms associated with advanced colorectal cancer are not established.

6. Benefit-risk balance following re-examination

6.1. Therapeutic Context

6.1.1. Disease or condition

MABp1 is intended for the control or relief of debilitating symptoms associated with advanced colorectal cancer.

The aim of therapy with MABp1b is to achieve reversal of tumour-related symptoms in terms of improvement or stabilisation of lean body mass (LBM), as well as to improve QoL in this advanced cancer population.

Unintentional weight loss associated with cancer is a well-known phenomenon, which is commonly known as "cancer cachexia". Approximately half of all patients with cancer experience cachexia with the prevalence rising as high as 86 % in the last 1–2 weeks of life. Around 45 % of cancer patients lose more than 10 % of their original body weight during disease progression (Vaughan *et al*. 2013). Cancer cachexia is defined as a complex condition of tissue wasting, which develops as a secondary disorder in cancer patients and leads to progressive functional impairment (Fearon *et al.* 2011). This condition is characterised by systemic inflammation, negative protein and energy balance and involuntary loss of LBM, with or without wasting of adipose tissue. Clinically, cachexia is represented by significant weight loss in adults, accompanied by alterations in body composition and disturbed balance of biological systems. Generally, an unintentional weight loss of >5% from historical weight is associated with cachexia as a clinically relevant metabolic symptom, except patients with a body mass index of <20 kg/m^2. Death usually occurs once weight loss has reached 30% of the patients' historical stable body weight, with cachexia being directly attributable for 20% of cancer deaths (Vaughan *et al*. 2013).

6.1.2. Available therapies and unmet medical need

As the pivotal study attempted to demonstrate symptom control in advanced cancer patients based on the assessments of LBM and QoL, corticosteroids could in theory be an option for the target population. Although these drugs are frequently used in palliative care of patients with advanced cancer, the benefit/risk balance is poorly documented (Cochrane 2013). Megesterol acetate, a synthetic derivative of progesterone, has been found to improve appetite and cause a weight gain and also an improvement of QoL in cancer patients compared to placebo. However, the exact mechanism behind this weight gain and whether the drug actually increases muscle mass is unclear.

Currently, there are no approved therapies that can effectively reverse cancer related cachexia and other tumour-related symptoms, and all available treatment options are considered palliative. There is therefore still an unmet need for treatment of advanced CRC cancer patients.

6.1.3. Main clinical studies

The pivotal study 2014-PT026 was a randomised, double-blind, placebo-controlled multi-centre study conducted in advanced CRC patients with ECOG status 1 or 2, who were refractory to two lines of standard of care therapies and also exhibited symptomatic disease. Patients had to have evidence of metabolic dysfunction (either any degree of unintentional weight loss in previous 6 months at baseline or an interleukin-6 level of >10 pg/ml) and evidence of reduced function or presence of cancer-related symptoms (e.g. pain or fatigue or reduced appetite as assessed by EORTC QLQ-C30 Questionnaire). Eligible patients were randomised (2:1) to receive 7.5 mg/kg IV MABp1+ best supportive care (BSC), or IV placebo + BSC once every 2 weeks (one cycle) for a total of 4 IV infusions. BSC included mainly psychological support, dietary advice, exercise advice,

antibiotics, anti-emetics, and analgesics. Duration of treatment was 8 weeks, during which almost all concomitant anti-cancer or symptomatic/palliative treatments (e.g. corticosteroids, megesterol acetate) were restricted. After this period, all subjects could enter an open label extension phase, in which they could receive MABp1 until progression or unacceptable toxicity; all other anti-cancer therapies were allowed during this phase.

The primary efficacy endpoint was ORR, a composite endpoint, which assessed change in LBM (based on DEXA scans) and change in QoL in terms of fatigue, pain, and appetite (based on EORTC QLQ-C30 Questionnaire) from baseline to week 8. In order to be considered a responder, patients had to show: (i) stabilisation or improvement of LBM and (ii) improvement or no worsening on 2 of 3 QoL-symptom scales.

A total of 458 patients were screened and of these 333 patients were randomised into the study arms. The primary analysis population for efficacy evaluation was the mITT population, which consisted of 309 subjects, i.e., 207 subjects in the MABp1 arm and 102 patients in the Placebo arm.

6.2. Favourable effects

The efficacy analysis of the composite endpoint in mITT population demonstrated a statistically significant difference of 14% between responders in the MABp1 arm (33%) and the placebo arm (19%); unadjusted odds ratio=2.14 (95% CI: 1.21, 3.78); one-sided test p=0.004.

A sensitivity analysis of ORR (excluding pain which is subject to bias) in the mITT population showed a 11% difference between responders in the MABp1 arm (26%) and the placebo arm (15%); unadjusted odds ratio=2.00 (95% CI: 1.06, 3.75; one-sided test p=0.01).

The updated analysis of ORR in the PP population showed a 17% difference between responders in the MABp1 arm (40%) and the placebo arm (23%); unadjusted odds ratio=2.27 (95% CI: 1.25, 4.12; one-sided test p=0.003). A sensitivity analysis of ORR (excluding pain) in the PP population showed a 13% difference between responders in the MABp1 arm (31%) and the placebo arm (18%); unadjusted odds ratio=2.07 (95% CI: 1.08, 3.95; one-sided test p=0.01).

6.3. Uncertainties and limitations about favourable effects

The analysis of the individual components of the composite endpoint did not demonstrate any clinically meaningful differences between the study arms, it is therefore not possible to ascertain how individual components might have contributed to the efficacy of MABp1. Whereas the only objective measure “change in LBM” resulted in no differences between the arms, i.e. mean LBM change was comparable for placebo-treated and MABp1-treated patients, 0.60±0.32 kg vs 0.53±0.22 kg, respectively (p=0.87). Also, the other individual component of the composite endpoint based on patient reported outcomes (i.e. change in the mean EORTC scores for pain, fatigue and appetite scales) showed no clinically or statistically significant changes from baseline and no differences between the arms.

6.4. Unfavourable effects

In the pivotal study, the most common AEs reported (≥10%, based on N=238) were abdominal pain, fatigue, peripheral oedema, nausea, anaemia, asthenia, constipation, decrease in weight, and decreased appetite. Of the most common AEs, abdominal pain and peripheral oedema were more frequently reported in the MABp1 arm (23% and 18% vs. 15% and 9%, again based on N=238). The majority of these events were grade 1 or 2.

The grade 3 AEs in MABp1 treated patients occurring in more than 1% of patients were abdominal pain, peripheral oedema, fatigue, anaemia, ascites, 'blood alkaline phosphatase increased', 'aspartate aminotransferase increased', 'blood bilirubin increased', and jaundice.

Infections: There is an imbalance of infections (12.1% MABp1 vs. 8.8% placebo) and severe infections (3% MABp1 vs. 1% placebo) in disfavour of the MABp1 arm in the pivotal study. All seven of the infection SAEs in the MABp1 treatment arm were however considered as "not related" by both the investigator and the sponsor.

SAEs: There were two reported serious adverse events occurring during the study and assessed as possibly or probably related to therapy. Both cases seemed to be thromboembolic events. There was one case of DVT in the MABp1 arm reported as a SUSAR, and the other SAE is a thromboembolic event of moderate severity.

6.5. Uncertainties and limitations about unfavourable effects

The safety database is currently limited, regarding both total number of patients treated and duration of treatment.

MABp1 was not studied in patients with renal, hepatic or cardiac impairment, patients with ECOG <2 and patients with brain metastases.

6.6. Effects Table

Table 33: **Effects Table for MABp1 for the treatment of metastatic colorectal cancer as a single agent in adult patients who have failed oxaliplatin- and irinotecan-based chemotherapy**

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Favourable Effects						
ORR (Primary endpoint)	Composite measure, including improvement/stabilisation of LBM and improvement/no worsening of QoL (fatigue, appetite and pain) using EORTC QLQ-C30 Questionnaire, as determined from screening to Week 8	%	MABp1	Placebo	Critical uncertainties regarding the robustness of data due to the following: (i) Unknown whether patients had at least 5% weight loss at baseline. The number of patients included based only on IL-6 threshold is unknown. (ii) Uncertainty regarding the reliability of the LBM estimates by DEXA. (iii) 5 responders in placebo arm were excluded from PP analysis as they erroneously received one dose of MABp1.	2014-PT 0026
mITT			33%	19%		
PP			40%	23%		
Unfavourable Effects						
Duration of study	Intended (max. 4 infusions)		Up to 8 weeks	Up to 8 weeks	The majority (ca. 75%) treated for 31-45 days (4-7 weeks) in both arms	

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Infections			12.1% (25/207)	8.8% (9/102)	Of which 6 serious infections occurred in the MABp1 arm (3%), versus one observed on placebo (1%)	
SAEs			47 SAEs in 44 pts	33 SAEs in 26 pts	Two SAEs related to treatment according to investigator, one DVT, one reason not given, but should be submitted.	

Abbreviations: DEXA: Dual X-ray absorptiometry, EORTC: European Organisation for Research and Treatment of Cancer, LBM: Lean body mass, QoL: Quality of life, ORR: Objective response rate

Notes: Safety parameters between the two arms in study 2014-PT026 were compared for the 8-week, double blind phase only.

6.7. Benefit-risk assessment and discussion

6.7.1. Importance of favourable and unfavourable effects

From a quality point of view, this application is not approvable due to concerns on the control of the Drug Substance and Drug Product. A control strategy that would ensure consistent manufacture of a product of acceptable quality and with characteristics that are equivalent to the product used in pivotal clinical studies has not been provided.

The primary efficacy analysis based on the composite endpoint of CRR demonstrated a statistically significant difference between the MABp1 and placebo arms (33% vs 19%, respectively; $p<0.01$). However, the analysis of the individual components of the composite endpoint did not demonstrate any clinically meaningful differences between the study arms, and hence it is not possible to ascertain how individual components might have contributed to the efficacy of MABp1. Whereas the only objective measure “change in LBM” resulted in no differences between the arms, i.e. mean LBM change was comparable for placebo-treated and MABp1-treated patients, 0.60±0.32 kg vs 0.53±0.22 kg, respectively ($p=0.87$). Also, the other individual component of the composite endpoint based on patient reported outcomes (i.e. change in the mean EORTC scores for pain, fatigue and appetite scales) showed no clinically or statistically significant changes from baseline and no differences between the arms. Therefore, there is lack of clear evidence in support of beneficial effects of MABp1 on both components of the composite endpoint, hence efficacy cannot be established based on the primary analysis.

Despite the fact that the composite endpoint measures clinically relevant disease aspects, patients were considered as having met the efficacy outcome although they might potentially have had a worsening in any one of the 3 QoL symptoms of pain, appetite or fatigue, according to the definition of the primary composite endpoint and the primary analysis. This in itself is considered contradictory from an efficacy point of view. Furthermore, in the absence of positive treatment effects on the components of the composite endpoint when analysed separately, the fact that there is a higher proportion of patients having met a favourable efficacy outcome (‘responders’) to treatment with MABp1 as measured by the composite endpoint gives rise to the question whether some patients could be detrimentally affected by treatment. However, the possibility of detrimental effects of the treatment has not been fully investigated and cannot be excluded. The lack of information on potential detrimental effects hampers inherently the overall assessment of benefit/risk.

Although any degree of prior weight loss within last 6 months was part of the main inclusion criteria as an evidence of metabolic dysregulation, no data were collected on the degree of patients’ prior weight loss at

baseline. Therefore, distribution of patients with different degrees of weight loss at baseline to the study arms remains unknown. In addition, ~33% of all patients were probably enrolled only based on IL-6 threshold of >10 pg/ml, which is not an acknowledged biomarker of metabolic dysregulation. Due to the above-mentioned shortcomings and uncertainties, it is difficult to evaluate the clinical relevance of the observed modest difference in the CRR (i.e. 14% in favour of MABp1) as the magnitude of any potential benefit cannot be put into context appropriately.

Regarding secondary endpoint analyses for change in IL-6 level or platelet count from baseline, the clinical relevance of the observed changes from baseline or any potential clinical benefit for the MABp1-treated patients remain unclear. The reliability of reported IL-6 levels is questionable as handling of outliers was not predefined and the outcome changed significantly when analysing with or without the outliers. Moreover, the mean IL-6 levels (excluding the outliers) were still >10 pg/ml in both arms at Week 8, indicating no clinically significant changes from baseline in the inflammation status. Mean platelet counts at baseline vs Week 8 were within normal range and comparable between the arms. Notably, the analysis of functional and global QoL scales of EORTC QLQ-C30 Questionnaire showed neither statistically significant nor clinically relevant changes from baseline in MABp1-treated patients compared to the placebo patients. Consequently, secondary analyses do not provide any additional evidence in support of efficacy.

The safety database is currently limited, regarding both total number of patients treated and duration of treatment. The observed imbalance of infections (12.1% MABp1 vs. 8.8% placebo) and severe infections (3% MABp1 vs. 1% placebo) in disfavour of the MABp1 arm in the pivotal study could be considered of concern, particularly in light of the claimed indication. However, given the low number of patients with serious infections and since none of the infection events were considered to be treatment-related by the investigators, this risk is not considered worrisome anymore.

6.7.2. Balance of benefits and risks

This application is not approvable from a quality point of view due to concerns on the control of the Drug Substance and Drug Product.

The submitted data derived from one single pivotal trial do not provide compelling evidence of efficacy. It is also difficult to contextualise the true magnitude of the overall efficacy and benefits for advanced CRC patients due the questionable difference in the ORR (mITT) in favour of MABp1 combined with the lack of any significant differences in LBM and none of the QoL measures. Furthermore, the total safety database is currently limited, both regarding patient population and duration of treatment.

The benefit/risk balance of MABp1 is therefore considered negative.

6.7.3. Additional considerations on the benefit-risk balance

N/A

6.8. Conclusions

The overall B/R of Human IgG1 monoclonal antibody specific for human interleukin-1 alpha XBiotech is negative.

7. Recommendations following re-examination

Based on the arguments of the applicant and all the supporting data, the CHMP re-examined its initial opinion

and in its final opinion concluded by consensus that the quality and efficacy of Human IgG1 monoclonal antibody specific for human interleukin-1 alpha XBiotech are not sufficiently demonstrated, and, therefore recommends the refusal of the granting of the marketing authorisation for the above mentioned medicinal product.

The CHMP considers that:

- A control strategy that would ensure consistent manufacture of a product with characteristics that are equivalent to the product used in pivotal clinical studies has not yet been provided.
- Robust evidence of therapeutic efficacy is insufficiently substantiated.
  - The robustness and meaningfulness of the observed differences of MABp1 compared to placebo in terms of the primary composite, clinical response rate (CRR), is questioned in the absence of positive treatment effects on symptoms and lean body mass separately. It is not possible to fully evaluate the clinical relevance of the observed potential efficacy in a sufficient context due to the lack of important baseline data regarding the degree of patients' prior weight loss as well as inclusion of substantial number of patients only based on the IL-6 threshold.
  - In the absence of positive treatment effects on the components of the composite endpoint when analysed separately, the fact that there are more patients having met a favourable efficacy outcome ('responders') to treatment with MABp1 as measured by the composite endpoint gives rise to the question whether some patients could be detrimentally affected by treatment. However, the possibility of detrimental effects of the treatment has not been fully investigated and cannot be excluded.
  - Secondary endpoint analyses did not provide any additional evidence of clinically relevant efficacy. Importantly, there were no statistically significant or clinically relevant changes from baseline in the functional and global QoL scales based on EORTC QLQ-C30 assessments in MABp1-treated patients compared to the placebo patients.

Due to the aforementioned concerns a satisfactory summary of product characteristics, labelling, package leaflet, pharmacovigilance system, risk management plan and post-authorisation measures to address other concerns cannot be agreed.