MabThera®

Rituximab

1. DESCRIPTION

1.1 THERAPEUTIC/PHARMACOLOGIC CLASS OF DRUG

Antineoplastic agent.

ATC Code: L01FA01

1.2 TYPE OF DOSAGE FORM

Intravenous (IV) formulation: concentrate for solution for infusion.

Subcutaneous (SC) formulation: solution for subcutaneous injection.

1.3 ROUTE OF ADMINISTRATION

Intravenous formulation: intravenous infusion

Subcutaneous formulation: subcutaneous injection

1.4 STERILE / RADIOACTIVE STATEMENT

Sterile product.

1.5 QUALITATIVE AND QUANTITATIVE COMPOSITION

Active ingredient: rituximab

Intravenous Formulation

MabThera IV is a clear, colorless liquid supplied in sterile, preservative-free, non-pyrogenic single-dose vials.

Excipients: As registered locally.

Single-dose vials. Vials contain 100 mg/10 mL and 500 mg/50 mL.

Subcutaneous Formulation

MabThera SC is a colorless to yellowish, clear to opalescent solution supplied in sterile, preservative-free, non-pyrogenic single-dose vials.

MabThera SC contains recombinant human hyaluronidase (rHuPH20), an enzyme used to increase the dispersion and absorption of co-administered drugs when administered subcutaneously.

All other excipients described as per local requirements.

Subcutaneous formulation for non-Hodgkin's lymphoma:

Single dose vials contain 1400 mg/11.7 mL (in 15 mL vial)

Subcutaneous formulation for chronic lymphocytic leukaemia:

Single dose vials contain 1600 mg/13.4 mL (in 20 mL vial)

2. CLINICAL PARTICULARS

2.1 THERAPEUTIC INDICATION(S)

Non-Hodgkin's Lymphoma

MabThera IV/SC is indicated for the treatment of:

- adult patients with relapsed or chemoresistant low-grade or follicular, CD20-positive, B cell non-Hodgkin's lymphoma.
- previously untreated adult patients with stage III-IV follicular lymphoma in combination with chemotherapy.
- adult patients with follicular lymphoma as maintenance treatment, after response to induction therapy.
- adult patients with CD20-positive diffuse large B-cell non-Hodgkin's lymphoma in combination with CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone) chemotherapy.

MabThera IV in combination with chemotherapy is indicated for the treatment of:

- Pediatric patients (aged ≥ 6 months to < 18 years old) with previously untreated advanced stage CD20 positive diffuse large B-cell lymphoma (DLBCL), Burkitt lymphoma (BL)/Burkitt leukemia (mature B-cell acute leukaemia) (BAL) or Burkitt-like lymphoma (BLL).

Chronic Lymphocytic Leukaemia

MabThera IV/SC in combination with chemotherapy is indicated for the treatment of patients with previously untreated and relapsed/refractory chronic lymphocytic leukaemia (CLL) .

Rheumatoid Arthritis

MabThera IV in combination with methotrexate is indicated in adult patients for:

- the treatment of moderate to severe, active rheumatoid arthritis when the response to disease-modifying anti-rheumatic drugs including methotrexate has been inadequate.

- treatment of moderate to severe, active rheumatoid arthritis in patients with an inadequate response or intolerance to one or more tumour necrosis factor (TNF) inhibitor therapies.

MabThera IV has been shown to reduce the rate of progression of joint damage as measured by X-ray, to improve physical function and to induce major clinical response, when given in combination with methotrexate.

Adult and Pediatric Patients with Granulomatosis with Polyangiitis (Wegener's) (GPA) and Microscopic Polyangiitis (MPA)

MabThera IV in combination with glucocorticoids is indicated for the treatment of adult patients with severe active granulomatosis with polyangiitis (GPA, also known as Wegener's granulomatosis) and microscopic polyangiitis (MPA) (see section 3.1.2 Clinical/Efficacy Trials).

MabThera IV in combination with glucocorticoids is indicated for the treatment of pediatric patients (aged ≥ 2 to < 18 years old) with active GPA and MPA.

Pemphigus Vulgaris

MabThera IV is indicated for the treatment of patients with moderate to severe pemphigus vulgaris (PV).

2.2 DOSAGE AND ADMINISTRATION

General

Intravenous and Subcutaneous Formulations

Substitution by any other biological medicinal product requires the consent of the prescribing physician.

It is important to check the product labels to ensure that the appropriate formulation (IV or SC) and strength is being given to the patient, as prescribed.

MabThera should always be administered in an environment where full resuscitation facilities are immediately available and under the close supervision of an experienced healthcare professional.

The safety and efficacy of alternating or switching between MabThera and products that are biosimilar but not deemed interchangeable has not been established. Therefore, the benefit-risk of alternating or switching needs to be carefully considered.

Premedication and Prophylactic Medications

Premedication consisting of an analgesic/anti-pyretic (e.g., paracetamol /acetaminophen) and an anti-histaminic drug (e.g., diphenhydramine) should always be given before each administration of MabThera.

Premedication with glucocorticoids should be administered in order to reduce the frequency and severity of infusion-related reactions. Patients with RA, PV or adult and pediatric GPA/MPA should receive 100 mg IV methylprednisolone to be completed 30 minutes prior to each MabThera IV infusion (see section 2.4 Warnings and Precautions).

In adult patients with NHL or CLL premedication with glucocorticoids should also be considered, particularly if MabThera is not given in combination with steroid-containing chemotherapy (see section 2.4 Warnings and Precautions).

In pediatric patients with NHL, premedication with paracetamol and H1 antihistamine (= diphenhydramine or equivalent) should be administered 30 to 60 minutes before the start of each MabThera IV infusion. In addition, patients will also receive prednisone as part of the 1stcourse of cyclophosphamide, oncovin (vincristine), prednisolone, adriamycin (doxorubicin), methotrexate (COPADM) at the time of the first MabThera IV administration. In the 2nd COPADM and following courses of MabThera, cytarabine (Aracytine, Ara-C), VePesid (VP-16) (CYVE) (R-CYVE), prednisone is not given at the time of MabThera IV administration (see Table 1).

Pneumocystis jiroveci pneumonia (PJP) prophylaxis is recommended for adult and pediatric patients with GPA/MPA and adult patients with PV during and following MabThera IV treatment, as appropriate according to local clinical practice guidelines.

Prophylaxis with adequate hydration and administration of uricostatics starting 48 hours prior to start of therapy is recommended for CLL patients to reduce the risk of tumour lysis syndrome. For CLL patients whose lymphocyte counts are > 25 x109/L it is recommended to administer prednisone/ prednisolone 100 mg intravenously shortly before administration with MabThera to decrease the rate and severity of acute infusion reactions and/or cytokine release syndrome.

Dosage adjustments during treatment

No dose reductions of MabThera are recommended [61]. When MabThera is given in combination with chemotherapy, standard dose reductions for the chemotherapeutic drugs should be applied.

Intravenous Formulation

MabThera IV formulation is not intended for subcutaneous administration (see section 4.2 Special Instructions for Use, Handling and Disposal).

Do not administer the prepared infusion solutions as an intravenous push or bolus (see section 4.2 Special Instructions for Use, Handling and Disposal).

Intravenous Formulation Infusion Rate

First intravenous infusion

The recommended initial infusion rate is 50 mg/hour; after the first 30 minutes, the rate can be escalated in 50 mg/hour increments every 30 minutes to a maximum of 400 mg/hour.

Pediatric patients – non-Hodgkin's lymphoma

The recommended initial rate for infusion is 0.5 mg/kg/hour (maximum 50 mg/hour); it can be escalated by 0.5 mg/kg/hour every 30 minutes if there is no hypersensitivity or infusion-related reactions, to a maximum of 400 mg/hour.

Subsequent intravenous infusions

Subsequent infusions of MabThera IV can be started at a rate of 100 mg/hour and increased by 100 mg/hour increments every 30 minutes to a maximum of 400 mg/hour.

Pediatric patients – non-Hodgkin's lymphoma

Subsequent infusions of MabThera IV can be administered at an initial rate of 1 mg/kg/hour (maximum 50 mg/hour); it can be increased by 1 mg/kg/hour every 30 minutes to a maximum of 400 mg/hour.

Subcutaneous Formulation

MabThera SC formulation is not intended for intravenous administration (see section 4.2 Special Instructions for Use, Handling and Disposal).

MabThera SC 1400 mg is intended for use in non-Hodgkin's lymphoma (NHL) only.

MabThera SC 1600 mg is intended for use in chronic lymphocytic leukemia (CLL) only.

MabThera SC should be injected subcutaneously into the abdominal wall and never into areas where the skin is red, bruised, tender, or hard or areas where there are moles or scars. No data are available on performing the injection in other sites of the body therefore injections should be restricted to the abdominal wall.

During the treatment course with MabThera SC, other medications for subcutaneous administration should preferably be administered at different sites.

MabThera SC 1400 mg injection should be administered over approximately 5 minutes.

MabThera SC 1600 mg injection should be administered over approximately 7 minutes.

If an injection is interrupted it can be resumed or another location may be used, if appropriate.

Standard dosage

Adult Low-grade or Follicular Non-Hodgkin's Lymphoma

Intravenous Formulation

Initial treatment

- Intravenous monotherapy

The recommended dosage of MabThera IV used as monotherapy for adult patients is 375 mg/m^2 body surface area (BSA), administered as an intravenous infusion (see "Intravenous Formulation Infusion Rate" sub-section, above) once weekly for 4 weeks.

- Intravenous combination therapy

The recommended dosage of MabThera IV (R-IV) in combination with any chemotherapy is 375 mg/m^2 BSA per cycle for a total of:

- 8 cycles R-IV with CVP (21 days/cycle)
- 8 cycles R-IV with MCP (28 days/cycle)
- 8 cycles R-IV with CHOP (21 days/cycle); 6 cycles if a complete remission is achieved after 4 cycles
- 6 cycles R-IV with CHVP-Interferon (21 days/cycle)

MabThera IV should be administered on day 1 of each chemotherapy cycle after intravenous administration of the glucocorticoid component of the chemotherapy, if applicable.

Alternative 90-minute subsequent intravenous infusions

Patients who do not experience a Grade 3 or 4 infusion-related adverse event with Cycle 1 are eligible for an alternative 90-minute subsequent infusion in Cycle 2. The alternative infusion rate can be started at a rate of 20% of the total dose given in the first 30 minutes and the remaining 80% of the total dose given over the next 60 minutes for a total infusion time of 90 minutes. Patients who tolerate the first 90-minute MabThera IV infusion (Cycle 2) can continue to receive subsequent MabThera IV infusions at the 90-minute rate for the remainder of the treatment regimen (through Cycle 6 or Cycle 8). Patients who have clinically significant cardiovascular disease or who have a circulating lymphocyte count > 5000/mm^3 before Cycle 2 should not receive the 90-minute infusion (see section 2.6 Undesirable Effects, Clinical Trials and section 3.1.2 Clinical/Efficacy Studies).

Re-treatment following relapse

Patients who have responded to MabThera IV initially may receive MabThera IV at a dose of 375 mg/m^2 BSA, administered as an IV infusion once weekly for 4 weeks (see section 3.1.2 Clinical/Efficacy Studies, Re-treatment, weekly for 4 doses).

Maintenance treatment

Previously untreated patients after response to induction treatment may receive maintenance therapy with MabThera IV given at 375 mg/m^2 BSA once every 2 months until disease progression or for a maximum period of two years (12 infusions in total).

Relapsed/refractory patients after response to induction treatment may receive maintenance therapy with MabThera IV given at 375 mg/m^2 BSA once every 3 months until disease progression or for a maximum period of two years (8 infusions in total).

Subcutaneous Formulation (1400 mg)

All patients must always receive their first dose of MabThera by intravenous administration. During their first cycle the patient is at the highest risk of experiencing an infusion/administration related reaction. Beginning therapy with MabThera IV infusion allows management of infusion/administration related reactions by slowing or stopping the intravenous infusion (see section 2.4 Warnings and Precautions). The subcutaneous formulation must only be given at the second or subsequent cycles (see "First administration: Intravenous formulation" and "Subsequent administrations: Subcutaneous formulation" sub-sections, below).

First administration: Intravenous formulation

The first administration of MabThera must always be given by intravenous infusion at a dose of 375 mg/m^2 BSA (see "Intravenous Formulation Infusion Rate" sub-section, above).

Subsequent administrations: Subcutaneous formulation

Patients unable to receive the full MabThera intravenous infusion dose should continue to receive subsequent cycles with MabThera IV until a full IV dose is successfully administered.

For patients who are able to receive the full MabThera IV infusion dose the second or subsequent MabThera dose can be given subcutaneously using the MabThera SC formulation (see section 2.4 Warnings and Precautions).

Initial treatment

- Subcutaneous monotherapy

The recommended dosage of MabThera SC used as monotherapy for adult patients is subcutaneous injection at a fixed dose of 1400 mg irrespective of the patient's BSA, once weekly for 3 weeks following MabThera IV at week 1 (1st week R-IV then 3 weeks R-SC; 4 weeks in total).

- Subcutaneous combination therapy

MabThera SC should be administered on day 0 or day 1 of each chemotherapy cycle after administration of the glucocorticoid component of the chemotherapy, if applicable.

The recommended dosage in combination with any chemotherapy is MabThera IV (R-IV) 375 mg/m^2 BSA intravenously for the first cycle followed by subcutaneous injection of MabThera SC (R-SC) at a fixed dose of 1400 mg, irrespective of the patient's BSA.

- 1st cycle R-IV with CVP + 7 cycles R-SC with CVP (21 days/ cycle)
- 1st cycle R-IV with MCP + 7 cycles R-SC with MCP (28 days/ cycle)
- 1st cycle R-IV with CHOP + 7 cycles R-SC with CHOP (21 days/ cycle); or a total of 6 cycles (1st cycle R-IV then 5 cycles R-SC) if complete remission is achieved after 4 cycles
- 1st cycle R-IV with CHVP-Interferon + 5 cycles R-SC with CHVP-Interferon (21 days/ cycle).

Re-treatment following relapse

Patients who have responded to MabThera IV or SC initially may be treated again with MabThera SC at a fixed dose of 1400 mg, administered as a subcutaneous injection once weekly, following a first administration of MabThera given by intravenous infusion at a dose of 375 mg/m^2 BSA (1st week R-IV then 3 weeks R-SC; 4 weeks in total) (see section 3.1.2 Clinical/Efficacy Studies, Re-treatment, weekly for 4 doses).

Maintenance treatment

Previously untreated patients after response to induction treatment may receive maintenance therapy with MabThera SC given at a fixed dose of 1400 mg once every 2 months until disease progression or for a maximum period of two years (12 administrations in total).

Relapsed/refractory patients after response to induction treatment may receive maintenance therapy with MabThera SC given at a fixed dose of 1400 mg once every 3 months until disease progression or for a maximum period of two years (8 administrations in total).

Adult Diffuse Large B-cell Non-Hodgkin's Lymphoma

<u>Intravenous Formulation</u>

In patients with diffuse large B cell non-Hodgkin's lymphoma MabThera IV should be used in combination with CHOP (cyclophosphamide, doxorubicin, prednisone and vincristine) chemotherapy. The recommended dosage of MabThera IV is 375 mg/m^2 BSA, administered on day 1 of each chemotherapy cycle for 8 cycles after IV administration of the glucocorticoid component of CHOP (see "Intravenous Formulation Infusion Rate" sub-section, above).

Alternative 90-minute subsequent intravenous infusions

Patients who do not experience a Grade 3 or 4 infusion-related adverse event with Cycle 1 are eligible for an alternative 90-minute subsequent infusion in Cycle 2. The alternative infusion rate can be started at a rate of 20% of the total dose given in the first 30 minutes and the remaining 80% of the total dose given over the next 60 minutes for a total infusion time of 90 minutes. Patients who tolerate the first 90-minute MabThera IV infusion (Cycle 2) can continue to receive subsequent MabThera IV infusions at the 90-minute rate for the remainder

of the treatment regimen (through Cycle 6 or Cycle 8). Patients who have clinically significant cardiovascular disease or who have a circulating lymphocyte count > 5000/mm^3 before Cycle 2 should not receive the 90-minute infusion (see section 2.6 Undesirable Effects, Clinical Trials and section 3.1.2 Clinical/Efficacy Studies).

Subcutaneous Formulation (1400 mg)

All patients must always receive their first dose of MabThera by intravenous administration. During their first cycle the patient is at the highest risk of experiencing an infusion/administration related reaction. Beginning therapy with MabThera IV infusion allows management of infusion/administration related reactions by slowing or stopping the intravenous infusion (see section 2.4 Warnings and Precautions). The subcutaneous formulation must only be given at the second or subsequent cycles (see "First administration: Intravenous formulation" and "Subsequent administrations: Subcutaneous formulation" sub-sections, below).

In patients with diffuse large B cell non-Hodgkin's lymphoma MabThera SC 1400 mg should be used in combination with CHOP (cyclophosphamide, doxorubicin, prednisone and vincristine) chemotherapy.

First administration: Intravenous formulation

The first administration of MabThera must always be given by intravenous infusion at a dose of 375 mg/m^2 BSA (see "Intravenous Formulation Infusion Rate" sub-section, above).

Subsequent administrations: Subcutaneous formulation

Patients unable to receive the full MabThera intravenous infusion dose should continue to receive subsequent cycles with MabThera IV until a full IV dose is successfully administered.

For patients who are able to receive the full MabThera IV infusion dose, the second or subsequent MabThera doses can be given subcutaneously using the MabThera SC formulation (see section 2.4 Warnings and Precautions).

The recommended dosage of MabThera SC is a fixed dose of 1400 mg, irrespective of the patient's BSA, administered on day 1 of each chemotherapy cycle for 8 cycles (1st cycle R-IV with CHOP + 7 cycles R-SC with CHOP; 8 cycles in total) after IV administration of the glucocorticoid component of CHOP.

Pediatric Patients with B-cell Non-Hodgkin's Lymphoma

Intravenous Formulation Only

In pediatric patients from ≥ 6 months to < 18 years of age with previously untreated, advanced stage CD20 positive DLBCL/BL/BAL/BLL, MabThera IV should be used in combination with systemic Lymphome Malin B (LMB) chemotherapy. In total six infusions of MabThera IV will be added to the chemotherapy induction courses COPDAM1 and COPDAM2 and the two consolidation courses of CYM/CVVE, two during each of the two induction courses and one during each of the two consolidation courses, (for details see Tables 1 and 2). The recommended dosage of MabThera is 375 mg/m^2 BSA, administered as an IV infusion.

Table 1 Posology of MabThera IV Administration for Non-Hodgkin's Lymphoma Pediatric Patients

Cycle	Day of treatment	Administration details
Prephase (COP)	No MabTthera/Rituxan given	-
Induction course 1 (COPDAM1)	Day -2 (corresponding to day 6 of the prephase) 1st MabThera infusion	During the 1st induction course, prednisone is given as part of the chemotherapy course, and should be administered prior to MabThera.
	Day 1 2nd MabThera infusion	MabThera will be given 48 hours after the first infusion of MabThera.
Induction course 2 (COPDAM2)	Day -2 3rd MabThera infusion	In the 2nd induction course, prednisone is not given at the time of MabThera administration.
	Day 1 4th MabThera infusion	MabThera will be given 48 hours after the third infusion of MabThera.
Consolidation course 1 (CYM/CYVE)	Day 1 5th MabThera infusion	Prednisone is not given at the time of MabThera administration.
Consolidation course 2 (CYM/CYVE)	Day 1 6th MabThera infusion	Prednisone is not given at the time of MabThera administration.
Maintenance course 1 (M1)	Day 25 to 28 of consolidation course 2 (CYVE) No MabThera given	Starts when peripheral counts have recovered from consolidation course 2 (CYVE) with ANC> 1.0 x 10^9/l and platelets > 100 x 10^9/l
Maintenance course 2 (M2)	Day 28 of maintenance course 1 (M1) No MabThera given	-
ANC = Absolute Neutrophil Count; COP = Cyclophosphamide, Oncovin (vincristine), Prednisone; COPDAM = Cyclophosphamide, Oncovin (vincristine), Prednisolone, Adriamycin (doxorubicin), Methotrexate; CYM = CYtarabine (Aracytine, Ara-C), Methotrexate; CYVE = CYtarabine (Aracytine, Ara-C), VEposide (VP16)		

Table 2 Treatment Plan for Non-Hodgkin's Lymphoma Pediatric Patients: Concomitant Chemotherapy with MabThera IV

Treatment Plan	Patient Staging*	Administration details
Group B**	Stage III with high LDH level (> N x 2),	Prephase followed by 4 courses:

	Stage IV CNS negative	2 induction courses (COPADM) with HDMTX 3g/m^2 and 2 consolidation courses (CYM)
Group C	Group C1***: B- AL CNS negative, Stage IV & B-AL CNS positive and CSF negative	Prephase followed by 6 courses: 2 induction courses (COPADM) with HDMTX 8g/m², 2 consolidation courses (CYVE) and 2 maintenance courses (M1 and M2)
	Group C3****: B-AL CSF positive, Stage IV CSF positive	
Consecutive courses should be given as soon as blood count recovery and patient's condition allows except for the maintenance courses which are given at 28 day intervals. BAL = Burkitt leukaemia (mature B-cell acute leukaemia); CSF = Cerebrospinal Fluid; CNS = Central Nervous System; HDMTX = High-dose Methotrexate; LDH = Lactic Acid Dehydrogenase		

*In study BO25380, patients were assigned to therapeutic groups B, C1, and C3 based on the disease stage and in line with the LMB scheme, as follows:
**Therapeutic Group B: stage III lymphoma with high LDH level (>ULN × 2) or stage IV lymphoma without CNS involvement.
***Therapeutic Group C1: B-AL without CNS involvement; stage IV lymphoma and B-AL with CNS involvement but no lymphoma cells in the spinal fluid.
****Therapeutic Group C3: B-AL and stage IV lymphoma with lymphoma cells present in the spinal fluid.

Chronic Lymphocytic Leukaemia

Intravenous Formulation

The recommended dosage of MabThera IV in combination with chemotherapy for previously untreated and relapsed/refractory CLL patients is 375 mg/m^2 BSA administered on day 1 of the first treatment cycle followed by 500 mg/m^2 BSA administered on day 1 of each subsequent cycle for 6 cycles in total (see section 3.1.2 Clinical/Efficacy Studies). The chemotherapy should be given after the MabThera IV infusion (see "Intravenous Formulation Infusion Rate" sub-section, above).

Subcutaneous Formulation (1600 mg)

All patients must always receive their first dose of MabThera by intravenous administration. During their first cycle the patient is at the highest risk of experiencing an infusion/administration related reaction. Beginning therapy with MabThera IV infusion allows management of infusion/administration related reactions by slowing or stopping the intravenous infusion (see section 2.4 Warnings and Precautions). The subcutaneous formulation must only be given at the second or subsequent cycles (see "First administration: Intravenous formulation" and "Subsequent administrations: Subcutaneous formulation" sub-sections, below).

First administration: Intravenous formulation

The first administration of MabThera must always be given by intravenous infusion at a dose of 375 mg/m^2 BSA (see "Intravenous Formulation Infusion Rate" sub-section, above).

Subsequent administrations: Subcutaneous formulation

Patients unable to receive the full MabThera intravenous dose should continue to receive subsequent cycles with MabThera IV until a full IV dose is successfully administered.

For patients who are able to receive the full MabThera IV infusion dose the second or subsequent MabThera dose can be given subcutaneously using the MabThera SC formulation (see section 2.4 Warnings and Precautions).

The recommended dosage of MabThera SC in combination with chemotherapy is a fixed dose of 1600 mg irrespective of the patient's BSA, administered on day 1 of each chemotherapy cycle for 5 cycles (1st cycle R-IV + 5 cycles R-SC; 6 cycles in total). The chemotherapy should be given after MabThera administration.

Rheumatoid Arthritis

Intravenous Formulation Only

A course of MabThera IV consists of two 1000 mg IV infusions. The recommended dosage of MabThera is 1000 mg by IV infusion followed two weeks later by the second 1000 mg IV infusion (see "Intravenous Formulation Infusion Rate" sub-section, above).

The need for further courses should be evaluated 24 weeks following the previous course with retreatment given based on residual disease or disease activity returning to a level above a DAS28-ESR of 2.6 (treatment to remission) (see section 3.1.2 Clinical/Efficacy Studies, Rheumatoid Arthritis). Patients may receive further courses no sooner than 16 weeks following the previous course.

Alternative 120-minute subsequent infusions with the concentration of 4 mg/mL in a 250 mL volume:

If patients did not experience a serious infusion-related adverse event with their previous infusion administered over the original administration schedule, a 120-minute infusion can be administered for subsequent infusions. Initiate at a rate of 250 mg/hour for the first 30 minutes and then 600 mg/hour for the next 90 minutes. If the 120-minute infusion is tolerated, the same alternative 120-minute infusion rate can be used when administering subsequent infusions and courses.

Patients who have clinically significant cardiovascular disease including arrhythmias or previous serious infusion reactions to any prior biologic therapy or to MabThera, should not be administered the 120-minute infusion

Adult Patients with Granulomatosis with Polyangiitis (Wegener's) (GPA) and Microscopic Polyangiitis (MPA)

Intravenous Formulation Only

Induction of remission

The recommended dosage of MabThera IV for treatment of adult patients with severe active GPA and MPA is 375 mg/m^2 BSA, administered as an IV infusion (see "Intravenous Formulation Infusion Rate" sub-section, above) once weekly for 4 weeks.

Methylprednisolone given IV for 1 to 3 days at a dose of 1000 mg per day is recommended in combination with MabThera IV to treat severe vasculitis symptoms, followed by oral prednisone 1 mg/kg/day (not to exceed 80 mg/day, and tapered as rapidly as possible based on clinical need) during and after the 4 week induction course of MabThera IV treatment.

Maintenance treatment

Following induction of remission with MabThera IV, maintenance treatment should be initiated no sooner than 16 weeks after the last MabThera IV infusion.

Following induction of remission with other standard of care immunosuppressants, MabThera IV maintenance treatment should be initiated during the 4 week period that follows disease remission.

Administer MabThera IV as two 500 mg IV infusions separated by two weeks, followed by a 500 mg IV infusion at month 6, 12 and 18 and then every 6 months thereafter based on clinical evaluation.

Pediatric Patients with Granulomatosis with Polyangiitis (Wegener's) (GPA) and Microscopic Polyangiitis (MPA)

Intravenous Formulation Only

Induction of remission

The recommended dosage of MabThera IV for the treatment of pediatric patients with active GPA/MPA is 375 mg/m^2 BSA, administered as an IV infusion once weekly for 4 weeks.

Prior to the first MabThera IV infusion, methylprednisolone should be given IV for three daily doses of 30 mg/kg (not to exceed 1 g/day) to treat severe vasculitis symptoms. Up to three additional daily doses of 30 mg/kg IV methylprednisolone can be given prior to the first MabThera IV infusion.

Following completion of IV methylprednisolone administration, patients should receive oral prednisone 1 mg/kg/day (not to exceed 60 mg/day) and tapered as rapidly as possible per clinical need (see section 3.1.2 Clinical/Efficacy Studies).

Maintenance treatment

Administer MabThera as two 250 mg/m^2 IV infusions separated by two weeks, followed by a 250 mg/m^2 IV infusion every 6 months thereafter based on clinical evaluation. The 250 mg/m^2 dose is based on an extrapolation approach which is expected to provide pediatric GPA/MPA patients with exposure comparable to the observed exposure in adults.

If induction treatment of active disease was with MabThera, maintenance treatment with MabThera should be initiated within 24 weeks after the last MabThera induction infusion or based on clinical evaluation, but no sooner than 16 weeks after the last MabThera induction infusion.

If induction treatment of active disease was with other standard of care immunosuppressants, MabThera maintenance treatment should be initiated within the 4 week period that follows achievement of disease control.

Pemphigus Vulgaris

Intravenous Formulation Only

The recommended dosage of MabThera IV for the treatment of pemphigus vulgaris is 1000 mg administered as an IV infusion followed two weeks later by a second 1000 mg IV infusion in combination with a tapering course of glucocorticoids (see section 2.2 Dosage and Administration, General).

Maintenance treatment

Maintenance infusions of 500 mg IV should be administered at month 12 and then every 6 months thereafter based on clinical evaluation.

Treatment of relapse

In the event of relapse during the course of MabThera IV therapy, patients may receive 1000 mg IV [186]. The healthcare provider should also consider resuming or increasing the patient's glucocorticoid dose based on clinical evaluation.

Subsequent infusions may be administered no sooner than 16 weeks following the previous infusion.

2.2.1 Special Dosage Instructions

Pediatric use

GPA/MPA

No dose adjustments are recommended in pediatric patients (≥ 2 to < 18 years of age) with active GPA/MPA. Currently available data are described in sections 2.5.4 Use in Special Populations, Pediatric Use, 3.1.2 Clinical/Efficacy Studies, 3.2.2 Distribution and 3.2.5 Pharmacokinetics in Special Populations.

The safety and efficacy of MabThera IV in children and adolescents (≥ 2 to <18 years) have not been established in autoimmune indications other than active GPA/MPA. MabThera IV should not be used in pediatric patients with active GPA/MPA < 2 years of age (see section 2.5.4 Use in Special Populations, Pediatric Use).

B-cell Non-Hodgkin's Lymphoma

No MabThera IV dose adjustments, other than by BSA, are required. Currently available data are described in sections 2.5.4 Use in Special Populations, Pediatric Use, 3.1.2 Clinical/Efficacy Studies, 2.6.1 Clinical Trials and 3.2.2 Distribution).

MabThera IV should not be used in pediatric patients from birth to < 6 months of age with CD20 positive diffuse large B-cell lymphoma.

Only limited data are available for B-NHL patients under 3 years of age. The safety and efficacy of MabThera IV in pediatric patients ≥ 6 months to < 18 years of age has not been established in oncology indications other than previously untreated advanced stage CD20 positive DLBCL/BL/BAL/BLL.

Geriatric use

No dose adjustment is required in patients aged ≥65 years of age.

2.3 CONTRAINDICATIONS

MabThera is contraindicated in patients with known hypersensitivity to rituximab, to any of its excipients or to murine proteins.

2.4 WARNINGS AND PRECAUTIONS

2.4.1 General

In order to improve the traceability of biological medicinal products, the trade name and batch number of the administered product should be clearly recorded (or stated) in the patient file.

Non-Hodgkin's Lymphoma and Chronic Lymphocytic Leukaemia Patients

Infusion/administration-related reactions

MabThera is associated with infusion/administration-related reactions, which may be related to release of cytokines and/or other chemical mediators. Cytokine release syndrome may be clinically indistinguishable from acute hypersensitivity reactions

- Infusion-related reactions for MabThera IV

Severe infusion-related reactions (IRRs) with fatal outcome have been reported during post-marketing use. Severe IRRs usually manifested within 30 minutes to 2 hours after starting the first MabThera IV infusion, were characterized by pulmonary events and included, in some cases, rapid tumour lysis and features of tumour lysis syndrome in addition to fever, chills, rigors, hypotension, urticaria, angioedema and other symptoms (see section 2.6 Undesirable Effects). Patients with a high tumour burden or with a high number (>25 x 10^9/L) of circulating malignant cells such as patients with CLL and mantle cell lymphoma may be at higher risk of developing severe IRRs. Infusion reaction symptoms are usually reversible with interruption of the infusion. Treatment of infusion-related symptoms with diphenhydramine and paracetamol/acetaminophen is recommended. Additional treatment with bronchodilators or IV saline may be indicated. In most cases, the infusion can be resumed at a 50% reduction in rate (e.g., from 100 mg/hour to 50 mg/hour) when symptoms have completely resolved. Most patients who have experienced non-life threatening IRRs have been able to complete the full course of MabThera IV therapy. Further treatment of patients after complete resolution of signs and symptoms has rarely resulted in repeated severe IRRs.

Patients with a high number (>25 x 10^9/L) of circulating malignant cells or high tumour burden such as patients with CLL and mantle cell lymphoma, who may be at higher risk of especially severe IRRs, should only be treated with extreme caution. These patients should be very closely monitored throughout the first infusion. Consideration should be given to the use of a reduced infusion rate for the first infusion in these patients or a split dosing over two days during the first cycle and any subsequent cycles if the lymphocyte count is still >25 x 10^9/L.

- Hypersensitivity reactions / Anaphylaxis

Anaphylactic and other hypersensitivity reactions have been reported following the intravenous administration of proteins to patients. Epinephrine, antihistamines and glucocorticoids should be available for immediate use in the event of a hypersensitivity reaction to MabThera IV.

- Administration-related reactions for MabThera SC

Local cutaneous reactions, including injection site reactions, have been reported in patients receiving MabThera SC. Symptoms included pain, swelling, induration, haemorrhage, erythema, pruritus and rash (see section 2.6 Undesirable Effects). Some local cutaneous reactions occurred more than 24 hours after the SC drug administration. The majority of local cutaneous reactions seen following administration of the SC formulation were mild or moderate and resolved without any specific treatment.

All patients must always receive their first dose of MabThera by intravenous administration in order to avoid an irreversible administration of the full MabThera SC dose during Cycle 1. During this cycle the patient would have the highest risk of experiencing an IRR that can be treated effectively by slowing or stopping the infusion. The subcutaneous formulation must only be given at the second or subsequent cycles. Patients unable to receive the full MabThera IV infusion dose should continue to receive subsequent cycles with MabThera IV until a full IV dose is successfully administered. For patients who are able to receive the full MabThera IV infusion dose the second or subsequent MabThera dose can be given subcutaneously using the MabThera SC formulation (see section 2.2 Dosage and Administration). As with the intravenous formulation, MabThera SC should be administered in an environment where full resuscitation facilities are immediately available and under the close supervision of a healthcare professional. Premedication consisting of an analgesic/antipyretic and an antihistamine should always be administered before each dose of MabThera SC. Premedication with glucocorticoids should also be considered.

Patients should be observed for at least 15 minutes following MabThera SC administration. A longer period may be appropriate in patients with an increased risk of hypersensitivity reactions.

Patients should be instructed to contact their treating physician immediately if symptoms that are suggestive of severe hypersensitivity reactions or cytokine release syndrome occur at any time after drug administration.

Pulmonary events

Pulmonary events have included hypoxia, lung infiltration, and acute respiratory failure. Some of these events have been preceded by severe bronchospasm and dyspnea. In some cases, symptoms worsened over time, while in others initial improvement was followed by

clinical deterioration. Therefore, patients experiencing pulmonary events or other severe infusion-related symptoms should be closely monitored until complete resolution of their symptoms occurs. Patients with a history of pulmonary insufficiency or those with pulmonary tumour infiltration may be at greater risk of poor outcome and should be treated with increased caution. Acute respiratory failure may be accompanied by events such as pulmonary interstitial infiltration or edema, visible on a chest X-ray. The syndrome usually manifests itself within one or two hours of initiating the first infusion. Patients who experience severe pulmonary events should have their MabThera administration interrupted immediately (see section 2.2 Dosage and Administration) and should receive aggressive symptomatic treatment.

Rapid tumour lysis

MabThera mediates the rapid lysis of benign and malignant CD20-positive cells. Signs and symptoms (e.g., hyperuricemia, hyperkalemia, hypocalcaemia, hyperphosphataemia, acute renal failure, elevated LDH) consistent with tumour lysis syndrome (TLS) have been reported to occur after the first MabThera IV infusion in patients with high numbers of circulating malignant lymphocytes. Prophylaxis for TLS should be considered for patients at risk of developing rapid tumour lysis (e.g., patients with a high tumour burden or with a high number [$>25 \times 10^9$/L] of circulating malignant cells such as patients with CLL or mantle cell lymphoma). These patients should be followed closely and appropriate laboratory monitoring performed. Appropriate medical therapy should be provided for patients who develop signs and symptoms consistent with rapid tumour lysis. Following treatment and complete resolution of signs and symptoms, subsequent MabThera IV therapy has been administered in conjunction with prophylactic therapy for TLS in a limited number of cases.

Cardiovascular

Since hypotension may occur during MabThera administration consideration should be given to withholding antihypertensive medications 12 hours prior to and throughout MabThera IV/SC administration. Angina pectoris, cardiac arrhythmia, such as atrial flutter and fibrillation, heart failure or myocardial infarction have occurred in patients treated with MabThera IV/SC. Therefore patients with a history of cardiac disease should be monitored closely.

Monitoring of blood counts

Although MabThera is not myelosuppressive in monotherapy, caution should be exercised when considering treatment of patients with neutrophil counts of $<1.5 \times 10^9$/L and/or platelet counts of $<75 \times 10^9$/L, as clinical experience with such patients is limited. MabThera IV has been used in patients who underwent autologous bone marrow transplantation and in other risk groups with a presumable reduced bone marrow function without inducing myelotoxicity.

Consideration should be given to the need for regular full blood counts, including platelet counts, during monotherapy with MabThera. When MabThera is given in combination with CHOP or CVP chemotherapy, regular full blood counts should be performed according to usual medical practice.

Infections

MabThera treatment should not be initiated in patients with severe active infections.

Hepatitis B infections

Cases of hepatitis B reactivation, including reports of fulminant hepatitis, some of which were fatal, have been reported in subjects receiving MabThera IV, although the majority of these subjects were also exposed to cytotoxic chemotherapy. The reports are confounded by both the underlying disease state and the cytotoxic chemotherapy.

Hepatitis B virus (HBV) screening should be performed in all patients before initiation of treatment with MabThera. At minimum this should include HBsAg-status and HBcAb-status. These can be complemented with other appropriate markers as per local guidelines. Patients with active hepatitis B disease should not be treated with MabThera. Patients with positive hepatitis B serology should consult liver disease experts before start of treatment and should be monitored and managed following local medical standards to prevent hepatitis B reactivation.

Progressive multifocal leukoencephalopathy

Cases of progressive multifocal leukoencephalopathy (PML) have been reported during use of MabThera IV in NHL and CLL (see section 2.6 Undesirable Effects, Post Marketing). The majority of patients had received MabThera IV in combination with chemotherapy or as part of a haematopoietic stem cell transplant. Physicians treating patients with NHL or CLL should consider PML in the differential diagnosis of patients reporting neurological symptoms and consultation with a neurologist should be considered as clinically indicated.

Skin reactions

Severe skin reactions such as toxic epidermal necrolysis and Stevens-Johnson syndrome, some with fatal outcome, have been reported (see section 2.6 Undesirable Effects, Post Marketing). In case of such an event with a suspected relationship to MabThera, treatment should be permanently discontinued.

Immunization

The safety of immunization with live viral vaccines following MabThera IV/SC therapy has not been studied and vaccination with live virus vaccines is not recommended.

Patients treated with MabThera may receive non-live vaccinations. However, with non-live vaccines response rates may be reduced. In a non-randomized study, patients with relapsed low-grade NHL who received MabThera IV monotherapy when compared to healthy untreated controls had a lower rate of response to vaccination with tetanus recall antigen (16% vs. 81%) and Keyhole Limpet Haemocyanin (KLH) neoantigen (4% vs. 76% when assessed for >2-fold increase in antibody titer).

Mean pre-therapeutic antibody titers against a panel of antigens (Streptococcus pneumoniae, influenza A, mumps, rubella, varicella) were maintained for at least 6 months after treatment with MabThera IV.

Rheumatoid Arthritis (RA), Granulomatosis with Polyangiitis (Wegener's) (GPA) and Microscopic Polyangiitis (MPA) and Pemphigus Vulgaris (PV) Patients

The efficacy and safety of MabThera IV for the treatment of autoimmune diseases other than rheumatoid arthritis, granulomatosis with polyangiitis (Wegener's) and microscopic polyangiitis and pemphigus vulgaris have not been established.

Infusion-related reactions

MabThera IV is associated with infusion-related reactions (IRRs), which may be related to release of cytokines and/or other chemical mediators.

For RA patients, most infusion-related events reported in clinical trials were mild to moderate in severity. Severe IRRs with fatal outcome have been reported in the post-marketing setting (see section 2.6 Undesirable Effects, Post Marketing). Closely monitor patients with pre-existing cardiac conditions and those who experienced prior cardiopulmonary adverse reactions. The most common symptoms were headache, pruritus, throat irritation, flushing, rash, urticaria, hypertension, and pyrexia. In general, the proportion of patients experiencing any infusion reaction was higher following the first infusion of any treatment course than following the second infusion. Subsequent MabThera IV infusions were better tolerated by patients than the initial infusion. Less than 1% of patients experienced serious IRRs, with most of these reported during the first infusion of the first course (see section 2.6 Undesirable Effects). The reactions reported were usually reversible with a reduction in rate or interruption of MabThera IV infusion, and administration of an anti-pyretic, an antihistamine and occasionally oxygen, intravenous saline, bronchodilators, or glucocorticoids as required. Depending on the severity of the IRR and the required interventions, temporarily or permanently discontinue MabThera IV. In most cases, the infusion can be resumed at a 50% reduction in rate (e.g., from 100 mg/hour to 50 mg/hour) when symptoms have completely resolved.

Infusion-related reactions in GPA/MPA and PV patients were consistent with those seen in RA patients in clinical trials and in the post-marketing setting (see section 2.6 Undesirable Effects).

Hypersensitivity reactions / Anaphylaxis

Anaphylactic and other hypersensitivity reactions have been reported following the intravenous administration of proteins to patients. Medicinal products for the treatment of hypersensitivity reactions (e.g., epinephrine, antihistamines and glucocorticoids) should be available for immediate use in the event of an allergic reaction during administration of MabThera IV.

Cardiovascular

Since hypotension may occur during MabThera IV infusion, consideration should be given to withholding anti-hypertensive medications 12 hours prior to the MabThera infusion IV.

Angina pectoris, cardiac arrhythmias such as atrial flutter and fibrillation, heart failure or myocardial infarction have occurred in patients treated with MabThera IV. Therefore, patients with a history of cardiac disease should be monitored closely (see Infusion-related reactions sub-section, above).

Infections

Based on the mechanism of action of MabThera and the knowledge that B-cells play an important role in maintaining normal immune response, patients may have an increased risk of infection following MabThera IV therapy (see section 3.1.1 Mechanism of Action). MabThera IV should not be administered to patients with an active infection or severely immunocompromised patients (e.g., where levels of CD4 or CD8 are very low). Physicians should exercise caution when considering the use of MabThera IV in patients with a history of recurring or chronic infections or with underlying conditions which may further predispose patients to serious infection (see section 2.6 Undesirable Effects). Patients who develop infection following MabThera IV therapy should be promptly evaluated and treated appropriately.

Hepatitis B infections

Cases of hepatitis B reactivation including those with a fatal outcome have been reported in RA, GPA and MPA patients receiving MabThera IV.

Hepatitis B virus (HBV) screening should be performed in all patients before initiation of treatment with MabThera IV. At minimum this should include HBsAg-status and HBcAb-status. These can be complemented with other appropriate markers as per local guidelines. Patients with active hepatitis B disease should not be treated with MabThera IV. Patients with positive hepatitis B serology should consult liver disease experts before start of treatment and should be monitored and managed following local medical standards to prevent hepatitis B reactivation.

Skin reactions

Severe skin reactions such as toxic epidermal necrolysis and Stevens-Johnson syndrome, some with fatal outcome, have been reported (see section 2.6 Undesirable Effects, Post Marketing). In case of such an event with a suspected relationship to MabThera IV, treatment should be permanently discontinued.

Progressive multifocal leukoencephalopathy

Cases of fatal progressive multifocal leukoencephalopathy (PML) have been reported following use of MabThera IV for the treatment of autoimmune diseases including RA. Several, but not all of the reported cases had potential risk factors for PML , including the underlying disease, long-term immunosuppressive therapy or chemotherapy. PML has also been reported in patients with autoimmune disease not treated with MabThera IV. Physicians treating patients with autoimmune diseases should consider PML in the differential diagnosis of patients reporting neurological symptoms and consultation with a neurologist should be considered as clinically indicated.

Immunization

The safety of immunization with live viral vaccines following MabThera IV therapy has not been studied. Therefore, vaccination with live virus vaccines is not recommended whilst receiving MabThera IV or whilst peripherally B-cell depleted. Patients treated with MabThera IV may receive non-live vaccinations. However, response rates to non-live vaccines may be reduced.

For patients treated with MabThera IV, physicians should review the patient's vaccination status and patients should, if possible, be brought up-to-date with all immunizations in agreement with current immunization guidelines prior to initiating MabThera IV therapy. Vaccinations should be completed at least 4 weeks prior to first administration of MabThera IV.

In a randomized study, patients with RA treated with MabThera IV and methotrexate had comparable response rates to tetanus recall antigen (39% vs. 42%), reduced rates to pneumococcal polysaccharide vaccine (43% vs. 82% to at least 2 pneumococcal antibody serotypes), and KLH neoantigen (34% vs. 80%), when given at least 6 months after MabThera IV as compared to patients only receiving methotrexate. Should non-live vaccinations be required whilst receiving MabThera IV therapy, these should be completed at least 4 weeks prior to commencing the next course of MabThera IV.

In the overall experience of MabThera IV repeat treatment in RA patients over one year, the proportions of patients with positive antibody titers against S. pneumoniae, influenza, mumps, rubella, varicella and tetanus toxoid were generally similar to the proportions at baseline.

Methotrexate naïve RA populations

The use of MabThera IV is not recommended in methotrexate-naïve patients since a favourable benefit risk relationship has not been established.

2.4.2 Drug Abuse and Dependence

No data to report.

2.4.3 Ability to Drive and Use Machines

MabThera has no or negligible effect on the ability to drive and use machines.

2.5 USE IN SPECIAL POPULATIONS

2.5.1 Females and Males of Reproductive Potential

Intravenous and Subcutaneous Formulations

Fertility

No preclinical fertility studies have been conducted.

Animal data

Developmental toxicity studies performed in cynomolgus monkeys revealed no evidence of embryotoxicity in utero. Newborn offspring of maternal animals exposed to MabThera were noted to have depleted B-cell populations during the post-natal phase.

Subcutaneous Formulation

Pharmacokinetic and toxicology studies in animals demonstrate reduction in fetal weight and increase in the number of resorptions following injection of rHuPH20 at maternal systemic exposure levels comparable to those that could occur after accidental bolus IV administration

of a single vial of the MabThera SC formulation in humans, based on the most conservative assumptions possible (see section 3.3 Preclinical Safety, Subcutaneous Formulation).

Contraception

Women of childbearing age must employ effective contraceptive methods during and for 12 months after treatment with MabThera.

2.5.2 Pregnancy

Intravenous and Subcutaneous Formulations

IgG immunoglobulins are known to cross the placental barrier.

B-cell levels in human neonates following maternal exposure to MabThera have not been studied in clinical trials. There are no adequate and well-controlled data from studies in pregnant women, however transient B-cell depletion and lymphocytopenia have been reported in some infants born to mothers exposed to rituximab during pregnancy. For these reasons MabThera should not be administered to pregnant women unless the possible benefit outweighs the potential risk.

Subcutaneous Formulation

The subcutaneous formulation contains recombinant human hyaluronidase (rHuPH20) (see section 1.5 Qualitative and Quantitative Composition).

2.5.3 Lactation

Maternal IgG enters breast milk, and rituximab has been reported to be excreted at low concentrations in human breast milk. Given that the clinical significance of this finding for infants is not known, MabThera should not be administered to nursing mothers.

Limited data on rituximab excretion into breast milk suggest very low rituximab concentrations in milk (relative infant dose less than 0.4%). Few cases of follow-up of breastfed infants describe normal growth and development up to 2 years [221]. However, as these data are limited and the long-term outcomes of breastfed infants remain unknown, breast-feeding is not recommended while being treated with rituximab and optimally for 6 months following rituximab treatment

2.5.4 Pediatric Use

Pediatric Patients with Granulomatosis with Polyangiitis (Wegener's) (GPA) and Microscopic Polyangiitis (MPA)

In a study, twenty-five pediatric patients (6 children ≥ 2 years to < 12 years and 19 adolescents ≥ 12 years to < 18 years) with active GPA/MPA were administered IV MabThera (see sections 3.1.2 Clinical/Efficacy Studies).

In general, the adverse drug reactions observed in MabThera IV-treated pediatric patients with active GPA/MPA during the overall study period were consistent in type, nature and severity to those seen in adult patients (see section 2.6 Undesirable Effects, Clinical Trials).

The efficacy of MabThera IV in pediatric active GPA/MPA patients is based on PK exposure from WA25615 (PePRS) and extrapolation from the established efficacy of MabThera IV in adult GPA/MPA patients (see sections 3.1.2 Clinical/Efficacy Studies and 3.2.5 Pharmacokinetics in Special Populations).

The safety and efficacy of MabThera in pediatric patients has not been studied in autoimmune diseases other than GPA/MPA. MabThera IV should not be used in pediatric patients with GPA/MPA < 2 years of age as there is a possibility of an inadequate immune response towards childhood vaccinations against common, vaccine preventable childhood diseases (e.g. measles, mumps, rubella, and poliomyelitis).

Hypogammaglobulinaemia has been observed in pediatric patients treated with MabThera IV, in some cases severe and requiring long-term immunoglobulin substitution therapy (see section 2.6 Undesirable Effects, Clinical Trails). The consequences of long term B-cell depletion in pediatric patients are unknown.

Pediatric Patients with B-cell Non-Hodgkin's Lymphoma

In a prospective phase III, multicenter, open-label, randomized study, 309 pediatric patients (aged ≥ 6 months to < 18 years) were assigned to therapeutic groups B, C1, and C3 based on the disease stage (see section 3.1.2 Clinical/Efficacy Studies).

The addition of MabThera IV to LMB chemotherapy resulted in a clinically relevant benefit in pediatric patients (aged ≥ 6 months to < 18 years old) with first-line B-NHL compared to LMB chemotherapy alone.

The safety profile of MabThera IV in pediatric patients (aged ≥ 6 months to < 18 years old) with previously untreated DLBCL/BL/BAL/BLL was generally consistent in type, nature and severity with the known safety profile in adult NHL and CLL patients. Only limited data are available for B-NHL patients under 3 years of age.

MabThera IV should not be used in pediatric patients from birth to < 6 months of age with CD20 positive diffuse large B-cell lymphoma.

2.5.5 Geriatric Use

The safety and efficacy of MabThera in geriatric patients has not been established.

2.5.6 Renal Impairment

The safety and efficacy of renal impairment in MabThera patients has not been established.

2.5.7 Hepatic Impairment

The safety and efficacy of hepatic impairment in MabThera patients has not been established.

2.6 UNDESIRABLE EFFECTS

2.6.1 Clinical Trials

Experience from Clinical Trials in Haemato-Oncology in Adults

Intravenous Formulation

The frequencies of adverse drug reactions (ADRs) reported with MabThera IV alone or in combination with chemotherapy are summarized in the tables below and are based on data from clinical trials. These ADRs had either occurred in single arm studies or had occurred with at least a 2% difference compared to the control arm in at least one of the major randomized clinical trials. ADRs are added to the appropriate category in the tables below according to the highest incidence seen in any of the major clinical trials. Within each frequency grouping ADRs are listed in descending order of severity. Frequencies are defined as very common (≥ 1/10), common (≥ 1/100 to < 1/10), and uncommon (≥ 1/1,000 to < 1/100).

MabThera IV Monotherapy / Maintenance Therapy

The ADRs in Table 3, are based on data from single-arm studies including 356 patients with low-grade or follicular lymphoma, treated with MabThera IV weekly as single agent for the treatment or re-treatment of non-Hodgkin's lymphoma (see section 3.1.2 Clinical/Efficacy Studies). The table also contains ADRs based on data from 671 patients with follicular lymphoma who received MabThera IV as maintenance therapy for up to 2 years following response to initial induction with CHOP, R-CHOP, R-CVP or R-FCM (see section 3.1.2 Clinical/Efficacy Studies). The ADRs were reported up to 12 months after treatment with monotherapy and up to 1 month after treatment with MabThera IV maintenance.

Table 3 Summary of ADRs Reported in Patients with Low-Grade or Follicular Lymphoma Receiving MabThera IV Monotherapy (n=356) or MabThera IV Maintenance Treatment (n=671) in Clinical Trials.

System Organ Class	Very Common (≥ 10%)	Common (≥1% - < 10%)	Uncommon (≥0.1% - < 1%)
Infections and infestations	bacterial infections, viral infections,	sepsis , [+]pneumonia, [+]febrile infection, [+]herpes zoster, [+]respiratory tract infection, fungal infections, infections of unknown aetiology	
Blood and the lymphatic system disorders	neutropenia, leucopenia	anaemia, thrombocytopenia	coagulation disorders, transient aplastic anaemia, haemolytic anaemia, lymphadenopathy
Immune system disorders	angioedema	Hypersensitivity	

System Organ Class	Very Common (≥ 10%)	Common (≥1% - < 10%)	Uncommon (≥0.1% - < 1%)
Metabolism and nutrition disorders		hyperglycaemia, weight decrease, peripheral edema, face edema, increased LDH, hypocalcemia	
Psychiatric disorders			depression, nervousness
Nervous system disorders		paresthesia, hypoesthesia, agitation, insomnia, vasodilatation, dizziness, anxiety	dysgeusia
Eye disorders		lacrimation disorder, conjunctivitis	
Ear and labyrinth disorders		tinnitus, ear pain	
Cardiac disorders		[+] myocardial infarction, arrhythmia , [+]atrial fibrillation, tachycardia, [+]cardiac disorder	[+]left ventricular failure, [+]supraventricular tachycardia, [+]ventricular tachycardia, [+]angina, [+]myocardial ischaemia, bradycardia
Vascular disorders		hypertension , orthostatic hypotension, hypotension	
Respiratory, thoracic and mediastinal disorders		bronchospasm, respiratory disease, chest pain, dyspnoea, cough, rhinitis	asthma , bronchiolitis obliterans, lung disorder, hypoxia
Gastrointestinal disorders	nausea	vomiting , diarrhea, abdominal pain , dysphagia , stomatitis, constipation dyspepsia, anorexia, throat irritation	abdominal enlargement
Skin and subcutaneous tissue disorders	pruritus, rash	urticaria , [+]alopecia, sweating, night sweats	
Musculoskeletal, connective tissue and bone disorders		hypertonia, myalgia , arthralgia , back pain , neck pain, pain	
General disorders and administration site conditions	fever , chills , asthenia , headache	tumour pain, flushing, malaise, cold syndrome	infusion site pain
Investigations	decreased IgG levels		

For each term, the frequency count was based on reactions of all grades (from mild to severe), except for terms marked with "+" where the frequency count was based only on severe (≥ grade 3 NCI common toxicity criteria) reactions. Only the highest frequency observed in either trial is reported.

MabThera IV in Combination with Chemotherapy in NHL [65] and CLL

The ADRs listed in Table 4 are based on MabThera IV-arm data from controlled clinical trials that occurred in addition to those seen with monotherapy/maintenance therapy and/or at a higher frequency grouping: 202 patients with diffuse large B-cell lymphoma (DLBCL) treated with R-CHOP, and from 234 and 162 patients with follicular lymphoma treated with R-CHOP or R-CVP, respectively and from 397 previously untreated CLL patients and 274 relapsed/refractory CLL patients, treated with MabThera IV in combination with fludarabine and cyclophosphamide (R-FC) (see section 3.1.2 Clinical/Efficacy Studies).

Table 4 Summary of Severe ADRs Reported in Patients Receiving R-CHOP in DLBCL (n=202), R-CHOP in Follicular Lymphoma (n=234), R-CVP in Follicular Lymphoma (n=162), R-FC in Previously Untreated (n=397) or Relapsed/Refractory (n=274) Chronic Lymphocytic Leukaemia

System Organ Class	Very Common (≥ 10%)	Common (≥ 1% - <10%)
Infections and infestations	bronchitis	acute bronchitis, sinusitis hepatitis B*,
Blood and the lymphatic system disorders	neutropenia[#] febrile neutropenia, thrombocytopenia	pancytopenia, granulocytopenia
Skin and subcutaneous tissue disorders	Alopecia	skin disorder
General disorders and administration site conditions		fatigue, shivering,

*Includes reactivation and primary infections; frequency based on R-FC regimen in relapsed/refractory CLL
Frequency count was based on only severe reactions defined in clinical trials as ≥ grade 3 NCI common toxicity criteria
Only the highest frequency observed in any trial is reported
prolonged and/or delayed onset neutropenia after completion of an R-FC course in previously untreated or relapsed/refractory CLL

The following terms have been reported as adverse events, however, were reported at a similar (<2% difference between the groups) or lower incidence in the MabThera IV-arms compared to control arms: Haematotoxicity, neutropenic infection, urinary tract infection, septic shock, superinfection lung, implant infection, septicaemia staphylococcal, lung infection, rhinorrheoa, pulmonary oedema, cardiac failure, sensory disturbance, venous thrombosis, mucosal inflammation nos, influenza-like illness, oedema lower limb, abnormal ejection fraction, pyrexia, general physical health deterioration, fall, multi-organ failure, venous thrombosis deep limb, positive blood culture, diabetes mellitus inadequate control.

The safety profile for MabThera IV in combination with other chemotherapies (e.g., MCP, CHVP-IFN) is comparable to the safety profile as described for the combination of MabThera IV and CVP, CHOP or FC in equivalent populations.

Experience from Pediatric DLBCL/BL/BAL/BLL

A multicenter, open-label randomized study of Lymphome Malin B (LMB) chemotherapy with or without MabThera IV was conducted in pediatric patients (aged ≥ 6 months to < 18 years old) with previously untreated advanced stage CD20 positive DLBCL/BL/BAL/BLL. A total of 309 pediatric patients received MabThera IV and were included in the safety analysis population. Pediatric patients randomized to the LMB chemotherapy arm with MabThera, or enrolled in the single arm part of the study, were administered MabThera at a dose of 375mg/m^2 BSA and received a total of six IV infusions of MabThera (two during each of the two induction courses and one during each of the two consolidation courses of the LMB scheme).

The safety profile of MabThera IV in pediatric patients (aged ≥ 6 months to < 18 years old) with previously untreated DLBCL/BL/BAL/BLL was generally consistent in type, nature and severity with the known safety profile in adult NHL and CLL patients. Addition of MabThera IV to chemotherapy did result in an increased risk of some adverse events such as infections (including sepsis) compared to chemotherapy only. There were no pediatric specific ADRs identified and the current list of ADRs for adult oncology patients is applicable to the pediatric B-NHL population.

Subcutaneous Formulation

Local cutaneous reactions, including injection site reactions, were very common (≥ 1/10) in patients receiving MabThera SC. In the phase 3 SABRINA (BO22334) study, local cutaneous reactions were reported in up to 23% of patients receiving MabThera SC. The most common local cutaneous reactions in the MabThera SC arm were: injection site erythema (13%), injection site pain (8%), and injection site oedema (4%). Similar events were observed in the SAWYER (BO25341) study and were reported in up to 42% of patients in the MabThera SC arm. The most common local cutaneous reactions were: injection site erythema (26%), injection site pain (16%), and injection site swelling (5%).

Events seen following subcutaneous administration were mild or moderate, apart from one patient in the SABRINA study who reported a local cutaneous reaction of Grade 3 intensity (injection site rash) and two patients in the SAWYER study who experienced Grade 3 local cutaneous reactions (injection site erythema, injection site pain, and injection site swelling). Local cutaneous reactions of any Grade in the MabThera SC arm were most common during the first subcutaneous cycle (Cycle 2), followed by the second, and the incidence decreased with subsequent injections.

The safety profile of MabThera SC was otherwise comparable to that of the IV formulation.

No cases of anaphylaxis or severe hypersensitivity reactions, cytokine release syndrome or tumour lysis syndrome were observed following subcutaneous administration during the MabThera SC development program.

Further information on selected, serious adverse drug reactions

Intravenous Formulation

Administration-related reactions

Monotherapy 4 weeks treatment

Signs and symptoms suggestive of an infusion-related reaction (IRR) were reported in more than 50% of patients in clinical trials, and were predominantly seen during the first infusion [16]. Hypotension, fever, chills, rigors, urticaria, bronchospasm, sensation of tongue or throat swelling (angioedema), nausea, fatigue, headache, pruritus, dyspnea, rhinitis, vomiting, flushing, and pain at disease sites have occurred in association with MabThera IV infusion as part of an infusion-related symptom complex. Some features of tumor lysis syndrome have also been observed.

Combination Therapy (R-CVP in NHL; R-CHOP in DLBCL, R-FC in CLL)

Severe IRRs occurred in up to 12% of all patients at the time of the first treatment cycle with MabThera IV in combination with chemotherapy. The incidence of infusion-related symptoms decreased substantially with subsequent infusions and in <1% of patients by the eighth cycle. Additional reactions reported were: dyspepsia, rash, hypertension, tachycardia, and features of tumour lysis syndrome. Isolated cases of myocardial infarction, atrial fibrillation, pulmonary oedema and acute reversible thrombocytopenia were also reported.

Subcutaneous Formulation

The risk of acute administration-related reactions associated with the subcutaneous formulation of MabThera was assessed in three clinical studies.

In the SparkThera (BP22333) study no severe administration-related reactions were reported.

In the SABRINA (BO22334) study severe administration-related reactions (Grade ≥3) were reported in two patients (1%) following MabThera SC administration. These events were Grade 3 injection site rash and dry mouth.

In the SAWYER (BO25341) study severe administration-related reactions (Grade ≥3) were reported in four patients (5%) following MabThera SC administration. These events were Grade 4 thrombocytopenia and Grade 3 anxiety, injection-site erythema and urticaria.

Intravenous Formulation

Combination Therapy at 90-Minute Infusion Rate (R-CVP in f-NHL; R-CHOP in DLBCL)

In a study to characterize the safety profile of 90-minute MabThera IV infusions in patients who well tolerated their first standard MabThera IV infusion (Study U4391g), the incidence of Grade 3 and4 IRRs on the day of and/or the day after the 90-minute MabThera IV infusion at Cycle 2 in the 363 evaluable patients was 1.1% (95% CI [0.3%, 2.8%]). The incidence of Grade 3 and 4 IRRs at any cycle (Cycles 2 to 8) at the 90-minute infusion rate was 2.8% (95%

CI [1.3%, 5.0%]). No acute fatal IRRs were observed (see section 3.1.2 Clinical/Efficacy Studies).

Infections

Monotherapy 4 weeks treatment

MabThera IV induced B-cell depletion in 70% to 80% of patients but was associated with decreased serum immunoglobulins in only a minority of patients. Bacterial, viral, fungal and unknown etiology infections, irrespective of causal assessment, occurred in 30.3% of 356 patients. Severe infectious events (Grade 3 or 4), including sepsis occurred in 3.9% of patients.

Maintenance Treatment (NHL) up to 2 years

Higher frequencies of infections overall, including Grade 3 and 4 infections, were observed during MabThera IV treatment. There was no cumulative toxicity in terms of infections reported over the 2-year maintenance period.

Data from clinical trials included cases of fatal PML in NHL patients that occurred after disease progression and retreatment (see section 2.4 Warnings and Precautions).

Combination Therapy (R-CVP in NHL; R-CHOP in DLBCL, R-FC in CLL)

No increase in the frequency of infections or infestations was observed. The most common infections were upper respiratory tract infections which were reported for 12.3% patients on R-CVP and 16.4% patients receiving CVP. Serious infections were reported in 4.3% of the patients receiving R-CVP and 4.4% of the patients receiving CVP. No life-threatening infections were reported during this study.

In the R-CHOP study the overall incidence of Grade 2 to 4 infections was 45.5% in the R-CHOP group and 42.3% in the CHOP group. Grade 2 to 4 fungal infections were more frequent in the R-CHOP group (4.5% vs. 2.6% in the CHOP group); this difference was due to a higher incidence of localized Candida infections during the treatment period. The incidence of Grade 2 to 4 herpes zoster was higher in the R-CHOP group (4.5%) than in the CHOP group (1.5%) [20, 61]. The proportion of patients with Grade 2 to 4 infections and/or febrile neutropenia was 55.4% in the R-CHOP group and 51.5% in the CHOP group.

In patients with CLL, the incidence of Grade 3 and 4 hepatitis B infection (reactivation and primary infection) was 2% in the R-FC group vs. 0% in the FC group.

Haematologic events

Monotherapy 4 weeks treatment

Severe (Grade 3 and 4) neutropenia was reported in 4.2% of patients, severe anaemia was reported in 1.1% of patients and severe thrombocytopenia was reported in 1.7% of patients.

Maintenance Treatment (NHL) up to 2 years

There was a higher incidence of Grade 3 and 4 leucopenia (observation 2% vs. MabThera IV 5%) and neutropenia (observation 4% vs. MabThera IV 10%) in the MabThera IV arm compared to the observation arm. The incidence of Grade 3 and 4 thrombocytopenia

(observation 1% vs. MabThera IV <1%) was low. In approximately half of the patients with available data on B-cell recovery after end of MabThera IV induction treatment, it took 12 months or more for their B-cell levels to return to normal values.

Combination Therapy (R-CVP in NHL; R-CHOP in DLBCL, R-FC in CLL)

During treatment course in studies with MabThera IV in combination with chemotherapy, Grade 3 and 4 leucopenia (R-CHOP 88% vs. CHOP 79%, R-FC 23% vs. FC 12%) and neutropenia (R-CVP 24% vs. CVP 14%; R-CHOP 97% vs. CHOP 88%, R-FC 30% vs. FC 19% in previously untreated CLL) were usually reported with higher frequencies when compared to chemotherapy alone. However, the higher incidence of neutropenia in patients treated with MabThera IV and chemotherapy was not associated with a higher incidence of infections and infestations compared to patients treated with chemotherapy alone. Studies in previously untreated and relapsed/refractory CLL have established that in some cases neutropenia was prolonged or with a late onset following treatment in the MabThera IV plus FC group.

No relevant difference between the treatment arms was observed with respect to Grade 3 and 4 anaemia or thrombocytopenia. In the CLL first-line study Grade 3 and 4 anaemia was reported by 4% of patients treated with R-FC compared to 7% of patients receiving FC, and Grade 3 and 4 thrombocytopenia was reported by 7% of patients in the R-FC group compared to 10% of patients in the FC group. In the relapsed/refractory CLL study, adverse events of Grade 3 and 4 anaemia were reported in 12% of patients treated with R-FC compared to 13% of patients receiving FC and Grade 3 and 4 thrombocytopenia was reported by 11% of patients in the R-FC group compared to 9% of patients in the FC group.

Cardiovascular events

Monotherapy 4 weeks treatment

Cardiovascular events were reported in 18.8% of patients during the treatment period. The most frequently reported events were: hypotension and hypertension [48]. Cases of Grade 3 and 4 arrhythmia (including ventricular and supraventricular tachycardia) and angina pectoris during a MabThera IV infusion were reported.

Maintenance Treatment (NHL) up to 2 years

The incidence of Grade 3 and 4 cardiac disorders was comparable between the two treatment groups. Cardiac events were reported as serious adverse event in <1% of patients on observation and in 3% of patients on MabThera IV: atrial fibrillation (1%), myocardial infarction (1%), left ventricular failure (<1%), myocardial ischemia (<1%).

Combination Therapy (R-CVP in NHL; R-CHOP in DLBCL, R-FC in CLL)

In the R-CHOP study the incidence of Grade 3 and 4 cardiac arrhythmias, predominantly supraventricular arrhythmias such as tachycardia and atrial flutter/fibrillation, was higher in the R-CHOP group (6.9%) as compared to the CHOP group (1.5%). All arrhythmias either occurred in the context of a MabThera IV infusion or were associated with predisposing conditions such as fever, infection, acute myocardial infarction or pre-existing respiratory and

cardiovascular disease (see section 2.4 Warnings and Precautions). No difference between the R-CHOP and CHOP group was observed in the incidence of other Grade 3 and 4 cardiac events including heart failure, myocardial disease and manifestations of coronary artery disease.

In CLL, the overall incidence of Grade 3 and 4 cardiac disorders was low both in the first-line study (4% R-FC vs. 3% FC) and in the relapsed/refractory study (4% R-FC vs. 4% FC).

IgG levels

Maintenance Treatment (NHL) up to 2 years

After induction treatment, median IgG levels were below the lower limit of normal (LLN) (<7 g/L) in both the observation and the MabThera IV groups. In the observation group, the median IgG level subsequently increased to above the LLN, but remained constant during MabThera IV treatment. The proportion of patients with IgG levels below the LLN was about 60% in the MabThera IV group throughout the 2 year treatment period, while it decreased in the observation group (36% after 2 years).

Neurologic events

Combination Therapy (R-CVP in NHL; R-CHOP in DLBCL, R-FC in CLL)

During the treatment period, 2% of patients in the R-CHOP group, all with cardiovascular risk factors, experienced thromboembolic cerebrovascular accidents during the first treatment cycle. There was no difference between the treatment groups in the incidence of other thromboembolic events. In contrast, 1.5% of patients had cerebrovascular events in the CHOP group, all of which occurred during the follow-up period.

In CLL, the overall incidence of Grade 3 and 4 nervous system disorders was low both in the first-line study (4% R-FC vs. 4% FC) and in the relapsed/refractory study (3% R-FC vs. 3% FC).

Subpopulations

Monotherapy 4 weeks treatment

Elderly patients (≥65 years):

The incidence of any ADR and of Grade 3 and 4 ADRs was similar in elderly (≥ 65 years of age) and younger patients (88.3% vs. 92.0% for any ADR and 16.0% vs. 18.1% for Grade 3 and 4 ADRs).

Combination Therapy

Elderly patients (≥65 years):

The incidence of Grade 3 and 4 blood and lymphatic adverse events was higher in elderly patients (≥ 65 years of age) compared to younger patients with previously untreated or relapsed/refractory CLL.

Bulky disease:

Patients with bulky disease had a higher incidence of Grade 3 and 4 ADRs than patients without bulky disease (25.6% vs. 15.4%). The incidence of any ADR was similar in these two groups (92.3% in bulky disease vs. 89.2% in non-bulky disease).

Re-treatment with monotherapy:

The percentage of patients reporting any ADR and Grade 3 and 4 ADRs upon re-treatment with further courses of MabThera IV was similar to the percentage of patients reporting any ADR and Grade 3 and 4 ADRs upon initial exposure (95.0% vs. 89.7% for any ADR and 13.3% vs. 14.8% for Grade 3 and 4 ADRs).

Experience from Rheumatoid Arthritis Clinical Trials

Intravenous Formulation

The safety profile of MabThera IV in the treatment of patients with moderate to severe RA is summarized below. In the all-exposure population more than 3000 patients received at least one treatment course and were followed for periods ranging from 6 months to over 5 years with an overall exposure equivalent to 7198 patient years; approximately 2300 patients received two or more courses of treatment during the follow up period.

The ADRs listed in Table 5 are based on data from placebo-controlled periods of four multicenter, RA clinical trials. The patient populations receiving MabThera IV differed between studies, ranging from early active RA patients who were methotrexate (MTX) naïve, through MTX inadequate responders (MTX-IR) to patients who had inadequate response to anti-tumour necrosis factor (TNF) therapies (TNF-IR) (see section 3.1.2 Clinical/Efficacy Studies).

Patients received 2 x 1000 mg or 2 x 500 mg of MabThera IV separated by an interval of two weeks; in addition to methotrexate (10 to 25 mg/week) (see section 2.2 Dosage and Administration, Rheumatoid Arthritis).

The ADRs listed in Table 5 are those which occurred at a rate of at least 2%, with at least 2% difference compared to the control arm and are presented regardless of dose. Frequencies in Table 5 and the corresponding footnote are defined as very common (≥1/10), common (≥1/100 to <1/10) and uncommon (≥ 1/1,000 to < 1/100).

Table 5 Summary of ADRs Reported in Patients with Rheumatoid Arthritis within Control Period of Clinical Trials †.

System Organ Class	Very Common	Common
Infections and Infestations	Upper respiratory tract infection, Urinary tract infection	Bronchitis. Sinusitis, Gastroenteritis, Tinea pedis
Immune System Disorders/	Infusion related reactions	*Infusion related reactions: (Hypertension, Nausea, Rash, Pyrexia, Pruritus, Urticaria,

System Organ Class	Very Common	Common
General disorders and administration site conditions		Throat irritation, Hot flush, Hypotension, Rhinitis, Rigors, Tachycardia, Fatigue, Oropharyngeal pain, Peripheral Oedema, Erythema)
Metabolism and Nutritional Disorders		Hypercholesterolemia
Nervous System disorders	Headache	Paraesthesia, Migraine, Dizziness, Sciatica
Skin & Subcutaneous Tissue disorders		Alopecia
Psychiatric Disorders		Depression, Anxiety
Gastrointestinal Disorders		Dyspepsia, Diarrhoea, Gastro-oesophageal reflux, Mouth ulceration, Abdominal pain upper
Musculoskeletal and connective tissue disorders		Arthralgia/Musculoskeletal pain, Osteoarthritis, Bursitis
† This table includes all events with an incidence difference of ≥ 2 % for MabThera IV compared to placebo. * In addition, medically significant events reported uncommonly associated with IRRs include: generalized oedema, bronchospasm, wheezing, laryngeal oedema, angioneurotic oedema, generalized pruritus, anaphylaxis, anaphylactoid reaction.		

In the all-exposure population the safety profile was consistent with that seen in the controlled period of the clinical trials with no new ADRs identified.

Multiple courses

Multiple courses of treatment are associated with a similar ADR profile to that observed following first exposure. The safety profile improved with subsequent courses due to a decrease in IRRs, RA exacerbation and infections, all of which were more frequent in the first 6 months of treatment.

Further information on selected adverse drug reactions

Infusion-related reactions

The most frequent ADRs following receipt of MabThera IV in RA clinical studies were IRRs. Among the 3095 patients treated with MabThera IV, 1077 (35%) experienced at least one IRR. The vast majority of IRRs were CTC Grade 1 or 2. In clinical studies less than 1% (14/3095 patients) of patients with RA who received an infusion of MabThera IV at any dose experienced a serious IRR. There were no CTC Grade 4 IRRs and no deaths due to IRRs in the clinical studies (see section 2.6 Undesirable Effects, Post-Marketing). The proportion of

CTC Grade 3 events and IRRs leading to withdrawal decreased by course and were rare from course 3 onwards.

Signs and/or symptoms suggesting an IRR (i.e., nausea, pruritus, fever, urticaria/rash, chills, pyrexia, rigors, sneezing, angioneurotic oedema, throat irritation, cough and bronchospasm, with or without associated hypotension or hypertension) were observed in 720/3095 (23%) patients following the first infusion of the first exposure to MabThera IV. Premedication with IV glucocorticoid significantly reduced the incidence and severity of these events (see section 2.4 Warnings and Precautions).

In a study designed to evaluate the safety of a 120-minute MabThera IV infusion in patients with RA, patients with moderate-to-severe active RA who did not experience a serious IRR during or within 24 hours of their first studied infusion were allowed to receive a 120-minute infusion of MabThera IV. Patients with a history of a serious infusion reaction to a biologic therapy for RA were excluded from entry. The incidence, types and severity of IRRs were consistent with that observed historically. No serious IRRs were observed (see section 3.1.2 Clinical/Efficacy Studies).

Infections

The overall rate of infection reported in clinical trials was approximately 97 per 100 patient years in MabThera IV treated patients. The infections were predominately mild to moderate and consisted mostly of upper respiratory tract infections and urinary tract infections. The rate of serious infections was approximately 4 per 100 patient years, some of which were fatal. In addition to the ADRs in Table5, medically serious events reported also include pneumonia at a frequency of 1.9%.

Malignancies

The incidence of malignancy following exposure to MabThera IV in RA clinical studies (0.8 per 100 patient years) lies within the range expected for an age- and gender-matched population.

Clinical Trial Experience in Adult and Pediatric Granulomatosis with Polyangiitis (Wegener's) (GPA) and Microscopic Polyangiitis (MPA)

<u>Intravenous Formulation</u>

Adult Induction of Remission (GPA/MPA Study 1)

In GPA/MPA Study 1 99 adult GPA/MPA patients were treated for induction of remission of GPA and MPA with MabThera IV (375 mg/m^2, once weekly for 4 weeks) and glucocorticoids (see section 3.1.2 Clinical/Efficacy Studies).

The ADRs listed in Table 6 were all adverse events which occurred at an incidence of ≥ 10% in the MabThera IV-treated group. Frequencies in Table 6 are defined as very common (≥1/10).

Table 6 Incidence of Very Common (≥ 10%) ADRs for MabThera IV-treated Adult Patients in GPA/MPA Study 1 up to Month 6*

Adverse reactions	Rituximab n=99	Cyclophosphamide n=98
Infections and infestations		
Infections[a]	61 (61.6%)	46 (46.9%)
Gastrointestinal disorders		
Nausea	18 (18.2%)	20 (20.4%)
Diarrhea	17 (17.2%)	12 (12.2%)
Nervous system disorders		
Headache	17 (17.2%)	19 (19.4%)
Musculoskeletal and connective tissue disorders		
Muscle spasm	17 (17.2%)	15 (15.3%)
Arthralgia	13 (13.1%)	9 (9.2%)
Blood and lymphatic system disorders		
Anemia	16 (16.2%)	20 (20.4%)
Leukopenia	10 (10.1%)	26 (26.5%)
General disorders and administration site conditions		
Peripheral edema	16 (16.2%)	6 (6.1%)
Fatigue	13 (13.1%)	21 (21.4%)
Psychiatric disorders		
Insomnia	14 (14.1%)	12 (12.2%)
Investigations		
Increased ALT	13 (13.1%)	15 (15.3%)
Respiratory, thoracic and mediastinal disorders		
Cough,	13 (13.1%)	11 (11.2%)

Adverse reactions	Rituximab n=99	Cyclophosphamide n=98
Epistaxis, Dyspnea	11 (11.1%) 10 (10.1%)	6 (6.1%) 11 (11.2%)
Vascular disorders Hypertension	12 (12.1%)	5 (5.1%)
Injury, poisoning and procedural complications Infusion related reactions[b]	12 (12.1%)	11 (11.2%)
Skin and subcutaneous tissue disorders Rash	10 (10.1%)	17 (17.3%)
*The study design allowed for crossover or treatment by best medical judgment, and 13 patients in each treatment group received a second therapy during the 6 month study period. [a]Most common infections in the rituximab group of the induction of remission clinical trial included upper respiratory tract infections, urinary tract infections, and herpes zoster. [b]Most common terms reported in the rituximab group of the induction of remission clinical trial included cytokine release syndrome, flushing, throat irritation, and tremor.		

Adult Maintenance Treatment (GPA/MPA Study 2)

In GPA/MPA Study 2, a total of 57 adult patients with severe active GPA and MPA were treated for the maintenance of remission (see section 3.1.2 Clinical/Efficacy Studies).

No new safety concerns were identified and the safety profile was consistent with the well-established safety profile for MabThera IV in approved autoimmune indications, including GPA/MPA. Overall, 4% of patients in the MabThera IV arm experienced adverse events leading to discontinuation. Most adverse events in the MabThera IV arm were mild or moderate in intensity. No patients in the MabThera IV arm had fatal adverse events.

ADRs were all adverse events which occurred at an incidence of ≥ 10% in the MabThera IV-treated group. The very commonly (≥ 10%) reported events considered ADRs were: infusion-related reactions and infections.

Adult Long-term Follow-up (GPA/MPA Study 3)

In a long-term observational safety study, 97 adult GPA/MPA patients received treatment with MabThera (mean of 8 infusions [range 1-28]) for up to 4 years, according to their physician's standard practice and discretion. The overall safety profile was consistent with the well-established safety profile of MabThera in RA and GPA/MPA and no new adverse drug reactions were reported.

Pediatric Population

An open-label, single arm study was conducted in 25 pediatric patients with active GPA/MPA. The overall study period consisted of a 6-month remission induction phase and a minimum 18-month follow-up phase, up to 4.5 yrs. During the follow-up phase, MabThera was given at the discretion of the investigator (17 out of 25 patients received additional MabThera treatment). Concomitant treatment with other immunosuppressive therapy was permitted (see section 3.1.2 Clinical/Efficacy Studies).

All identified ADRs were considered all adverse events that occurred at an incidence of ≥ 10%. These included: infections (17 patients [68%] in the remission induction phase; 23 patients [92%] in the overall study period), IRRs (15 patients [60%] in the remission induction phase; 17 patients [68%] in the overall study period), and nausea (4 patients [16%] in the remission induction phase; 5 patients [20%] in the overall study period).

During the overall study period, the safety profile of MabThera IV was consistent with that reported during the remission induction phase. The safety profile of MabThera IV in pediatric GPA/MPA patients was consistent in type, nature and severity with the known safety profile in adult patients with autoimmune diseases in the approved indications, including adult GPA/MPA.

Further information on selected adverse drug reactions

Infusion-related reactions (GPA/MPA Study 1)

In GPA/MPA Study 1 (adult induction of remission study) infusion-related reactions (IRRs) were defined as any adverse event occurring within 24 hours of an infusion and considered to be infusion-related by investigators. Of the 99 patients treated with MabThera IV 12/99 patients (12%) experienced at least one IRR. All IRRs were CTC Grade 1 or 2. The most common IRRs included cytokine release syndrome, flushing, throat irritation and tremor. MabThera IV was given in combination with intravenous glucocorticoids which may reduce the incidence and severity of these events.

In GPA/MPA Study 2 (adult maintenance study), 7/57 (12%) patients in the MabThera IV arm reported infusion-related reactions. The incidence of IRR symptoms was highest during or after the first infusion (9%) and decreased with subsequent infusions (<4%). All IRR symptoms were mild to moderate and most were reported from the Respiratory, Thoracic and Mediastinal Disorders and Skin and Subcutaneous Tissue disorders SOCs.

In the pediatric GPA/MPA study, the reported IRRs were predominantly seen with the first infusion (8 patients [32%]), and then decreased over time with the number of MabThera IV infusions (20% with the second infusion, 12% with the third infusion and 8% with the fourth infusion). The most common IRR symptoms reported during the remission induction phase were: headache, rash, rhinorrhea and pyrexia (8%, for each symptom). The observed symptoms of IRRs were similar to those known in adult GPA/MPA patients treated with MabThera IV. The majority of IRRs were Grade 1 and Grade 2, there were two non-serious Grade 3 IRRs, and no Grade 4-5 IRRs reported. One serious Grade 2 IRR (generalized oedema which resolved with treatment) was reported in one patient (see section 2.4 Warning and Precautions).

Infections

In GPA/MPA Study 1, the overall rate of infection was approximately 210 per 100 patient years (95% CI 173-256). Infections were predominately mild to moderate and consisted mostly of upper respiratory tract infections, herpes zoster and urinary tract infections. The rate of serious infections was approximately 25 per 100 patient years. The most frequently reported serious infection in the MabThera IV group was pneumonia at a frequency of 4%.

In GPA/MPA Study 2, 30/57 (53%) patients in the MabThera IV arm and 33/58 (57%) in the azathioprine arm reported infections. The incidence of all grade infections was similar between the arms. Infections were predominately mild to moderate. The most common infections in the MabThera IV arm included upper respiratory tract infections, gastroenteritis, urinary tract infections and herpes zoster. The incidence of serious infections was similar in both arms (12%). The most commonly reported serious infection in the MabThera IV arm was mild or moderate bronchitis.

In the pediatric GPA/MPA study, 91% of the reported infections were non-serious and 90% were mild to moderate. The most common infections in the overall study period were: upper respiratory tract infections (URTIs) (48%), influenza (24%), conjunctivitis (20%), nasopharyngitis (20%), lower respiratory tract infections (16%), sinusitis (16%), viral URTIs (16%), ear infection (12%), gastroenteritis (12%), pharyngitis (12%), urinary tract infection (12%). Serious infections were reported in 7 patients (28%), and included: influenza (2 patients [8%]) and lower respiratory tract infection (2 patients [8%]) as the most frequently reported events.

Malignancies

In GPA/MPA Study 1, the incidence of malignancy in MabThera IV treated patients was 2.05 per 100 patient years. On the basis of standardized incidence ratios, this malignancy rate appears to be similar to rates previously reported in GPA and MPA populations.

In the pediatric GPA/MPA study, no malignancies were reported with a follow-up period of up to 54 months.

Laboratory Abnormalities

Hypogammaglobulinaemia (IgG or IgM below the lower limit of normal) has been observed in pediatric GPA/MPA patients treated with MabThera IV. During the overall study period, 3/25 (12%) patients reported an event of hypogammaglobulinaemia, 18 patients (72%) had prolonged (defined as Ig levels below lower limit of normal for at least 4 months) low IgG levels (of whom 15 patients also had prolonged low IgM). Three patients received treatment with intravenous immunoglobulin (IV-IG). There was no association between prolonged low IgG and IgM and an increased risk of serious infection.

Clinical Trial Experience in Pemphigus Vulgaris

PV Study 1 (Study ML22196)

Summary of the safety profile in PV Study 1

The safety profile of MabThera IV in combination with short term, low dose, glucocorticoids in the treatment of patients with pemphigus vulgaris was studied in a randomized, controlled, multicenter, open-label study in 38 pemphigus vulgaris (PV) and 8 pemphigus foliaceus (PF)

patients (PV Study 1). Patients randomized to the MabThera IV group received an initial 1000 mg IV on Study Day 1 and a second 1000 mg IV on Study Day 15. Maintenance doses of 500 mg IV were administered at Months 12 and 18. Patients could receive 1000 mg IV at the time of relapse (see section 3.1.2 Clinical/Efficacy Studies).

The safety profile of MabThera IV in patients with PV was consistent with that observed in RA and GPA/MPA patients (see sections Experience from Rheumatoid Arthritis Clinical Trials and Clinical Trial Experience in Granulomatosis with Polyangiitis (Wegener's) (GPA) and Microscopic Polyangiitis (MPA)).

Adverse drug reactions from PV Study 1 are presented in Table 7and were adverse events which occurred at a rate of $\geq$ 5% among MabThera IV treated PV patients, with a $\geq$ 2% absolute difference in incidence between the MabThera IV treated group and the standard dose prednisone group up to Month 24. No patients were withdrawn due to ADRs [188]. Frequencies in Table 7 are defined as very common ($\geq$1/10) and common ($\geq$1/100).

Table 7 ADRs for MabThera IV-treated Pemphigus Vulgaris Patients from PV Study 1 (up to Month 24)

Adverse drug reactions			MabThera IV + low dose prednisone N = 38	Standard dose prednisone N = 36
System Organ Class	**Very Common (≥ 1/10)**	**Common (≥ 1/100)**		
Injury, Poisoning and Procedural Complications	Infusion related reactions*		22 (58%)	N/A
Skin and Subcutaneous Tissue Disorders	Alopecia		5 (13%)	0
		Pruritus	2 (5%)	0
		Urticaria	2 (5%)	0
		Skin disorder	2 (5%)	0
Psychiatric Disorders	Persistent depressive disorder		5 (13%)	3 (8%)
		Major depression	2 (5%)	1 (3%)
		Irritability	2 (5%)	0
Infections and Infestations		Herpes virus infection	3 (8%)	0
		Herpes zoster	2 (5%)	1 (3%)
		Oral herpes	2 (5%)	1 (3%)
		Conjunctivitis	2 (5%)	0
General Disorders and Administration Site Conditions		Fatigue	3 (8%)	2 (6%)
		Pyrexia	2 (5%)	0
Nervous System Disorders		Headache	2 (5%)	1 (3%)
		Dizziness	2 (5%)	0
Gastrointestinal Disorders		Abdominal pain upper	2 (5%)	1 (3%)
Cardiac Disorders		Tachycardia	2 (5%)	0
Musculoskeletal and Connective Tissue Disorders		Musculoskeletal pain	2 (5%)	0
Neoplasms Benign, Malignant and Unspecified (incl cysts and polyps)		Skin papilloma	2 (5%)	0

Note: * Infusion-related reactions included symptoms collected on the next scheduled visit after each infusion, and adverse events occurring on the day of or one day after the infusion. The most common infusion-related reaction symptoms/Preferred Terms included headaches, chills, high blood pressure, nausea, asthenia and pain. Adverse drug reactions were defined as adverse events which occurred at a rate of ≥ 5%, with an absolute ≥ 2% difference in incidence between the MabThera IV + low dose prednisone group and the standard dose prednisone group. ADRs are listed in descending order of frequency by system organ class.

PV Study 2 (Study WA29330)

Summary of the safety profile in PV Study 2

In PV Study 2, a randomized, double-blind, double-dummy, active-comparator, multicenter study evaluating the efficacy and safety of MabThera IV compared with mycophenolate mofetil (MMF) in patients with moderate-to-severe active PV requiring oral corticosteroids, 67 PV patients received treatment with MabThera IV (initial 1000 mg IV on Study Day 1 and a second 1000 mg IV on Study Day 15 repeated at Weeks 24 and 26) for up to 52 weeks (see section 3.1.2 Clinical/Efficacy Studies).

In PV Study 2, the safety profile of MabThera IV was consistent with the established safety profile in other approved autoimmune indications. In PV Study 2, ADRs were defined as adverse events occurring in ≥5% of patients in the MabThera IV arm and assessed as related and are presented in Table8.

Table 8 ADRs for MabThera IV-treated Pemphigus Vulgaris Patients (N=67) from PV Study 2 (up to Week 52).

System Organ Class	Very Common (≥ 1/10)	Common (≥ 1/100)	MabThera IV (N=67)
Injury, Poisoning and Procedural Complications	Infusion related reaction*		15 (22%)
Nervous System disorders	Headache		10 (15%)
		Dizziness	4 (6)%
Infections and Infestations	Upper respiratory tract infection		7 (10%)
		Nasopharyngitis	6 (9%)
		Oral candidiasis	6 (9%)
		Urinary tract infection	5 (8%)
Musculoskeletal and connective tissue disorders		Arthralgia	6 (9%)
		Back pain	6 (9%)
General Disorders and Administration Site Conditions		Fatigue	5 (8%)
		Asthenia	4 (6%),

System Organ Class	Very Common (≥ 1/10)	Common (≥ 1/100)	MabThera IV (N=67)
*The most common infusion-related reaction symptoms/Preferred Terms for PV Study 2 were dyspnoea, erythema, hyperhidrosis, flushing/hot flush, hypotension/low blood pressure and rash/rash pruritic.			

Further information on selected adverse drug reactions

Infusion-related reactions

In PV Study 1, infusion-related reactions were retrospectively collected and assessed, and included symptoms of intolerance or adverse events considered to be infusion-related. Infusion-related reactions were reported very commonly (58%). All infusion-related reactions were mild to moderate (Grade 1 or 2) except one Grade 3 serious infusion-related reaction (arthralgia) associated with the Month 12 maintenance infusion. The proportion of patients experiencing an infusion- related reaction was 29% (11 patients), 40% (15 patients), 13% (5 patients), and 10% (4 patients) following the first, second, third, and fourth infusions, respectively. There were no fatal infusion-related reactions and no patients were withdrawn from treatment due to infusion-related reactions. Symptoms of infusion-related reactions were similar in type and severity to those seen in RA and GPA/MPA patients.

In PV Study 2, IRRs occurred primarily at the first infusion and the frequency of IRRs decreased with subsequent infusions: 17.9%, 4.5%, 3% and 3% of patients experienced IRRs at the first, second, third, and fourth infusions, respectively. In 11/15 patients who experienced at least one IRR, the IRRs were Grade 1 or 2. In 4/15 patients, Grade ≥3 IRRs were reported and led to discontinuation of MabThera treatment; three of the four patients experienced serious [life-threatening] IRRs. Serious IRRs occurred at the first (2 patients) or second (1 patient) infusion and resolved with symptomatic treatment.

Infections

In PV Study 1, 14 patients (37%) in the MabThera IV group experienced treatment-related infections compared to 15 patients (42%) in the standard dose prednisone group. The most common infections in the MabThera IV group were herpes simplex and zoster infections, bronchitis, urinary tract infection, fungal infection and conjunctivitis. Three patients (8%) in the MabThera IV group experienced a total of 5 serious infections (Pneumocystis jirovecii pneumonia, infective thrombosis, intervertebral discitis, lung infection, Staphylococcal sepsis) and one patient (3%) in the standard dose prednisone group experienced a serious infection (Pneumocystis jirovecii pneumonia).

In PV Study 2, 42 patients (62.7%) in the MabThera IV arm experienced infections. The most common infections in the MabThera IV group were upper respiratory tract infection, nasopharyngitis, oral candidiasis and urinary tract infection. Six patients (9%) in the MabThera IV arm experienced serious infections.

Laboratory Abnormalities

<u>Intravenous Formulation</u>

Hypogammaglobulinaemia (IgG or IgM below the lower limit of normal) has been observed in RA, and adult and pediatric GPA/MPA, patients treated with MabThera IV. There was no increased rate in overall infections or serious infections after the development of low IgG or

IgM. In PV Study 2, low IgG levels were commonly observed and low IgM levels were very commonly observed, however, there was no evidence of an increased risk of serious infections after the development of low IgG or IgM.

Rheumatoid Arthritis Patients

Events of neutropenia associated with MabThera IV treatment, the majority of which were transient and mild or moderate in severity, were observed in clinical trials in RA patients after the first course of treatment. Neutropenia can occur several months after the administration of MabThera IV.

In placebo-controlled periods of clinical trials, 0.94% (13/1382) of MabThera IV treated patients and 0.27% (2/731) of placebo patients developed severe (Grade 3 or 4) neutropenia. In these studies, rates of severe neutropenia were 1.06 and 0.53 per 100 patient years, respectively after the first treatment course, and 0.97 and 0.88 per 100 patient years, respectively after multiple courses. Therefore, neutropenia can be considered an ADR for the first course only. Time to onset of neutropenia was variable. In clinical trials neutropenia was not associated with an observed increase in serious infection and most patients continued to receive additional courses of MabThera IV after episodes of neutropenia.

Adult Patients with Granulomatosis with Polyangiitis (Wegener's) (GPA) and Microscopic Polyangiitis (MPA) Patients

In the induction of remission clinical trial, at 6 months, in the MabThera IV group, 27%, 58% and 51% of patients with normal immunoglobulin levels at baseline had low IgA, IgG and IgM levels, respectively compared to 25%, 50% and 46%, respectively in the cyclophosphamide group.

In the maintenance therapy clinical trial, no clinically meaningful differences between the two treatment arms or decreases in total immunoglobulin, IgG, IgM or IgA levels were observed throughout the trial.

In the induction of remission clinical trial, 24% of patients in the MabThera IV group (single course) and 23% of patients in the cyclophosphamide group developed CTC Grade 3 or greater neutropenia. Neutropenia was not associated with an observed increase in serious infection in MabThera IV-treated patients.

In the maintenance therapy clinical trial, the incidence of all-grade neutropenia was 0% for MabThera IV treated patients vs 5% for azathioprine treated patients.

Pemphigus Vulgaris

In PV Study 2, in the MabThera arm, transient decreases in lymphocyte count, driven by decreases in the peripheral T-cell populations, as well as a transient decrease in phosphorus level were very commonly observed post-infusion. These were considered to be induced by IV methylprednisolone premedication infusion.

2.6.2 Postmarketing Experience

Intravenous Formulation

Non-Hodgkin's Lymphoma and Chronic Lymphocytic Leukaemia Patients

The reporting frequencies in this section (rare, very rare) are based on estimated marketed exposures and data largely derived from spontaneous reports.

Additional cases of severe IRRs have been reported during post-marketing use of MabThera IV (see section 2.4 Warnings and Precautions).

As part of the continuing post-marketing surveillance of MabThera IV safety, the following serious adverse reactions have been observed:

Cardiovascular system

Severe cardiac events, including heart failure and myocardial infarction have been observed, mainly in patients with prior cardiac condition and/or cardiotoxic chemotherapy and mostly associated with IRRs. Vasculitis, predominantly cutaneous, such as leukocytoclastic vasculitis, has been reported very rarely.

Respiratory system

Respiratory failure/insufficiency and lung infiltration in the context of IRRs have been observed (see section 2.4 Warnings and Precautions). In addition to pulmonary events associated with infusions, interstitial lung disease, some with fatal outcome, have been reported.

Blood and lymphatic system

Cases of infusion-related acute reversible thrombocytopenia have been reported.

Skin and appendages

Severe bullous skin reactions including some fatal cases of toxic epidermal necrolysis and Stevens-Johnson syndrome have been reported rarely.

Nervous system

Cases of posterior reversible encephalopathy syndrome (PRES) / reversible posterior leukoencephalopathy syndrome (RPLS) have been reported. Signs and symptoms include visual disturbance, headache, seizures and altered mental status, with or without associated hypertension. A diagnosis of PRES/RPLS requires confirmation by brain imaging. The reported cases had recognized risk factors for PRES/RPLS, including the patients underlying disease, hypertension, immunosuppressive therapy and/or chemotherapy.

Cases of cranial neuropathy with or without peripheral neuropathy have been reported rarely. Signs and symptoms of cranial neuropathy, such as severe vision loss, hearing loss, loss of other senses and facial nerve palsy, occurred at various times up to several months after completion of MabThera IV therapy.

Body as a whole

Serum sickness-like reactions have been reported rarely.

Infections and infestations

Cases of hepatitis B reactivation have been reported, the majority of which were in subjects receiving MabThera IV tin combination with cytotoxic chemotherapy [66] (see section 2.4 Warnings and Precautions). Other serious viral infections, either new, reactivation or exacerbation, some of which were fatal, have been reported with MabThera IV treatment. The majority of patients had received MabThera IV in combination with chemotherapy or as part of a haematopoietic stem cell transplant. Examples of these serious viral infections are infections caused by the herpes viruses (cytomegalovirus [CMV], varicella zoster virus and herpes simplex virus), JC virus (progressive multifocal leukoencephalopathy [PML] see section 2.4 Warnings and Precautions) and hepatitis C virus.

Progression of Kaposi's sarcoma has been observed in MabThera IV-exposed patients with pre-existing Kaposi's sarcoma. These cases occurred in non-approved indications and the majority of patients were HIV positive.

Gastrointestinal system

Gastrointestinal perforation, in some cases leading to death, has been observed in patients receiving MabThera IV in combination with chemotherapy for non-Hodgkin's lymphoma.

Rheumatoid Arthritis (RA), Granulomatosis with Polyangiitis (Wegener's) (GPA) and Microscopic Polyangiitis (MPA) and Pemphigus Vulgaris (PV) Patients

As part of the continuing post-marketing surveillance of MabThera IV safety, the following have been observed in the RA setting and are also expected, if not already observed, in GPA/MPA and PV patients:

Infections and Infestations

Progressive multifocal leukoencephalopathy (PML) and reactivation of hepatitis B infection have been reported. Other serious viral infections, some of which were fatal, have been reported in patients treated with MabThera

Body as a whole

Serum sickness-like reaction has been reported.

Skin and subcutaneous tissue disorders

Toxic epidermal necrolysis and Stevens-Johnson syndrome some with fatal outcome have been reported very rarely.

Blood and lymphatic system disorders

Neutropenic events, including severe late onset and persistent neutropenia, have been reported rarely, some of which were associated with fatal infections.

Nervous system

Cases of posterior reversible encephalopathy syndrome (PRES) / reversible posterior leukoencephalopathy syndrome (RPLS) have been reported. Signs and symptoms include visual disturbance, headache, seizures and altered mental status, with or without associated hypertension. A diagnosis of PRES/RPLS requires confirmation by brain imaging. The reported cases had recognized risk factors for PRES/RPLS, including hypertension, immunosuppressive therapy and/or other concomitant therapies.

General disorders and administration site conditions

Severe IRRs some with fatal outcome have been reported (see section 2.6 Undesirable Effects, Clinical Trials).

Laboratory Abnormalities

Intravenous Formulation

Non-Hodgkin's Lymphoma

Blood and lymphatic system

Rarely the onset of neutropenia has occurred more than four weeks after the last infusion of MabThera IV.

In studies of MabThera IV in patients with Waldenstrom's macroglobulinemia, transient increases in serum IgM levels have been observed following treatment initiation, which may be associated with hyperviscosity and related symptoms. The transient IgM increase usually returned to at least baseline level within 4 months.

2.7 OVERDOSE

Intravenous and Subcutaneous Formulations

Limited experience with doses higher than the approved intravenous doses of MabThera IV is available from clinical trials in humans. The highest IV dose tested in humans to date is 5000 mg (2250 mg/m^2), tested in a dose escalation study in patients with chronic lymphocytic leukaemia. No additional safety signals were identified. Patients who experience overdose should have immediate interruption of their infusion and be closely monitored.

Three patients in the MabThera SC SABRINA (BO22334) study were inadvertently administered the SC formulation through the IV route up to a maximum rituximab dose of 2780 mg, with no untoward effect. Patients who experience overdose or medication error with MabThera SC should be closely monitored.

Consideration should be given to the need for regular monitoring of blood cell count and for increased risk of infections while patients are B cell-depleted.

2.8 INTERACTIONS WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

At present, there are limited data on possible drug interactions with MabThera.

In CLL patients, co-administration with MabThera IV did not appear to have an effect on the pharmacokinetics of fludarabine or cyclophosphamide, in addition; there was no apparent effect of fludarabine and cyclophosphamide on the pharmacokinetics of MabThera.

Co-administration with methotrexate had no effect on the pharmacokinetics of MabThera IV in RA patients.

Patients with human anti-mouse antibody (HAMA) or human anti-chimeric anti-body (HACA) titers may develop allergic or hypersensitivity reactions when treated with other diagnostic or therapeutic monoclonal antibodies.

In the RA clinical trial program, 373 MabThera IV-treated patients received subsequent therapy with other disease-modifying antirheumatic drugs (DMARDs), of whom 240 received a biologic DMARD. In these patients the rate of serious infection while on MabThera IV (prior to receiving a biologic DMARD) was 6.1 per 100 patient years compared to 4.9 per 100 patient years following subsequent treatment with the biologic DMARD.

3. PHARMACOLOGICAL PROPERTIES AND EFFECTS

3.1 PHARMACODYNAMIC PROPERTIES

3.1.1 Mechanism of Action

Rituximab is a chimeric mouse/human monoclonal antibody that binds specifically to the transmembrane antigen CD20. This antigen is located on pre-B- and mature B-lymphocytes, but not on haemopoietic stem cells, pro-B-cells, normal plasma cells or other normal tissue. The antigen is expressed on >95% of all B-cell non-Hodgkin's lymphomas (NHLs). Following antibody binding, CD20 is not internalized or shed from the cell membrane into the environment. CD20 does not circulate in the plasma as a free antigen and, thus, does not compete for antibody binding.

Rituximab binds to the CD20 antigen on B-lymphocytes and initiates immunologic reactions that mediate B-cell lysis. Possible mechanisms of cell lysis include complement-dependent cytotoxicity (CDC), antibody-dependent cellular cytotoxicity (ADCC), and induction of apoptosis. Finally, in vitro studies have demonstrated that rituximab sensitizes drug-resistant human B-cell lymphoma lines to the cytotoxic effects of some chemotherapeutic agents.

Peripheral B-cell counts declined to levels below normal following the first dose of MabThera. In patients treated for haematological malignancies, B-cell recovery began within 6 months of treatment and generally returning to normal levels within 12 months after completion of therapy, although in some patients this may take longer (see section 2.6 Undesirable Effects, Clinical Trials, Experience from Clinical Trials in Haemato-Oncology).

In patients with rheumatoid arthritis, the duration of peripheral B-cell depletion was variable. The majority of patients received further treatment prior to full B-cell repletion. A small proportion of patients had prolonged peripheral B-cell depletion lasting 2 years or more after their last dose of MabThera IV.

In GPA and MPA patients, peripheral blood CD19 B-cells depleted to less than 10 cells/µl following the first two infusions of rituximab and remained at that level in most patients through month 6.

Of 67 patients evaluated for human anti-mouse antibody (HAMA), none were positive [16]. Of 356 non-Hodgkin's lymphoma patients evaluated for human anti-chimeric antibody (HACA) 1.1% (4 patients) were positive.

3.1.2 Clinical / Efficacy Studies

Intravenous Formulation

Low-grade or Follicular Non-Hodgkin's Lymphoma

MabThera IV Monotherapy

Initial treatment, weekly for 4 doses

In the pivotal study, 166 patients with relapsed or chemoresistant low-grade or follicular B-cell NHL received 375 mg/m^2 of MabThera as an IV infusion weekly for four doses. The overall response rate (ORR) in the intent-to-treat (ITT) population was 48% ($CI_{95\%}$ 41% – 56%) with a 6% complete response (CR) and a 42% partial response (PR) rate. The projected median time to progression (TTP) for responding patients was 13.0 months.

In a subgroup analysis, the ORR was higher in patients with IWF B, C, and D histologic subtypes as compared to IWF A subtype (58% vs. 12%), higher in patients whose largest lesion was <5 cm versus >7 cm in greatest diameter (53% vs. 38%), and higher in patients with chemosensitive relapse as compared to chemoresistant (defined as duration of response <3 months) relapse (50% vs. 22%). ORR in patients previously treated with autologous bone marrow transplant (ABMT) was 78% vs. 43% in patients with no ABMT. Neither age, sex, lymphoma grade, initial diagnosis, presence or absence of bulky disease, normal or high LDH nor presence of extranodal disease had a statistically significant effect (Fisher's exact test) on response to MabThera IV.

A statistically significant correlation was noted between response rates and bone marrow involvement. Forty percent of patients with bone marrow involvement responded compared to 59% of patients with no bone marrow involvement (p=0.0186). This finding was not supported by a stepwise logistic regression analysis in which the following factors were identified as prognostic factors: histologic type, bcl-2 positivity at baseline, resistance to last chemotherapy and bulky disease.

Initial treatment, weekly for 8 doses

In a multi-center, single-arm study, 37 patients with relapsed or chemoresistant, low grade or follicular B-cell NHL received 375 mg/m^2 of MabThera as IV infusion weekly for eight doses. The ORR was 57% ($CI_{95\%}$ 41% – 73%; CR 14%, PR 43%) with a projected median TTP for responding patients of 19.4 months (range 5.3 to 38.9 months).

Initial treatment, bulky disease, weekly for 4 doses

In pooled data from three studies, 39 patients with relapsed or chemoresistant, bulky disease (single lesion ≥10 cm in diameter), low grade or follicular B-cell NHL received 375 mg/m^2 of MabThera as IV infusion weekly for four doses. The ORR was 36% ($CI_{95\%}$ 21% – 51%; CR 3%, PR 33%) with a median TTP for responding patients of 9.6 months (range 4.5 to 26.8 months).

Re-treatment, weekly for 4 doses

In a multi-center, single-arm study, 58 patients with relapsed or chemoresistant low grade or follicular B-cell NHL, who had achieved an objective clinical response to a prior course of MabThera IV were re-treated with 375 mg/m^2 of MabThera as IV infusion weekly for four doses. Three of the patients had received two courses of MabThera IV before enrollment and thus were given a third course in the study. Two patients were re-treated twice in the study. For the 60 re-treatments on study, the ORR was 38% ($CI_{95\%}$ 26% – 51%; 10% CR, 28% PR) with a projected median TTP for responding patients of 17.8 months (range 5.4 – 26.6). This compares favorably with the TTP achieved after the prior course of MabThera IV (12.4 months).

MabThera IV in Combination With Chemotherapy

Initial treatment

In an open-label randomized trial, a total of 322 previously untreated patients with follicular lymphoma were randomized to receive either CVP chemotherapy (cyclophosphamide 750 mg/m^2, vincristine 1.4 mg/m^2 up to a maximum of 2 mg on day 1, and prednisolone 40 mg/m^2/day on days 1-5) every 3 weeks for 8 cycles or MabThera IV 375 mg/m^2 in combination with CVP (R-CVP). MabThera IV was administered on the first day of each treatment cycle. A total of 321 patients (162 R-CVP, 159 CVP) received therapy and were analyzed for efficacy.

The median follow-up of patients was 53 months. R-CVP led to a significant benefit over CVP for the primary endpoint, time to treatment failure (27 months vs. 6.6 months, p< 0.0001, log-rank test). The proportion of patients with a tumour response (CR, CRu, PR) was significantly higher (p< 0.0001 Chi-Square test) in the R-CVP group (80.9%) than the CVP group (57.2%). Treatment with R-CVP significantly prolonged the time to disease progression or death compared to CVP, 33.6 months and 14.7 months, respectively (p< 0.0001, log-rank test). The median duration of response was 37.7 months in the R-CVP group and was 13.5 months in the CVP group (p< 0.0001, log-rank test). The difference between the treatment groups with respect to overall survival showed a strong clinical benefit (p=0.029, log-rank test stratified by center): survival rates at 53 months were 80.9% for patients in the R-CVP group compared to 71.1% for patients in the CVP group.

Results from three other randomized trials using MabThera IV in combination with chemotherapy regimen other than CVP (CHOP, MCP, CHVP/Interferon-α) also demonstrated significant improvements in response rates, time-dependent parameters as well as in overall survival. Key results from all four studies are summarized in Table 9 below.

Table 9 Summary of Key Results from Four Phase III Randomized Studies Evaluating the Benefit of MabThera IV with Different Chemotherapy Regimens in Follicular Lymphoma.

Study	Treatment, n	Median FU, months	ORR, %	CR, %	Median TTF/PFS/ EFS mo	OS rates, %
M39021	CVP, 159 R-CVP, 162	53	57 81	10 41	Median TTP: 14.7	53-months 71.1

					33.6 P<0.0001	80.9 p=0.029
GLSG'00	CHOP, 205 R-CHOP, 223	18	90 96	17 20	Median TTF: 2.6 years Not reached p < 0.001	18-months 90 95 p = 0.016
OSHO-39	MCP, 96 R-MCP, 105	47	75 92	25 50	Median PFS: 28.8 Not reached p < 0.0001	48-months 74 87 p = 0.0096
FL2000	CHVP-IFN, 183 R-CHVP-IFN, 175	42	85 94	49 76	Median EFS: 36 Not reached p < 0.0001	42-months 84 91 p = 0.029

TTP – Time to progression or death, PFS – Progression-Free Survival, TTF – Time to Treatment Failure, OS rates – survival rates at the time of the analyses

MabThera IV Maintenance Therapy

Previously untreated follicular NHL

In a prospective, open label, international, multi-center, phase III trial 1193 patients with previously untreated advanced follicular lymphoma received induction therapy with R-CHOP (n=881), R-CVP (n=268) or R-FCM (n=44), according to the investigators' choice. A total of 1078 patients responded to induction therapy, of which 1018 were randomized to MabThera IV maintenance therapy (n=505) or observation (n=513). The two treatment groups were well balanced with regards to baseline characteristics and disease status. MabThera IV maintenance treatment consisted of a single infusion of MabThera IV at 375 mg/ m^2 BSA given every 2 months until disease progression or for a maximum period of two years.

The pre-specified primary analysis was conducted at a median observation time of 25 months from randomization, maintenance therapy with MabThera IV resulted in a clinically relevant and statistically significant improvement in the primary endpoint of investigator assessed progression-free survival (PFS) as compared to observation in patients with previously untreated follicular NHL (see Table 10 below). This improvement in PFS was confirmed by an independent review committee (IRC).

Significant benefit from maintenance treatment with MabThera IV was also seen for the secondary endpoints event-free survival (EFS), time to next anti-lymphoma treatment (TNLT) time to next chemotherapy (TNCT) and overall response rate (ORR) (see Table 10 below).

Data from extended follow-up of patients in the study (median follow-up 9 years) confirmed the long-term benefit of MabThera IV maintenance therapy in terms of PFS, EFS, TNLT and TNCT (see Table 10 below).

Table 10 Overview of Efficacy Results for Maintenance MabThera IV vs. Observation (25 Months and 9 Years Median Follow-up – Final Analysis)

	Primary analysis (median FU: 25 months)		Final analysis (median FU: 9.0 years)	
	Observation N=513	**MabThera N=505**	**Observation N=513**	**MabThera N=505**
Primary efficacy				
Progression-free survival (median)	NR	NR	4.06 years	10.49 years
log-rank p value	<0.0001		<0.0001	
hazard ratio (95% CI)	0.50 (0.39, 0.64)		0.61 (0.52, 0.73)	
risk reduction	50%		39%	
Secondary efficacy				
Overall survival (median)	NR	NR	NR	NR
log-rank p value	0.7246		0.7953	
hazard ratio (95% CI)	0.89 (0.45, 1.74)		1.04 (0.77, 1.40)	
risk reduction	11%		-6%	
Event-free survival (median)	38 months	NR	4.04 years	9.25 years
log-rank p value	<0.0001		<0.0001	
hazard ratio (95% CI)	0.54 (0.43, 0.69)		0.64 (0.54, 0.76)	
risk reduction	46%		36%	
TNLT (median)	NR	NR	6.11 years	NR
log-rank p value	0.0003		<0.0001	
hazard ratio (95% CI)	0.61 (0.46, 0.80)		0.66 (0.55, 0.78)	
risk reduction	39%		34%	
TNCT (median)	NR	NR	9.32 years	NR
log-rank p value	0.0011		0.0004	
hazard ratio (95% CI)	0.60 (0.44, 0.82)		0.71 (0.59, 0.86)	
risk reduction	40%		39%	
Overall response rate*	55%	74%	61%	79%
chi-squared test p value	<0.0001		<0.0001	
odds ratio (95% CI)	2.33 (1.73, 3.15)		2.43 (1.84, 3.22)	
Complete response (CR/CRu) rate*	48%	67%	53%	67%
chi-squared test p value	<0.0001		<0.0001	
odds ratio (95% CI)	2.21 (1.65, 2.94)		2.34 (1.80, 3.03)	

* at end of maintenance/observation; final analysis results based on median follow-up of 73 months.
FU: follow-up; NR: not reached at time of clinical cut off, TNCT: time to next chemotherapy treatment; TNLT: time to next anti lymphoma treatment,;

MabThera IV maintenance treatment provided consistent benefit in all subgroups tested: gender (male, female), age (<60 years, ≥60 years), FLIPI score (1, 2 or 3), induction therapy (R-CHOP, R-CVP or R-FCM) and regardless of the quality of response to induction treatment (CR or PR).

Relapsed/Refractory follicular NHL

In a prospective, open label, international, multi-centre, phase III trial, 465 patients with relapsed/refractory follicular NHL were randomized in a first step to induction therapy with either CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone; n=231) or MabThera IV plus CHOP (R-CHOP, n=234). The two treatment groups were well balanced with regard to baseline characteristics and disease status. A total of 334 patients achieving a complete or partial remission following induction therapy were randomized in a second step to MabThera IV maintenance therapy (n=167) or observation (n=167). MabThera IV maintenance treatment consisted of a single infusion of MabThera IV at 375 mg/m^2 BSA given every 3 months until disease progression or for a maximum period of two years.

The final efficacy analysis included all patients randomized to both parts of the study. After a median observation time of 31 months for patients randomized to the induction phase, R-CHOP significantly improved the outcome of patients with relapsed/refractory follicular NHL when compared to CHOP (see Table 11 below).

Table 11 Induction Phase: Overview of Efficacy Results for CHOP vs. R-CHOP (31 Months Median Observation Time)

	CHOP	**R-CHOP**	**p-value**	**Risk Reduction[1)]**
Primary Efficacy				
ORR[2)]	74%	87%	0.0003	Na
CR[2)]	16%	29%	0.0005	Na
PR[2)]	58%	58%	0.9449	Na
Secondary Efficacy				
OS (median)	NR	NR	0.0508	32%
PFS(median)	19.4 mo.	33.2 mo.	0.0001	38%

[1)] Estimates were calculated by hazard ratios
[2)] Last tumour response as assessed by the investigator. The "primary" statistical test for "response" was the trend test of CR versus PR versus non-response ($p < 0.0001$)
Abbreviations: NA, not available; NR, not reached; mo, months; ORR: overall response rate; CR: complete response; PR: partial response; OS: overall survival: PFS: progression free survival

For patients randomized to the maintenance phase of the trial, the median observation time was 28 months from maintenance randomization. Maintenance treatment with MabThera IV led to a clinically relevant and statistically significant improvement in the primary endpoint, PFS, (time from maintenance randomization to relapse, disease progression or death) when compared to observation alone ($p<0.0001$ log-rank test). The median PFS was 42.2 months in the MabThera IV maintenance arm compared to 14.3 months in the observation arm. Using a cox regression analysis, the risk of experiencing progressive disease or death was reduced by 61% with MabThera IV maintenance treatment when compared to observation (95% CI; 45%-72%). Kaplan-Meier estimated progression-free rates at 12 months were 78% in the MabThera IV maintenance group vs. 57% in the observation group. An analysis of overall survival confirmed the significant benefit of MabThera IV maintenance over observation ($p=0.0039$ log-rank test). MabThera IV maintenance treatment reduced the risk of death by 56% (95% CI; 22%-75%).

The median time to new anti-lymphoma treatment was significantly longer with MabThera IV maintenance treatment than with observation (38.8 months vs. 20.1 months, $p<0.0001$ log-rank test). The risk of starting a new treatment was reduced by 50% (95% CI; 30%-64%). In patients achieving a CR/CRu (complete response unconfirmed) as best response during

induction treatment, MabThera IV maintenance treatment significantly prolonged the median disease free survival (DFS) compared to the observation group (53.7 vs. 16.5 months, p=0.0003 log-rank test) (see Table 12below). The risk of relapse in complete responders was reduced by 67% (95% CI; 39%-82%).

Table 12 Maintenance Phase: Overview of Efficacy Results MabThera IV vs. Observation (28 Months Median Observation Time)

Efficacy Parameter	**Kaplan-Meier Estimate of Median Time to Event (Months)**			**Risk Reduction**
	Observation (n=167)	**MabThera (n=167)**	**Log-Rank p-value**	
Progression-free survival (PFS)	14.3	42.2	<0.0001	61%
Overall Survival	NR	NR	0.0039	56%
Time to new lymphoma treatment	20.1	38.8	<0.0001	50%
Disease-free survival[a]	16.5	53.7	0.0003	67%
Subgroup Analysis				
PFS				
CHOP	11.6	37.5	<0.0001	71%
R-CHOP	22.1	51.9	0.0071	46%
CR	14.3	52.8	0.0008	64%
PR	14.3	37.8	<0.0001	54%
OS				
CHOP	NR	NR	0.0348	55%
R-CHOP	NR	NR	0.0482	56%

NR: not reached; [a]: only applicable to patients achieving a CR

The benefit of MabThera IV maintenance treatment was confirmed in all subgroups analyzed, regardless of induction regimen (CHOP or R-CHOP) or quality of response to induction treatment (CR or PR) (see Table 12). MabThera IV maintenance treatment significantly prolonged median PFS in patients responding to CHOP induction therapy (median PFS 37.5 months vs. 11.6 months, p<0.0001) as well as in those responding to R-CHOP induction (median PFS 51.9 months vs. 22.1 months, p=0.0071). MabThera IV maintenance treatment also provided a clinically meaningful benefit in terms of overall survival for both patients responding to CHOP and patients responding to R-CHOP in the induction phase of the study [105].

MabThera IV maintenance treatment provided consistent benefit in all subgroups tested: gender, age (≤60 years, >60 years), stage (III, IV), WHO performance status (0 vs. >0), B symptoms (absent, present), bone marrow involvement (no vs. yes), IPI (0-2 vs. 3-5), FLIPI score (0-1, vs. 2 vs. 3-5), number of extra-nodal sites (0-1 vs. >1), number of nodal sites (< 5 vs. ≥ 5), number of previous regimens (1 vs. 2), best response to prior therapy (CR/PR vs.

NC/PD), haemoglobin (< 12 g/dL vs. ≥12 g/dL), β_2-microglobulin (< 3mg/L vs. ≥3 mg/L), LDH (elevated, not elevated) except for the small subgroup of patients with bulky disease.

Adult Diffuse Large B-cell Non-Hodgkin's Lymphoma

In a randomized, open-label trial, a total of 399 previously untreated elderly patients (age 60 to 80 years) with diffuse large B-cell lymphoma received standard CHOP chemotherapy (cyclophosphamide 750 mg/m^2, doxorubicin 50 mg/m^2, vincristine 1.4 mg/m^2 up to a maximum of 2 mg on day 1, and prednisolone 40 mg/m^2/day on days 1 - 5) every 3 weeks for eight cycles, or MabThera IV 375 mg/m^2 plus CHOP (R-CHOP). MabThera IV was administered on the first day of the treatment cycle.

The final efficacy analysis included all randomized patients (197 CHOP, 202 R-CHOP), and had a median follow-up duration of approximately 31 months. The two treatment groups were well balanced in baseline characteristics and disease status. The final analysis confirmed that R-CHOP significantly increased the duration of event-free survival (the primary efficacy parameter, where events were death, relapse or progression of lymphoma, or institution of a new anti-lymphoma treatment) (p=0.0001). Kaplan Meier estimates of the median duration of event-free survival were 35 months in the R-CHOP arm compared to 13 months in the CHOP arm, representing a risk reduction of 41%. At 24 months, estimates for overall survival were 68.2% in the R-CHOP arm compared to 57.4% in the CHOP arm. A subsequent analysis of the duration of overall survival, carried out with a median follow-up duration of 60 months, confirmed the benefit of R-CHOP over CHOP treatment (p=0.0071), representing a risk reduction of 32%.

The analysis of all secondary parameters (response rates, progression-free survival, disease-free survival, duration of response) verified the treatment effect of R-CHOP compared to CHOP. The complete response rate after Cycle 8 was 76.2% in the R-CHOP group and 62.4% in the CHOP group (p=0.0028). The risk of disease progression was reduced by 46% and the risk of relapse by 51%.

In all patient subgroups (gender, age, age-adjusted IPI, Ann Arbor stage, ECOG, Beta 2 Microglobulin, LDH, Albumin, B-symptoms, Bulky disease, extranodal sites, bone marrow involvement), the risk ratios for event-free survival and overall survival (R-CHOP compared with CHOP) were less than 0.83 and 0.95; respectively. R-CHOP was associated with improvements in outcome for both high- and low-risk patients according to age-adjusted IPI.

Previously Untreated and Relapsed/Refractory Chronic Lymphocytic Leukaemia

In two open-label randomized trials, a total of 817 previously untreated patients and 552 patients with relapsed/refractory CLL were randomized to receive either FC chemotherapy (fludarabine 25 mg/m^2, cyclophosphamide 250 mg/m^2, days 1-3) every 4 weeks for 6 cycles or MabThera IV in combination with FC (R-FC). MabThera IV was administered at a dosage of 375 mg/m^2 during the first cycle one day prior to chemotherapy and at a dosage of 500 mg/m^2 on day 1 of each subsequent treatment cycle. A total of 810 patients (403 R-FC, 407 FC) in the first line study (see Table 13 and Table 14 below) and 552 patients (276 R-FC, 276 FC) for the relapsed/refractory study (see Table 15) were analyzed for efficacy.

In the first line study, after a median observation time of 20.7 months, the median progression-free survival (primary endpoint) was 40 months in the R-FC group and 32 months in the FC group (p<0.0001, log-rank test) (Table 13). The analysis of overall survival

showed an improved survival in favour of the R-FC arm (p=0.0427, log-rank test). These results were confirmed with longer follow-up: after a median observation time of 48.1 months, the median PFS was 55 months in the R-FC group and 33 months in the FC group (p<0.0001, log-rank test) and overall survival analyses continued to show a significant benefit of R-FC treatment over FC chemotherapy alone (p=0.0319, log-rank test). The benefit in terms of PFS was consistently observed in most patient subgroups analyzed according to disease risk at baseline (i.e., Binet stages A-C) and was confirmed with longer follow-up (see Table 14).

Table 13 First-line Treatment of Chronic Lymphocytic Leukaemia - Overview of Efficacy Results for MabThera IV Plus FC vs. FC Alone- (20.7 Months Median Observation Time)

Efficacy Parameter	Kaplan-Meier Estimate of Median Time to Event (Months)			Hazard Ratio
	FC (n=407)	R-FC (n=403)	Log-Rank p-value	
Progression-free survival (PFS)	32.2 (32.8)***	39.8 (55.3)***	<0.0001 (<0.0001)***	0.56 (0.55)***
Overall Survival	NR (NR)***	NR (NR)***	0.0427 (0.0319)***	0.64 (0.73)***
Event Free Survival	31.1 (31.3)***	39.8 (51.8)***	<0.0001 (<0.0001)***	0.55 (0.56)***
Response rate (CR, nPR, or PR)	72.7%	86.1%	<0.0001	n.a.
CR rates	17.2%	36.0%	<0.0001	n.a.
Duration of response*	34.7 (36.2)***	40.2 (57.3)***	0.0040 (<0.0001)***	0.61 (0.56)***
Disease free survival (DFS)**	NR (48.9)***	NR (60.3)***	0.7882 (0.0520)***	0.93 (0.69)***
Time to new CLL treatment	NR (47.2)***	NR (69.7)***	0.0052 (<0.0001)***	0.65 (0.58)***

Response rate and CR rates analysed using Chi-squared Test.
***Values in parentheses correspond to 48.1 months median observation time (ITT population: 409 FC, 408 R-FC).
NR: not reached n.a: not applicable
*: only applicable to patients with CR, nPR or PR as end-of-treatment response;
**: only applicable to patients with CR as end-of-treatment response;

Table 14 Hazard Ratios of Progression-Free Survival According to Binet Stage (ITT) (20.7 Months Median Observation Time)

Progression-free survival (PFS)	Number of patients		Hazard Ratio (95% CI)	Log-Rank p value
	FC	R-FC		
Binet Stage A	22 (22)*	18 (18)*	0.13 (0.03; 0.61) (0.39 (0.15; 0.98))*	0.0025 (0.0370)*
Binet Stage B	257 (259)*	259 (263)*	0.45 (0.32; 0.63) (0.52 (0.41; 0.66))*	<0.0001 (<0.0001)*
Binet Stage C	126 (126)*	125 (126)*	0.88 (0.58; 1.33) (0.68 (0.49; 0.95))*	0.5341 (0.0215)*

CI: Confidence Interval
*Values correspond to 48.1 months median observation time (ITT population: 409 FC, 408 R-FC).

In the relapsed/refractory study, the median progression-free survival (primary endpoint) was 30.6 months in the R-FC group and 20.6 months in the FC group (p=0.0002, log-rank test). The benefit in terms of PFS was observed in almost all patient subgroups analyzed according to disease risk at baseline. A slight but not significant improvement in overall survival was reported in the R-FC compared to the FC arm.

Table 15 Treatment of Relapsed/Refractory Chronic Lymphocytic Leukaemia - Overview of Efficacy Results for MabThera IV Plus FC vs. FC Alone (25.3 Months Median Observation Time)

Efficacy Parameter	**Kaplan-Meier Estimate of Median Time to Event (Months)**			**Risk Reduction**
	FC (n=276)	**R-FC (n=276)**	**Log-Rank p-value**	
Progression-free survival (PFS)	20.6	30.6	0.0002	35%
Overall Survival	51.9	NR	0.2874	17%
Event Free Survival	19.3	28.7	0.0002	36%
Response rate (CR, nPR, or PR)	58.0%	69.9%	0.0034	n.a.
CR rates	13.0%	24.3%	0.0007	n.a.
Duration of response *	27.6	39.6	0.0252	31%
Disease free survival (DFS)**	42.2	39.6	0.8842	-6%
Time to new CLL treatment	34.2	NR	0.0024	35%
Response rate and CR rates analysed using Chi-squared Test. NR: not reached, n.a. not applicable * only applicable to patients with CR, nPR or PR as best overall response **: only applicable to patients with CR as best overall response				

Results from other supportive studies using MabThera IV in combination with other chemotherapy regimens (including CHOP, FCM, PC, PCM, bendamustine and cladribine) for the treatment of CLL patients have also demonstrated high overall response rates with promising PFS rates without adding relevant toxicity to the treatment.

MabThera IV 90-Minute Infusion Rate Study (U4391g)

Previously Untreated Follicular Non-Hodgkin's Lymphoma and Diffuse Large B-cell Non-Hodgkin's Lymphoma

In a prospective, open-label, phase III, multicenter, single-arm trial, 363 patients with previously untreated DLBCL receiving 375 mg/m^2 MabThera IV plus CHOP chemotherapy, or previously untreated follicular NHL receiving MabThera IV 375 mg/m^2 plus CVP chemotherapy, were treated with a 90-minute infusion of MabThera IV to evaluate the safety of a 90-minute infusion. Patients with clinically significant cardiovascular disease were excluded from the study.

Patients were eligible to continue in the study if they did not experience a Grade 3 or 4 infusion-related adverse event with Cycle 1 (at the standard MabThera IV infusion rate) and had a circulating lymphocyte count ≤ 5000/mm^3 before Cycle 2. Continuing patients received their Cycle 2 MabThera IV infusion as follows: 20% of the total dose given in the first 30 minutes and the remaining 80% of the total dose given over the next 60 minutes. Patients who tolerated the first 90-minute MabThera IV infusion (Cycle 2) continued to receive subsequent MabThera IV infusions at the 90-minute infusion rate for the remainder of the treatment regimen (through Cycle 6 or Cycle 8).

The primary endpoint of the study was the development of Grade 3 or 4 infusion-related toxicities (targeted adverse event) in patients who received MabThera IV by 90-minute infusion in Cycle 2.

The rate of Grade 3 and 4 IRRs on the day of and/or the day after the 90-minute MabThera IV infusion at Cycle 2 was 1.1% (95% CI [0.3%, 2.8%]). The rate of Grade 3 and 4 IRRs at any cycle (Cycles 2 to 8) at the 90-minute infusion rate was 2.8% (95% CI [1.3%, 5.0%]) (see Table 16). No acute fatal infusion related reactions were observed (see section 2.6 Undesirable Effects, Clinical Trials).

Table 16 Overview of Rate of Grade 3 and 4 Infusion-Related Reactions at Cycle 2 and any Cycle (Cycles 2 to 8)*

No (%) of patients experiencing:	**R-CHOP n=250**	**R-CVP n=113**	**Total n=363**
IRRs with onset on day of and/or day after faster MabThera IV infusion at Cycle 2			
- Grade 3-4 IRR (primary endpoint)	0 (0.0%)	4 (3.5%)	4 (1.1%)
IRRs with onset on day of and/or day after MabThera IV infusions at Cycles 2–8			
- Grade 3-4 IRR	4 (1.6%)	6 (5.3%)	10 (2.8%)

*AEs occurring prior to Cycle 2 are not summarized. IRRs are those infusion-related AEs listed in the SAP which occurred on the day of and/or the day after the MabThera IV infusion.

Pediatric population

A multicenter, open-label, randomized study of Lymphome Malin B (LMB) chemotherapy (corticosteroids, vincristine, cyclophosphamide, high-dose methotrexate, cytarabine, doxorubicin, etoposide and triple drug [methotrexate/cytarabine/ corticosteroid] intrathecal therapy) alone or in combination with MabThera IV was conducted in pediatric patients with previously untreated advanced stage CD20 positive DLBCL/BL/BAL/BLL. Advanced stage is defined as Stage III with elevated LDH level ("B-high"), [LDH > twice the institutional upper limit of the adult normal values (> Nx2)] or any stage IV or B-AL. Patients were randomized to receive either LMB chemotherapy or six IV infusions of MabThera at a dose of 375mg/m^2 BSA in combination with LMB chemotherapy (two during each of the two induction courses and one during each of the two consolidation courses) as per the Lymphome Malin B scheme. A total of 328 randomized patients were included in the efficacy analyses, of which one patient under 3 years of age received MabThera IV in combination with LMB chemotherapy.

The two treatment arms, LMB (LMB chemotherapy) and R-LMB (LMB chemotherapy with MabThera IV), were well balanced with regards to baseline characteristics. Patients had a median age of 7 and 8 years in the LMB and R-LMB arm, respectively. Approximately half of

patients were in Group B (50.6% in the LMB arm and 49.4% in the R-LMB arm), 39.6% in Group C1 in both arms, and 9.8% and 11.0% were in Group C3 in the LMB and R-LMB arms, respectively (see section 2.2 Dosage and Administration). Based on Murphy staging, most patients were either BL stage III (45.7% in the LMB arm and 43.3% in the R-LMB arm) or B-AL, CNS negative (21.3% in the LMB arm and 24.4% in the R-LMB arm). Less than half of the patients (45.1% in both arms) had bone marrow involvement, and most patients (72.6% in the LMB arm and 73.2% in the R-LMB arm) had no CNS involvement. The primary efficacy endpoint was EFS, where an event was defined as occurrence of progressive disease, relapse, second malignancy, death from any cause, or non-response as evidenced by detection of viable cells in residue after the second CYVE course, whichever occurs first. The secondary efficacy endpoints were OS and CR (complete remission).

At the pre-specified interim analysis with approximately 1 year of median follow-up, clinically relevant improvement in the primary endpoint of EFS was observed, with 1-year rate estimates of 94.2% (95% CI, 88.5% - 97.2%) in the R-LMB arm vs. 81.5% (95% CI, 73.0% - 87.8%) in the LMB arm, and adjusted Cox HR 0.33 (95% CI, 0.14 – 0.79). Upon IDMC (independent data monitoring committee) recommendation based on this result, the randomization was halted and patients in the LMB arm were allowed to cross over to receive MabThera IV.

Primary efficacy analyses were performed in 328 randomized patients with a median follow-up of 3.1 years. The results are described in Table 17.

Table 17 Overview of Primary Efficacy Results (ITT population)

Analysis	**LMB** **(N = 164)**	**R-LMB** **(N=164)**
EFS	28 events	10 events
	One-sided log-rank test p-value 0.0006	
	Adjusted Cox HR 0.32 (90% CI: 0.17, 0.58)	
3-year EFS rates	82.3% (95% CI: 75.7%, 87.5%)	93.9% (95% CI: 89.1%, 96.7%)
OS	20 deaths	8 deaths
	One-sided log-rank test p-value 0.0061	
	Adjusted Cox model HR 0.36 (95% CI: 0.16; 0.81)	
3-year OS rates	87.3% (95% CI: 81.2%, 91.6%)	95.1% (95% CI: 90.5%, 97.5%)
CR rate	93.6% (95% CI: 88.2%; 97.0%)	94.0% (95% CI: 88.8%, 97.2%)

The primary efficacy analysis showed an-EFS benefit of MabThera IV addition to LMB chemotherapy over LMB chemotherapy alone, with an EFS HR 0.32 (90% CI 0.17 - 0.58) from a Cox regression analysis adjusting for national group, histology, and therapeutic group. While no major differences in numbers of patients achieving CR was observed between the two treatment groups, the benefit of MabThera IV addition to LMB chemotherapy was also shown in the secondary endpoint of OS, with the OS HR of 0.36 (95% CI, 0.16 – 0.81).

Subcutaneous Formulation

Previously Untreated Follicular Non-Hodgkin's Lymphoma BO22334 (SABRINA)

A two-stage phase III, international, multicenter, randomized, controlled, open-label study was conducted in patients with previously untreated follicular lymphoma, to investigate the non-inferiority of the pharmacokinetic profile, together with efficacy and safety of MabThera SC in combination with CHOP or CVP vs. MabThera IV in combination with CHOP or CVP followed by MabThera maintenance therapy.

The objective of the first stage was to establish the MabThera SC dose that resulted in comparable rituximab serum C_{trough} levels compared with MabThera IV when given as part of induction treatment every 3 weeks for 8 cycles (see section 3.2 Pharmacokinetic Properties, Distribution). Stage 1 enrolled previously untreated patients with CD20-positive, follicular lymphoma (FL) Grade 1, 2 or 3a (n=127). Patients with a response at the end of induction therapy received maintenance therapy with the corresponding formulation (intravenous or subcutaneous) used in the induction treatment, every 8 weeks for 24 months.

The objective of Stage 2 was to provide additional efficacy and safety data for MabThera SC compared with MabThera IV using the 1400 mg subcutaneous dose established in Stage 1. Previously untreated patients with CD20-positive, follicular lymphoma Grade 1, 2 or 3a (n=283) were enrolled in Stage 2.

The overall study design was identical across Stage 1 and Stage 2. Patients were randomized into the following two treatment groups:

- MabThera SC arm (n=205): 1st cycle MabThera IV plus 7 cycles of MabThera SC in combination with up to 8 cycles of CHOP or CVP chemotherapy, administered every 3 weeks. MabThera IV was given at the standard dose of 375 mg/m^2. MabThera SC was given at a fixed dose of 1400 mg. Patients achieving at least partial response (PR) at the end of induction treatment were entered on to MabThera SC maintenance therapy administered once every 8 weeks for 24 months.
- MabThera IV arm (n=205): 8 cycles of MabThera IV in combination with up to 8 cycles of CHOP or CVP chemotherapy administered every 3 weeks. MabThera IV was given at the standard dose of 375 mg/m^2. Patients achieving at least PR at the end of induction were entered on to MabThera IV maintenance therapy administered once every 8 weeks for 24 months.

Overall response rate (ORR, comprising complete response [CR], unconfirmed response [CRu], and partial response [PR]) at the end of induction treatment was calculated using investigator assessment of response in the ITT population based on pooled data from Stages 1 and 2. Additionally, ORR and complete response rate (CRR, comprising CR and CRu) at the end of maintenance treatment and time-to-event endpoints (progression-free survival [PFS] and overall survival [OS]) were analyzed.

Key efficacy results are presented in Table 18 based on a median follow-up of 58 months.

Table 18 Efficacy Results for Study SABRINA/BO22334

	MabThera SC N=205	**MabThera IV** N=205
Overall Response Rate at End of Induction [a]		
Number of responders (CR/CRu, PR)	173	174
Overall response (CR/CRu, PR) rate (%, [95% CI])	84.4% [78.7; 89.1]	84.9% [79.2; 89.5]
Number of complete responders (CR/CRu)	66	65
Complete response (CR/CRu) rate (%, [95% CI])	32.2% [25.9; 39.1]	31.7% [25.4; 38.6]
Overall Response Rate at End of Maintenance		
Number of patients treated in maintenance (n)	172	178
Number of responders (CR/CRu, PR)	134	139
Overall response (CR/CRu, PR) rate (%, [95% CI])	77.9% [71.0; 83.9]	78.1% [71.3; 83.9]
Number of complete responders (CR/CRu)	87	103
Complete response (CR/CRu) rate (%, [95% CI])	50.6% [42.9; 58.3]	57.9% [50.3; 65.2]
Progression-free survival [b]		
Number of patients with event	65 (31.7%)	71 (34.6%)
Hazard Ratio [95% CI] (unstratified Cox model)	0.90 [0.64%, 1.26%]	
Overall survival [b]		
Number of patients with event	18 (8.8%)	26 (12.7%)
Hazard Ratio [95% CI] (unstratified Cox model)	0.70 [0.38; 1.27]	

[a] at end of Induction
[B] at time of final analysis (median follow-up 58 months)
Stage 2 primary efficacy endpoint was ORR at the end of induction, however pooled results which were preplanned are presented in this Table.
Response rates based on investigator assessment.
Response rates at end of maintenance based on patients who received at least one cycle of maintenance treatment (n).

Exploratory analyses showed response rates among BSA, chemotherapy and gender subgroups were not notably different from the overall ITT population.

Chronic Lymphocytic Leukaemia BO25341 (SAWYER)

A two-part phase Ib, multicenter, randomized, open-label, parallel-group study conducted in patients with previously untreated CLL to investigate the non-inferiority of the pharmacokinetic profile, together with efficacy and safety of MabThera SC in combination with chemotherapy.

The objective of Part 1 was to select a MabThera SC dose that resulted in comparable rituximab serum C_{trough} levels compared with MabThera IV. Previously untreated CLL patients (n=64) were enrolled at any point prior to Cycle 5 during their treatment with MabThera IV in combination with chemotherapy. The dose of 1600 mg of MabThera SC was selected for Part 2 of the study.

The objective of Part 2 was to establish non-inferiority in observed rituximab C_{trough} levels between the selected MabThera SC dose and the reference MabThera IV dose.

Previously untreated CLL patients (n=176) were randomized into the following two treatment groups:

- MabThera SC arm (n=88): 1st cycle of MabThera IV 375 mg/m2 in combination with chemotherapy plus subsequent cycles (Cycle 2 to 6) of MabThera SC 1600 mg in combination with chemotherapy.
- MabThera IV arm (n=88): 1st cycle of MabThera IV 375 mg/m2 in combination with chemotherapy followed by up to 5 cycles of MabThera IV 500 mg/m2 in combination with chemotherapy.

The response rates for the analysis of 176 patients in SAWYER Part 2 are shown in Table 19.

Table 19 Efficacy Results for Study SAWYER/BO25341

		Part 2 N = 176	
		MabThera IV (n = 88)	**MabThera SC** (n = 88)
ORR[a]	Point estimate	80.7% (n = 71)	85.2% (n = 75)
	95% CI	[70.9%, 88.3%]	[76.1%, 91.9%]
CRR[a]	Point estimate	31.8% (n = 28)	27.3% (n = 24)
	95% CI	[22.3%, 42.6%]	[18.3%, 37.8%]
PFS[b]	Proportion with PFS event	42.0% (n = 37)	34.1% (n = 30)
	HR 95% CI	0.76 [0.47%, 1.23%]	

ORR – Overall Response Rate
CRR – Complete Response Rate
PFS – Progression-Free Survival (proportion with event, disease progression/relapse or death from any cause)
[a] – at 3 month follow-up visit (Part 2)
[b] – at time of final analysis (median follow-up 53 months)

Overall the results confirm that MabThera SC 1600 mg has a comparable benefit/risk profile to that of MabThera IV 500 mg/m^2 .

Intravenous Formulation

Rheumatoid Arthritis

The efficacy of MabThera IV in rheumatoid arthritis has been demonstrated in three pivotal, phase III, randomized, placebo-controlled, double-blind, multi-center studies. Eligible patients had severe, active RA, diagnosed according to the criteria of the American College of Rheumatology (ACR). MabThera IV was administered as two IV infusions separated by an interval of 15 days. Each course was preceded by an IV infusion of 100 mg methylprednisolone. All patients received concomitant oral methotrexate. In addition, in Study WA17042, all patients received concomitant oral glucocorticoids on days 2 to 7 and on days 8 to 14 following the first infusion.

The retreatment criteria differed between the studies using one of two approaches: 'Treatment to Remission' whereby patients were treated no more frequently than every 6 months if not in DAS28 remission (i.e., DAS28-ESR ≥2.6) and 'Treatment as Needed' strategy ('Treatment PRN'), based on disease activity and/or return of clinical symptoms (swollen and tender joint counts ≥ 8) and treated no sooner than every 16 weeks.

Study WA17042 (REFLEX) included 517 patients that had experienced an inadequate response or intolerance to one or more tumour necrosis factor (TNF) inhibitor therapies (TNF-IR) [68]. The primary endpoint was the proportion of patients who achieved an ACR20 response at Week 24. Patients received 2 x 1000 mg MabThera IV or placebo. Patients were followed beyond Week 24 for long-term endpoints, including radiographic assessment at 56 weeks. During this time patients could receive further courses of MabThera IV under an open label extension study protocol. In the open-label protocol patients received further courses based on the 'Treatment PRN' criteria.

Study WA17045 (SERENE) included 511 patients that had experienced an inadequate response to methotrexate (MTX-IR) and had not received prior biologic therapy. The primary endpoint was the proportion of patients who achieved an ACR20 response at Week 24. Patients received placebo, 2 x 500 mg or 2 x 1000 mg MabThera IV infusion. Patients were followed beyond Week 24 for long-term endpoints and could receive further courses of MabThera IV based on the 'Treatment to Remission' criteria. An active dose comparison was made at Week 48.

Disease Activity Outcomes

In these studies, MabThera IV (2 x 1000 mg) significantly increased the proportion of patients achieving at least a 20% improvement in ACR score compared with patients treated with methotrexate alone (see Table 20). Across all development studies the treatment benefit was similar in patients independent of age, gender, body surface area, race, number of prior treatments or disease status. Patients seropositive for disease-related auto-antibodies (RF and/or anti-CCP) demonstrated consistently high efficacy compared to MTX alone across studies. Efficacy in seropositive patients was higher than that observed in seronegative patients in whom efficacy was modest.

Clinically and statistically significant improvement was also noted on all individual components of the ACR response (tender and swollen joint counts, patient and physician global assessment, disability index scores [HAQ], pain assessment and CRP [mg/dL]).

Table 20 Cross-Study Comparison of ACR Responses (ITT Population)

	Timepoint	**ACR Response**	**Placebo+MTX**	**RTX+MTX** (2 x 1000 mg)
Study WA17042 **(TNF-IR)**	Week 24		n=201	n=298
		ACR20	36 (18%)	153 (51%)***
		ACR50	11 (5%)	80 (27%)***
		ACR70	3 (1%)	37 (12%)***
Study WA17045 **(MTX-IR)**	Week 24		n=172	n=170
		ACR20	40 (23%)	86 (51%)***
		ACR50	16 (9%)	44 (26%)***
		ACR70	9 (5%)	17 (10%)
Significant difference from placebo at the primary timepoint: * $p \leq 0.05$, ** $p \leq 0.001$ *** $p \leq 0.0001$				

Patients treated with MabThera IV had a significantly greater reduction in disease activity score (DAS28) than patients treated with methotrexate alone. A good to moderate EULAR response was achieved by significantly more MabThera IV treated patients compared to patients treated with methotrexate alone (see Table 21).

Table 21 Cross-Study Comparison of DAS28-ESR and EULAR Responses (ITT Population)

	Placebo+MTX	**RTX +MTX** (2 × 1000mg)
Study WA17042 (TNF-IR)		
Change in DAS28 at Week 24		
n	**n=201**	**n=298**
Mean Change	-0.4	-1.9***
EULAR Response(Week 24)		n=298
n	n=201	
Moderate	20%	50%***
Good	2%	15%***
Study WA17045 (MTX-IR)		
Change in DAS28 at Week 24		
n	**n=171**	**n=168**
Mean Change	–0.8	–1.7***
EULAR response (Week 24)		
n	**n=172**	**n=170**
Moderate	29%	51%***
Good	5%	12%***

Significant difference from placebo at the primary timepoint: * $p \leq 0.05$, ** $p \leq 0.001$ *** $p \leq 0.0001$

Inhibition of Joint Damage

In Studies WA17042 and WA17047 structural joint damage was assessed radiographically and expressed as change in modified Total Sharp Score (TSS) and its components, the erosion score and joint space narrowing score.

Study WA17042 conducted in TNF-IR patients receiving MabThera IV in combination with methotrexate, demonstrated significantly less radiographic progression at 56 weeks than patients from the methotrexate alone group. A higher proportion of patients receiving MabThera IV also had no erosive progression over 56 weeks.

Study WA17047 conducted in methotrexate-naïve patients (755 patients with early RA of between 8 weeks to four years duration), assessed the prevention of structural joint damage as its primary objective (see section 2.4 Warnings and Precautions). Patients received placebo, 2 x 500 mg or 2 x 1000 mg MabThera IV infusion. From Week 24 patients could receive further courses of MabThera IV (or placebo to Week 104) based on the 'Treatment to Remission' criteria. The primary endpoint of change in modified Total Sharp Score (TSS) demonstrated that only treatment with MabThera IV at a dose of 2 x 1000 mg in combination with methotrexate significantly reduced the rate of progression of joint damage (PJD) at 52 weeks compared with placebo + methotrexate (see Table 22). The reduction in PJD was driven mainly by a significant reduction in the change in Erosion Score.

Inhibition of the rate of progressive joint damage was also observed long-term. Radiographic analysis at 2 years in Study WA17042 demonstrated significantly reduced progression of structural joint damage in patients receiving MabThera IV (2 x 1000 mg) + methotrexate compared to methotrexate alone as well as a significantly higher proportion of patients with no progression of joint damage over the 2 year period.

Table 22 Radiographic Outcomes at 1 Year in Studies WA17042 and WA17047 (MITT Population)

	Placebo+MTX	**RTX+MTX** (2 ×1000 mg)
Study WA17042 (TNF-IR)	**n=184**	**n=273**
Mean Change from Baseline:		
Modified Total Sharp Score	2.30	1.01*
Erosion Score	1.32	0.60*
Joint Space Narrowing Score	0.98	0.41**
Proportion of patients with no radiographic change	46%	53% NS
Proportion of patients with no erosive change	52%	60% NS
Study WA17047 (MTX- naïve)	**n=232**	**n=244**
Mean Change from Baseline:		
Modified Total Sharp Score	1.079	0.359**
Erosion Score	0.738	0.233***
Joint Space Narrowing Score	0.341	0.126
Proportion of patients with no radiographic change	53%	64%*
Proportion of patients with no erosive change	55%	67%*
Radiographic outcomes were assessed at Week 52 in Study WA17047 and Week 56 in Study WA17042 150 patients originally randomized to placebo + MTX in WA17042 received at least one course of RTX + MTX by one year * p <0 05, ** p < 0.001, *** p < 0.0001, NS Non Significant		

Quality of Life Outcomes

MabThera IV treated patients reported an improvement in all patient-reported outcomes (HAQ-DI, FACIT-Fatigue and SF-36 questionnaires). Significant reductions in disability index (HAQ-DI), fatigue (FACIT-Fatigue), and improvement in the physical health domain of the SF-36 were observed in patients treated with MabThera IV compared to patients treated with methotrexate alone.

Table 23 Cross Study Comparison of HAQ-DI and FACIT–Fatigue responses

	Placebo+MTX[1]	**RTX+MTX[1] (**2 × 1000mg**)**
Study WA17042 (TNF-IR) - Mean change in HAQa at Week 24 - % patients with HAQ MCID at Week 24 - Mean change in FACIT-Fatigue[b] at Week 24	**n=201** -0.1 20% -0.5	**n=298** -0.4*** 51% -9.1***
Study WA17045 (MTX-IR) • Mean change in HAQ[a] at Week 24 • % patients with HAQ MCID at Week 24 • Mean change in FACIT-Fatigue[b] at Week 24	**n=172[a] (170)[b]** -0.21 48% 2.7	**n=170[a] (168)[b]** -0.42*** 58%* 6.4***
[a] Health assessment questionnaire (HAQ),[b] Functional assessment of chronic illness therapy (FACIT-Fatigue) Significant difference from placebo at the primary timepoint: * p < 0.05, **p < 0.001 ***p ≤ 0.0001 (CMH test for categorical change, ANOVA for mean change, note that the unadjusted mean changes are displayed)		

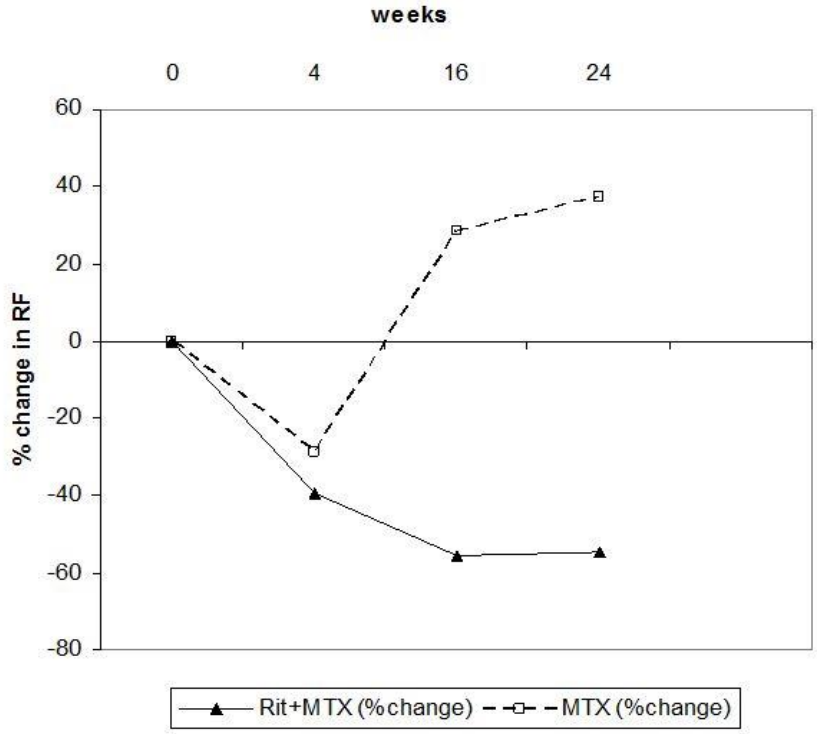
Table 24 Cross-study comparisons of Short Form Health Survey (SF-36).

	Placebo+MTX	**RTX +MTX** (2 × 1000 mg)
Study WA17042 (TNF-IR)	**n=197**	**n=294**
Physical Health		
Mean change at Week 24	0.9	5.8***
% patients with MCID at Week 24	13%	48%***
Mental Health		
Mean change at Week 24	1.3	4.7**
% patients with MCID at Week 24	20%	38%**
Study WA17045 (MTX-IR)	**n=147**	**n=155**
Physical Health		
Mean change at Week 24	2.7	5.9***
% patients with MCID at Week 24	31%	48%
Mental Health		
Mean change at Week 24	2.1	4.4**
% patients with MCID at Week 24	24%	35%*
MCID = minimum clinically important difference defined as an increase of: >6.33 for mental health score and >5.42 for physical health score, % of patients based on number of patients assessable (N) Significant difference from placebo at the primary timepoint: * p ≤ 0.05, ** p ≤ 0.001, *** p ≤ 0.0001 (CMH test for categorical change, ANOVA for mean change - note that unadjusted mean changes are displayed		

Laboratory Evaluations

In rheumatoid factor (RF) positive patients, marked decreases were observed in rheumatoid factor concentrations following treatment with MabThera IV in all three studies (range 45-64%, Figure 1).

Figure 1 Percentage Change in Total RF Concentration Over Time in Study 1 (ITT Population, RF-Positive Patients)



Plasma total immunoglobulin concentrations, total lymphocytes counts, and white cell counts generally remained within normal limits following MabThera IV treatment, with the exception of a transient drop in white cell counts over the first four weeks following therapy. Titers of IgG antigen specific antibody to mumps, rubella, varicella, tetanus toxoid, influenza and streptococcus pneumococci remained stable over 24 weeks following exposure to MabThera IV in rheumatoid arthritis patients.

Effects of rituximab on a variety of biomarkers were evaluated in patients enrolled into a clinical study. This sub-study evaluated the impact of a single treatment course of rituximab on levels of biochemical markers, including markers of inflammation (Interleukin 6, C Reactive protein, Serum amyloid type A protein, Protein S100 isotypes A8 and A9), autoantibody (RF and anti-cyclic citrullinated peptide immunoglobulin) production and bone turnover (osteocalcin and procollagen 1 N terminal peptide (P1NP)). MabThera IV treatment, whether as monotherapy or in combination with methotrexate or cyclophosphamide reduced the levels of inflammatory markers significantly, relative to methotrexate alone, over the first 24 weeks of follow-up. Levels of markers of bone turnover, osteocalcin and P1NP, increased significantly in the rituximab groups compared to methotrexate alone.

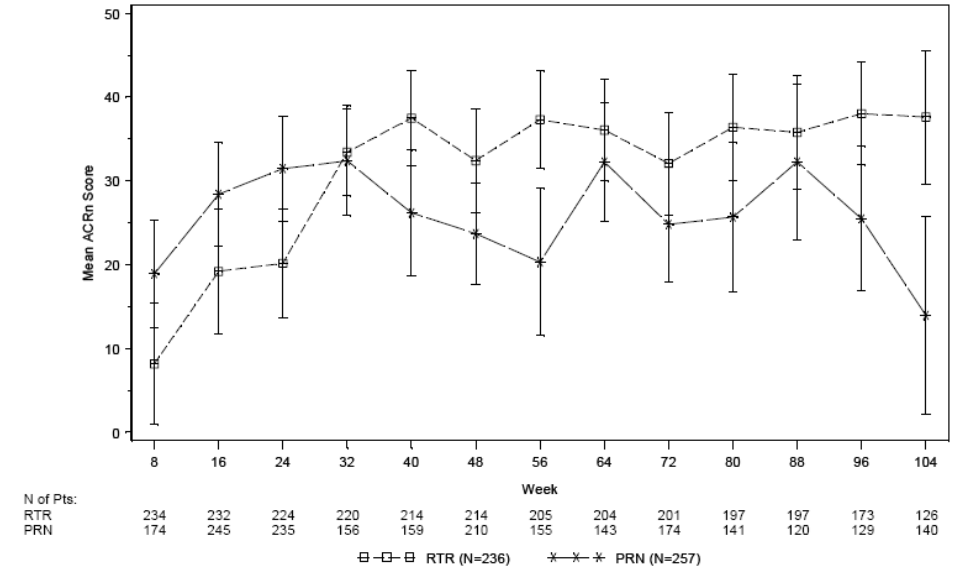
Long-term Efficacy with Multiple Course Therapy

In clinical studies patients were retreated based on either a 'Treatment to Remission' or a 'Treatment PRN' strategy. Repeat courses of MabThera IV maintained or improved treatment benefit, irrespective of the treatment strategy (Treatment to Remission or Treatment PRN) (Figure 2). However, Treatment to Remission generally provided better responses and tighter control of disease activity as indicated by ACRn, DAS28-ESR and HAQ-DI scores over time. Patients treated PRN also experienced returning disease symptoms between courses, as evidenced by DAS28-ESR scores which were close to pre-treatment levels prior to each course (Table 25).

Table25 Cross-study comparisons of Short Form Health Survey (SF-36).

Population	**Parameter**	**C1**	**C2**	**C3**	**C4**	**C5**
Treatment To Remission		**n=236**	**n=218**	**n=198**	**n=156**	**n=83**
	Mean BL DAS	6.6	4.9	4.6	4.6	4.7
	Median BL ACRn	-	22.7	25.5	26.5	26.3
Treatment PRN		**n=257**	**n=182**	**n=139**	**n=85**	**n=39**
	Mean BL DAS	6.7	6.2	6.2	5.9	6.0
	Median BL ACRn	-	-5.3	-11.1	-10.9	-4.2
Positive change in ACRn = improvement BL=Baseline						

Figure 2 Plot of Mean ACRn Over Time by Treatment Criteria (MTX-IR Population)



Error bars displayed are 95% confidence intervals about the mean.
No imputation made for missing data
RTR = Re-treat to Remission

120-minute Infusion Rate Study (ML25641)

In a multi-center, open-label single-arm trial, 351 patients with moderate-to-severe, active RA who had an inadequate response to at least one tumor necrosis factor inhibitor and were receiving methotrexate, were to receive 2 courses of MabThera IV treatment. Patients who were naïve to prior MabThera IV therapy (n=306) and those who had received 1 to 2 prior courses of MabThera IV 6 to 9 months prior to baseline (n=45), were eligible for enrollment.

Patients received 2 courses of MabThera IV (2 x 1000 mg) + methotrexate treatment with the first course administered on Days 1 and 15 and the second course six months later on Days 168 and 182. The first infusion of the first course (Day 1 infusion) was administered over a 4.25 hour (255 minutes) period. The second infusion of the first course (Day 15 infusion) and both infusions in the second course (Day 168 and 182 infusions) were administered over a 2 hour (120 minutes) period. Any patient experiencing a serious IRR with any infusion was withdrawn from the study.

The primary objective of the study was to assess the safety of administering the second infusion of the first study course of MabThera IV over a 2 hour (120 minutes) period.

The incidence of IRRs at Day 15 was 6.5% (95% CI [4.1%-9.7%]) consistent with the rate observed historically. There were no serious IRRs observed. Data observed for the infusions on Days 168 and 182 (120-minute infusion) demonstrates a low incidence of IRRs, similar to the rate observed historically, with no serious IRRs occurring (see section 2.6 Undesirable Effects, Clinical Trials).

Adult Patients with Granulomatosis with Polyangiitis (Wegener's) (GPA) and Microscopic Polyangiitis (MPA)

Adult induction of remission (GPA/MPA Study 1)

In GPA/MPA Study 1, a total of 197 patients with severe, active granulomatosis with polyangiitis (Wegener's) (GPA) and microscopic polyangiitis (MPA) were enrolled and treated in an active-controlled, randomized, double-blind, multicenter, non-inferiority study. Patients were 15 years of age or older, diagnosed with severely, active granulomatosis with polyangiitis (Wegener's) (75% of patients) or microscopic polyangiitis (MPA) (24% of patients) according to the Chapel Hill Consensus Conference Criteria. One percent of patients had unknown GPA and MPA type.

Patients were randomized in a 1:1 ratio to receive either oral cyclophosphamide daily (2 mg/kg/day) for 3 to 6 months, followed by azathioprine or MabThera IV (375 mg/m^2) once weekly for 4 weeks. Patients in both arms received 1000 mg of pulse IV methylprednisolone (or another equivalent-dose glucocorticoid) per day for 1 to 3 days, followed by oral prednisone (1 mg/kg/day, not exceeding 80 mg/day). Prednisone tapering was to be completed by 6 months from the start of study treatment.

The primary outcome measure was achievement of complete remission at 6 months defined as a Birmingham Vasculitis Activity Score for Wegener's Granulomatosis (BVAS/WG) of 0, and off glucocorticoid therapy. The prespecified non-inferiority margin for the treatment difference was 20%. The study demonstrated non-inferiority of MabThera IV to cyclophosphamide for complete remission at 6 months (see Table 26). In addition, the complete remission rate in the MabThera IV arm was significantly greater than the estimated complete remission rate in patients with severe GPA and MPA not treated or treated only with glucocorticoids, based on historical control data.

Efficacy was observed both for patients with newly diagnosed GPA and MPA and for patients with relapsing disease.

Table 26 Percentage of Patients Who Achieved Complete Remission at 6 Months (Intent-to-Treat Population)

	MabThera (n = 99)	Cyclophosphamide (n = 98)	Treatment Difference (MabThera – Cyclophosphamide)
Rate	63.6%	53.1%	10.6%
95.1%[b] CI	(54.1%, 73.2%)	(43.1%, 63.0%)	(–3.2%, 24.3%) [a]

CI = confidence interval.

[a] Non-inferiority was demonstrated since the lower bound (– 3.2%) was higher than the pre-determined non-inferiority margin (– 20%).

[b] The 95.1% confidence level reflects an additional 0.001 alpha to account for an interim efficacy analysis.

Adult maintenance treatment (GPA/MPA Study 2)

A total of 117 patients (88 with GPA, 24 with MPA, and 5 with renal-limited ANCA-associated vasculitis) in disease remission were randomized to receive azathioprine (59 patients) or MabThera IV (58 patients) in this prospective, multi-center, controlled, open-label

study. Eligible patients were 21 to 75 years of age and had newly diagnosed or relapsing disease in complete remission after combined treatment with glucocorticoids and pulse cyclophosphamide. Patients were ANCA-positive at diagnosis or during the course of their disease; had histologically confirmed necrotizing small-vessel vasculitis with a clinical phenotype of GPA/MPA, or renal limited ANCA-associated vasculitis; or both.

Remission-induction therapy included IV prednisone, administered as per the investigator's discretion, preceded in some patients by methylprednisolone pulses, and pulse cyclophosphamide until remission was attained after 4 to 6 months. At that time, and within a maximum of 1 month after the last cyclophosphamide pulse, patients were randomly assigned to receive either MabThera IV (two 500 mg IV infusions separated by two weeks (on Day 1 and Day 15) followed by 500 mg IV every 6 months for 18 months or azathioprine (administered orally at a dose of 2 mg/kg/day for 12 months, then 1.5 mg/kg/day for 6 months, and finally 1 mg/kg/day for 4 months (treatment discontinuation after these 22 months). Prednisone treatment was tapered and then kept at a low dose (approximately 5 mg per day) for at least 18 months after randomization. Prednisone dose tapering and the decision to stop prednisone treatment after month 18 were left at the investigator's discretion.

All patients were followed until month 28 (10 or 6 months, respectively, after the last MabThera IV infusion or azathioprine dose). Pneumocystis jirovecii pneumonia prophylaxis was required for all patients with CD4+ T-lymphocyte counts less than 250 per cubic millimeter.

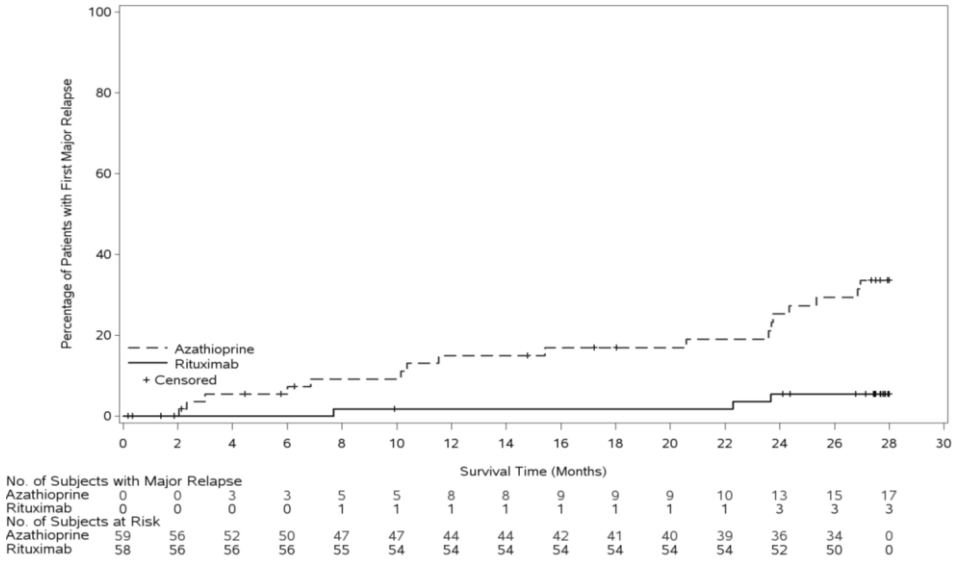
The primary outcome measure was the rate of major relapse at month 28.

Results

At month 28, major relapse (defined by the reappearance of clinical and/or laboratory signs of vasculitis activity ([BVAS] > 0) that could lead to organ failure or damage or could be life threatening) occurred in three patients (5%) in the MabThera IV group and 17 patients (29%) in the azathioprine group (p=0.0007). Adjusting for the stratification factor using Cox PH modeling, MabThera IV reduced the risk of major relapse by approximately 86% relative to azathioprine (hazard ratio [HR]: 0.14; 95% confidence interval [CI]: 0.04, 0.47). Minor relapses (not life threatening and not involving major organ damage) occurred in seven patients in the MabThera IV group (12%) and eight patients in the azathioprine group (14%).

The cumulative incidence rate curves showed that time to first major relapse was longer in patients with MabThera IV starting from Month 2 and was maintained up to Month 28 (Figure 3).

Figure 3 Cumulative Incidence Over Time of First Major Relapse



Note, patients were censored at Month 28 if they had no event.

Pediatric Patients with Granulomatosis with Polyangiitis (Wegener's) (GPA) and Microscopic Polyangiitis (MPA)

Study WA25615 (PePRS) was a multicenter, open-label, single-arm, uncontrolled study in 25 pediatric patients (≥ 2 to < 18 years old) with active GPA/MPA. The median age of patients in the study was: 14 years (range: 6-17 years) and the majority of patients (20/25 [80%]) were female. A total of 19 patients (76%) had GPA and 6 patients (24%) had MPA at baseline. Eighteen patients (72%) had newly diagnosed disease upon study entry (13 patients with GPA and 5 patients with MPA) and 7 patients had relapsing disease (6 patients with GPA and 1 patient with MPA).

The study design consisted of an initial 6-month remission induction phase, and a minimum 18-month follow-up phase up to a maximum of 54 months (4.5 years). The remission induction regimen consisted of four once weekly IV infusions of MabThera at a dose of 375 mg/m^2 BSA, on study days 1, 8, 15 and 22 in combination with oral prednisolone or prednisone at 1 mg/kg/day (max 60 mg/day) tapered to 0.2 mg/kg/day minimum (max 10 mg/day) by month 6. After the remission induction phase, patients could receive subsequent MabThera IV infusions on or after month 6 to maintain remission and control disease activity. Patients were to receive a minimum of 3 doses of IV methylprednisolone (30 mg/kg/day, not exceeding 1g/day) prior to the first MabThera IV infusion. If clinically indicated, additional daily doses (up to three), of IV methylprednisolone could be given.

All 25 patients completed all four once weekly IV infusions for the 6-month remission induction phase. A total of 24 out of 25 patients completed at least 18 months of follow-up.

The objectives of this study was to evaluate safety, PK parameters, and efficacy of MabThera IV in pediatric GPA/MPA patients (≥ 2 to < 18 years old). The efficacy objectives of the study were exploratory and principally assessed using the Pediatric Vasculitis Activity Score (PVAS).

Table 27 Study WA25615 (PePRS) - PVAS Remission by Month 6, 12 and 18

Time to Follow Up	Number of Responders in PVAS Remission* (response rate [%]) n=25	95% CI[α]
6 months	14 (56.0%)	34.9%, 75.6%
12 months	23 (92.0%)	74.0%, 99.0%
18 months	25 (100.0%)	86.3%, 100.0%

*PVAS remission is defined by a PVAS of 0 and achieved glucocorticoid taper to 0.2 mg/kg/day (or 10 mg/day, whichever is lower), or a PVAS of 0 on two consecutive readings ≥4 weeks apart irrespective of glucocorticoid dose
[α]the efficacy results are exploratory and no formal statistical testing was performed for these endpoints

Cumulative glucocorticoid dose (IV and Oral) by month 6

A clinically meaningful decrease in median overall oral glucocorticoid was observed from week 1 (median = 45 mg prednisone equivalent dose [IQR: 35 – 60]) to month 6 (median = 7.5 mg [IQR: 4-10]), which was subsequently maintained at month 12 (median = 5 mg [IQR: 2-10]) and month 18 (median =5 mg [IQR: 1-5]).

Follow-up treatment

After the 6-month remission induction phase, patients who had not achieved remission or who had progressive disease or flare that could not be controlled by glucocorticoids alone received additional treatment for GPA/MPA, that could include MabThera IV and/or other therapies, at the discretion of the investigator.

Fourteen out of 25 patients (56%) received additional MabThera IV treatment at or post month 6, up to month 18. Five patients received four once weekly doses (375 mg/m^2) of MabThera IV approximately every 6 months; 5 patients received a single dose (375 mg/m^2) of MabThera IV every 6 months, and a further 4 patients received various other MabThera doses/regimens according to their treating physician. Of the 14 patients, 9 patients achieved PVAS remission by month 6 and sustained remission through month 18; 4 patients achieved remission between month 6 and 12 and sustained remission through month 18. One patient first achieved remission between month 12 and 18.

Pemphigus Vulgaris

PV Study 1 (Study ML22196)

The efficacy and safety of MabThera IV in combination with short-term low dose glucocorticoid (prednisone) therapy were evaluated in newly diagnosed patients with

moderate to severe pemphigus (74 pemphigus vulgaris [PV] and 16 pemphigus foliaceus [PF]) in this randomized, open-label, controlled, multicenter study. Patients were between 19 and 79 years of age and had not received prior therapies for pemphigus. In the PV population, five (13%) patients in the MabThera IV group and three (8%) patients in the standard prednisone group had moderate disease and 33 (87%) patients in the MabThera IV group and 33 (92%) patients in the standard dose prednisone group had severe disease according to disease severity defined by Harman's criteria.

Patients were stratified by baseline disease severity (moderate or severe) and randomized 1:1 to receive either MabThera IV and low dose prednisone or standard dose prednisone. Patients randomized to the MabThera IV group received an initial intravenous infusion of 1000 mg MabThera IV on Study Day 1 in combination with 0.5 mg/kg/day oral prednisone tapered off over 3 months if they had moderate disease or 1 mg/kg/day oral prednisone tapered off over 6 months if they had severe disease, and a second intravenous infusion of 1000 mg on Study Day 15. Maintenance infusions of MabThera IV 500 mg were administered at months 12 and 18. Patients randomized to the standard dose prednisone group received an initial 1 mg/kg/day oral prednisone tapered off over 12 months if they had moderate disease or 1.5 mg/kg/day oral prednisone tapered off over 18 months if they had severe disease. Patients in the MabThera IV group who relapsed could receive an additional infusion of MabThera IV 1000 mg in combination with reintroduced or escalated prednisone dose. Maintenance and relapse infusions were administered no sooner than 16 weeks following the previous infusion.

The primary objective for the study was complete remission (complete epithelialization and absence of new and/or established lesions) at month 24 without the use of prednisone therapy for two months or more (CRoff for ≥2 months). Other efficacy parameters included evaluation of severe and moderate relapses (severity as defined by Harman's criteria and relapse defined as the appearance of ≥ 3 new lesions a month that did not heal spontaneously within 1 week, or the extension of established lesions in a patient who had achieved disease control), evaluation of the total median cumulative dose of prednisone, and the median duration of complete remission off corticosteroid therapy.

PV Study 1 Results

The study demonstrated superiority of MabThera IV and low dose prednisone over standard dose prednisone in achieving CRoff ≥ 2 months at month 24 in PV patients (see Table 28). Additionally, at month 24, the proportion of PV patients with CRoff ≥ 3 months was higher in the MabThera IV and low dose prednisone group compared to the standard dose prednisone group (34 patients [90%] vs. 10 patients [28%], p value <0.0001).

Table 28 Percentage of PV Patients Who Achieved Complete Remission Off Corticosteroid Therapy for Two Months or More at Month 24 (Intent-to-Treat Population - PV)

	Rituximab + Prednisone N=38	Prednisone N=36	p-value [a]
Number of responders (response rate [%])	34 (90%)	10 (28%)	<0.0001
[a]p-value is from Fisher's exact test with mid-p correction			

MabThera IV was considered steroid-sparing based on the duration that PV patients were off glucocorticoid therapy and cumulative exposure to glucocorticoids in the MabThera IV group compared to the standard dose prednisone group.

Duration off glucocorticoid therapy

Of PV patients who responded at month 24, the median duration of CRoff ≥2 months in the MabThera IV group was 498.5 [91, 609] days compared to 125 [56, 680] days in the standard dose prednisone group.

Glucocorticoid exposure

The median (min, max) cumulative prednisone dose at month 24 was 5800 mg (2304, 29303) in the MabThera IV group compared to 20520 mg (2409, 60565) in the standard dose prednisone group.

Severe or moderate relapses

At month 24, 9 (24%) PV patients in the MabThera IV group experienced at least one severe or moderate relapse vs. 18 (50%) PV patients in the standard dose prednisone group.

PV Study 2 (Study WA29330)

In a randomized, double-blind, double-dummy, active-comparator, multicenter study, the efficacy and safety of MabThera IV compared with mycophenolate mofetil (MMF) were evaluated in patients with moderate-to-severe PV receiving 60-120 mg/day oral prednisone or equivalent (1.0-1.5 mg/kg/day) at study entry and tapered to reach a dose of 60 or 80 mg/day by Day 1. Patients had a confirmed diagnosis of PV within the previous 24 months and evidence of moderate-to-severe disease (defined as a total PDAI activity score of ≥ 15). The study consisted of a screening period of up to 28 days, a 52-week double-blind treatment period, and a 48-week safety follow-up period.

One hundred and thirty-five patients were randomized to treatment with MabThera IV 1000 mg administered on Day 1, Day 15, Week 24 and Week 26 or oral MMF 2 g/day (starting at 1 g/day on Day 1 and titrated to achieve a goal of 2 g/day by Week 2) for 52 weeks in combination with an initial dose of 60 or 80 mg oral prednisone with the aim of tapering to 0 mg/day by Week 24. Randomization was stratified by duration of PV (within the 1-year prior to screening or greater than 1 year) and geographical region. A dual-assessor approach was used during the study for efficacy and safety evaluations to prevent potential unblinding.

The primary efficacy objective for this study was to evaluate at Week 52, the efficacy of MabThera IV compared with MMF in achieving sustained complete remission defined as achieving healing of lesions with no new active lesions (i.e. PDAI activity score of 0) while on 0 mg/day prednisone or equivalent and maintaining this response for at least 16 consecutive weeks, during the 52-week treatment period (see Table 29).

Secondary efficacy objectives evaluating the efficacy of MabThera IV compared with MMF included cumulative oral corticosteroid dose, the total number of disease flares, and change in health-related quality of life, as measured by the Dermatology Life Quality Index.

PV Study 2 Results

The study demonstrated the superiority of MabThera IV over MMF in combination with a tapering course of oral corticosteroids in achieving CRoff ≥ 16 weeks at Week 52 in PV patients (see Table 29).

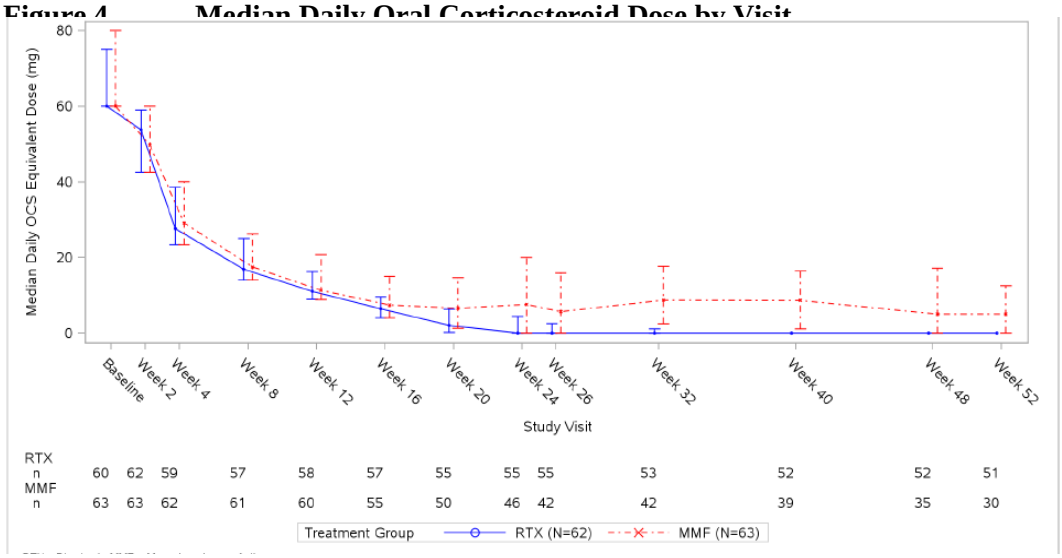
Table 29 Percentage of PV Patients Who Achieved Sustained Complete Remission Off Corticosteroid Therapy for 16 Weeks or More at Week 52 (Modified Intent-to-Treat Population)

	MabThera (N=62)	MMF (N=63)	Difference (95% CI)	p-value
Number of responders (response rate [%])	25 (40.3%)	6 (9.5%)	30.80% (14.70%, 45.15%)	<0.0001
MMF = Mycophenolate mofetil. CI = Confidence Interval. PDAI = Pemphigus Disease Area Index. Cochran-Mantel-Haenszel test is used for p-value.				

Glucocorticoid exposure

The cumulative oral corticosteroid dose was significantly lower in patients treated with MabThera. The median (min, max) cumulative prednisone dose at Week 52 was 2775 mg (450, 22180) in the MabThera IV group compared to 4005 mg (900, 19920) in the MMF group (p=0.0005). The median daily oral corticosteroid dose over time shows a steroid-sparing effect of MabThera (Figure 4).

Figure 4 Median Daily Oral Corticosteroid Dose by Visit



Disease flare

The total number of disease flares was significantly lower in patients treated with MabThera (6 vs. 44, p<0.0001) and there were fewer patients who had at least one disease flare (8.1% vs. 41.3%).

Dermatology Life Quality Index

Significantly greater improvements in health-related quality of life, as measured by the Dermatology Life Quality Index (DLQI), were observed in patients treated with MabThera (estimated mean change from Baseline = -8.87) compared to MMF (Estimated mean change from Baseline = -6.00) (p <0.05) at Week 52 from baseline.

In a post-hoc analysis 61.7% of patients in the MabThera arm achieved a DLQI score of 0 (indicating no impairment on health-related quality of life) at Week 52 compared to 25.0% of patients in the MMF arm.

3.1.3 IMMUNOGENICITY

As with all therapeutic proteins, there is the potential for an immune response in patients treated with MabThera. The data reflects the number of patients whose test results were considered positive for antibodies to rituximab using an enzyme-linked immunosorbent assay (ELISA). Immunogenicity assay results may be influenced by several factors including assay sensitivity and specificity, sample handling, timing of sample collection, concomitant medicinal products and underlying disease. For these reasons, comparison of incidence of antibodies to rituximab with the incidence of antibodies in other studies or to other products may be misleading.

Intravenous Formulation

Rheumatoid Arthritis

Approximately 10% of patients with rheumatoid arthritis tested positive for anti-drug antibodies (ADA) in the RA clinical studies. The emergence of ADA was not associated with clinical deterioration or with an increased risk of reactions to subsequent infusions in the majority of patients. The presence of ADA may be associated with worsening of infusion or allergic reactions after the second infusion of subsequent courses, and failure to deplete B cells after receipt of further treatment courses has been observed rarely.

Adult and Pediatric Patients with Granulomatosis with Polyangiitis (Wegener's) (GPA) and Microscopic Polyangiitis (MPA)

Twenty-three percent (23/99) of MabThera IV-treated patients from the adult GPA and MPA induction of remission trial and 18% (6/34) of MabThera IV-treated patients in the maintenance therapy clinical trial developed ADA.

In the pediatric clinical trial, a total of 4/25 patients (16%) developed ADA during the overall study period. Limited data shows there was no trend observed in the adverse reactions reported in ADA positive patients.

There was no apparent trend or negative impact of the presence of ADA on safety or efficacy in the adult and pediatric GPA and MPA clinical trials.

Pemphigus Vulgaris

In PV Study 1, by 18 months, a total of 19/34 (56%) (14 treatment-induced and 5 treatment-enhanced) MabThera IV treated PV patients tested positive for ADA.

In PV Study 2, by week 52, a total of 20/63 (31.7%) (19 treatment-induced and 1 treatment-enhanced) MabThera IV treated PV patients tested positive for ADA [204]. There was no apparent negative impact of the presence of ADA on safety or efficacy in the PV clinical trials.

Subcutaneous Formulation

Data from the subcutaneous formulation development program indicate that the formation of anti-rituximab antibodies after SC administration is comparable with that observed after IV administration. In the SABRINA study (BO22334) the incidence of treatment-induced/enhanced anti-rituximab antibodies in the SC group was low and similar to that observed in the IV group (1.9% IV vs. 2% SC). The incidence of treatment-induced/enhanced anti-rHuPH20 antibodies was 8% in the IV group compared with 15% in the SC group, and none of the patients who tested positive for anti-rHuPH20 antibodies tested positive for neutralizing antibodies. The overall proportion of patients found to have anti-rHuPH20 antibodies remained generally constant over the follow-up period in both cohorts.

In the SAWYER study (BO25341) the incidence of treatment-induced/enhanced anti-rituximab antibodies was similar in the two treatment arms; 15% IV vs. 12% SC. The incidence of treatment-induced/enhanced anti-rHuPH20 antibodies, only measured in patients in the SC arm was 12%. None of the patients who tested positive for anti-rHuPH20 antibodies tested positive for neutralizing antibodies.

The clinical relevance of the development of anti-rituximab or anti-rHuPH20 antibodies after treatment with MabThera SC is not known. There was no impact of the presence of anti-rituximab or anti-rHuPH20 antibodies on safety or efficacy in both studies.

3.2 PHARMACOKINETIC PROPERTIES

3.2.1 Absorption

Intravenous Formulation

Not applicable.

Subcutaneous Formulation (1400 mg)

SparkThera (BP22333)

MabThera at a fixed dose of 1400 mg was administered subcutaneously during maintenance, after at least one cycle of MabThera IV at a dose of 375 mg/m^2, in FL patients who had previously responded to MabThera IV in induction. The predicted median C_{max} for the every two months regimen (q2m) for MabThera SC and the q2m regimen for MabThera IV were comparable at 201 and 209 µg/mL, respectively. Similarly for the every three months regimen (q3m) for MabThera SC and the q3m regimen for MabThera IV the predicted median C_{max} were comparable at 189 and 184 µg/mL, respectively. The median t_{max} in the MabThera SC group was approximately 3 days as compared to the t_{max} occurring at, or close to the end of the infusion for the MabThera IV group.

SABRINA (BO22334)

MabThera at a fixed dose of 1400 mg was administered subcutaneously for 6 cycles during induction at 3-weekly intervals, following a first cycle of MabThera IV at a dose of 375 mg/m^2, in previously untreated FL patients in combination with chemotherapy. The serum rituximab C_{max} at Cycle 7 was similar between the two treatment arms, with geometric mean (CV%) values of 250.63 (19.01) µg/mL and 236.82 (29.41) µg/mL for MabThera IV and MabThera SC, respectively with the resulting geometric mean ratio ($C_{max,}$ SC/$C_{max,}$ IV) of 0.941 (90% CI: 0.872, 1.015).

Based on a population pharmacokinetic analysis an absolute bioavailability of 71.0% (95%CI: 70.0 – 72.1) was estimated.

Subcutaneous Formulation (1600 mg)

SAWYER (BO25341)

MabThera at a fixed dose of 1600 mg was administered subcutaneously for 5 cycles at 4-weekly intervals, following a first cycle of MabThera IV at a dose of 375 mg/m^2, in previously untreated CLL patients in combination with chemotherapy (fludarabine and cyclophosphamide [FC]). The serum rituximab C_{max} at Cycle 6 was lower in the MabThera SC arm than the MabThera IV arm (at a dose 500 mg/m^2 for Cycles 2 to 6), with geometric mean (CV%) values of 202 (36.1) µg/mL and 280 (24.6) µg/mL for MabThera SC and IV, respectively with the resulting geometric mean ratio ($C_{max,}$ SC/$C_{max,}$ IV) of 0.719 (90% CI: 0.653, 0.792). The geometric mean t_{max} in the MabThera SC group was approximately 3 days

as compared to the t_{max} occurring at or close to the end of the infusion for the MabThera IV group.

3.2.2 Distribution

Adult Non-Hodgkin's Lymphoma

Intravenous Formulation

Based on a population pharmacokinetic analysis in 298 NHL patients who received single or multiple infusions of MabThera IV as a single agent or in combination with CHOP therapy, the typical population estimates of nonspecific clearance (CL_1), specific clearance (CL_2) likely contributed by B cells or tumour burden, and central compartment volume of distribution (V_1) were 0.14 L/day, 0.59 L/day, and 2.7 L, respectively. The estimated median terminal elimination half-life of rituximab was 22 days (range, 6.1 to 52 days). Baseline CD19-positive cell counts and size of measurable tumour lesions contributed to some of the variability in CL_2 of rituximab in data from 161 patients given 375 mg/m^2 as an IV infusion for 4 weekly doses. Patients with higher CD19-positive cell counts or tumour lesions had a higher CL_2. However, a large component of inter-individual variability remained for CL_2 after correction for CD19-positive cell counts and tumour lesion size. V_1 varied by body surface area (BSA) and CHOP therapy. This variability in V_1 (27.1% and 19.0%) contributed by the range in BSA (1.53 to 2.32 m^2) and concurrent CHOP therapy, respectively, were relatively small. Age, gender, race, and WHO performance status had no effect on the pharmacokinetics of rituximab. This analysis suggests that dose adjustment of rituximab with any of the tested covariates is not expected to result in a meaningful reduction in its pharmacokinetic variability.

MabThera IV at a dose of 375 mg/m^2 was administered as an IV infusion at weekly intervals for 4 doses to 203 patients with NHL naive to rituximab. The mean C_{max} following the fourth infusion was 486 µg/mL (range, 77.5 to 996.6 µg/mL). The peak and trough serum levels of rituximab were inversely correlated with baseline values for the number of circulating CD19-positive B-cells and measures of disease burden. Median steady-state serum levels were higher for responders compared with non-responders. Serum levels were higher in patients with International Working Formulation (IWF) subtypes B, C, and D as compared with those with subtype A. Rituximab was detectable in the serum of patients 3 to 6 months after completion of last treatment.

MabThera IV at a dose of 375 mg/m^2 was administered as an IV infusion at weekly intervals for 8 doses to 37 patients with NHL [20]. The mean C_{max} increased with each successive infusion, spanning from a mean of 243 µg/mL (range, 16 - 582 µg/mL) after the first infusion to 550 µg/mL (range, 171 - 1177 µg/mL) after the eighth infusion.

The pharmacokinetic profile of MabThera IV when administered as 6 infusions of 375 mg/m^2 in combination with 6 cycles of CHOP chemotherapy was similar to that seen with MabThera IV alone.

Subcutaneous Formulation (1400 mg)

SparkThera (BP22333)

MabThera at a fixed dose of 1400 mg was administered subcutaneously during maintenance, after at least one cycle of MabThera IV at a dose of 375 mg/m^2, in FL patients who had previously responded to MabThera IV in induction. The predicted mean and geometric mean C_{trough} values at Cycle 2 were higher in the MabThera SC group than the MabThera IV group. The geometric mean values for the q2m regimen for MabThera SC and the q2m regimen for MabThera IV were 32.2 and 25.9 µg/mL, respectively and the q3m regimen for MabThera SC and the q3m regimen for MabThera IV were 12.1 and 10.9 µg/mL, respectively. Similarly, the predicted mean and geometric mean AUC_{tau} values at Cycle 2 were higher in the MabThera SC group compared with the MabThera IV group. The geometric mean for the q2m regimen for MabThera SC and the q2m regimen for MabThera IV were 5430 and 4012 µg•day/mL, respectively and the q3m regimen for MabThera SC and the q3m regimen for MabThera IV were 5320 and 3947 µg•day/mL, respectively.

SABRINA (BO22334)

MabThera at a fixed dose of 1400 mg was administered as a subcutaneous injection, in the abdomen, at 3-weekly intervals. Previously untreated patients with CD20+ FL Grade 1, 2, or 3a were randomized 1:1 to receive MabThera SC (first cycle MabThera IV at a dose of 375 mg/m^2 followed by 7 cycles of MabThera SC) or MabThera IV at a dose of 375 mg/m^2 (for 8 cycles) in combination with up to 8 cycles of CHOP or CVP chemotherapy administered every three weeks as part of induction treatment. The mean and geometric mean C_{trough} values at induction Cycle 7 (pre-dose Cycle 8) were higher among the MabThera SC group compared with the MabThera IV group. The geometric mean was 134.6 µg/mL for the MabThera SC group compared with 83.1 µg/mL for the MabThera IV group.

Similarly, the mean and geometric mean AUC values at induction Cycle 7 (pre-dose Cycle 8) were higher among the MabThera SC group than the MabThera IV group. The geometric mean AUC was 3778.9 µg•day/mL for the MabThera SC group compared with 2734.2 µg•day/mL for the MabThera IV group.

In a population pharmacokinetic analysis in FL patients who received single or multiple infusions of MabThera IV as a single agent or in combination with chemotherapy, the population estimates of nonspecific clearance (CL_1), initial specific clearance (CL_2) (likely contributed by B cells or tumour burden) and central compartment volume of distribution (V_1) were 0.194 L/day, 0.535 L/day, and 4.37 L, respectively. The estimated median terminal elimination half-life of MabThera SC was 29.7 days (range, 9.9 to 91.2 days).

In the final analysis dataset from 403 patients administered MabThera SC and/or IV in Studies BP22333 (277 patients) and BO22334 (126 patients) the mean (range) weight and BSA were 74.4 kg (43.9 to 130 kg) and 1.83 m^2 (1.34 to 2.48 m^2), respectively. Mean (range) age was 57.4 years (23 to 87 years). There were no differences between demographic and laboratory parameters for the two studies. However, the baseline B-cell counts were markedly lower in Study BP22333, than in Study BO22334, as patients in Study BP22333 entered the study having received a minimum of four cycles of MabThera IV in induction and at least one cycle of MabThera IV maintenance, whereas patients in Study BO22334 had not received MabThera prior to study enrollment. Data on baseline tumor load was available only for patients in Study BO22334.

BSA was identified as the main covariate. All clearance and volume parameters increased with the body size. Among other covariate dependencies, central volume increased with age and the absorption rate constant decreased with age (for patients aged > 60 years), but these

age dependencies were shown to result in negligible changes in rituximab exposure. Anti-drug antibodies were detected in only 13 patients and did not result in any clinically relevant increase in clearance.

Pediatric DLBCL/BL/BAL/BLL

Intravenous Formulation

In the clinical trial studying pediatric DLBCL/BL/BAL/BLL, the PK was studied in a subset of 35 patients aged 3 years and older. The PK was comparable between the two age groups (≥3 to <12 years vs. ≥12 to <18 years). After two MabThera IV infusions of 375 mg/m^2 in each of the two induction cycles (cycle 1 and 2) followed by one MabThera IV infusion of 375 mg/m^2 in each of the consolidation cycles (cycle 3 and 4) the maximum concentration was highest after the fourth infusion (cycle 2) with a geometric mean of 347 µg/mL followed by lower geometric mean maximum concentrations thereafter (Cycle 4: 247 µg/mL). With this dose regimen, trough levels were sustained (geometric means: 41.8 µg/mL (pre-dose Cycle 2; after 1 cycle), 67.7 µg/mL (pre-dose Cycle 3, after 2 cycles) and 58.5 µg/mL (pre-dose Cycle 4, after 3 cycles)). The median elimination half-life in pediatric patients aged 3 years and older was 26 days.

The PK characteristics of MabThera IV in pediatric patients with DLBCL/BL/BAL/BLL were similar to what has been observed in adult NHL patients.

No PK data are available in the ≥ 6 months to < 3 years age group, however, population PK prediction supports comparable systemic exposure (AUC, C_{trough}) in this age group compared to ≥ 3 years (Table 30). Smaller baseline tumor size is related to higher exposure due to lower time dependent clearance, however, systemic exposures impacted by different tumor sizes remain in the range of exposure that was efficacious and had an acceptable safety profile.

Table 30 Predicted PK Parameters following the MabThera IV Dosing Regimen in Pediatric DLBCL/BL/BAL/BLL.

Age group	**≥ 6 mo to < 3 years**	**≥ 3 to < 12 years**	**≥ 12 to < 18 years**
C_{trough} (µg/mL)	47.5 (0.01-179)	51.4 (0.00-182)	44.1 (0.00-149)
$AUC_{1\text{-}4\ cycles}$ (µg*day/mL)	13501 (278-31070)	11609 (135-31157)	11467 (110-27066)

Results are presented as median (min – max); C_{trough} is pre-dose Cycle 4.

Chronic Lymphocytic Leukaemia

Intravenous Formulation

MabThera was administered as an IV infusion at a first-cycle dose of 375 mg/m^2 increased to 500 mg/m^2 each cycle for 5 doses in combination with fludarabine and cyclophosphamide in CLL patients. The mean C_{max} (n=15) was 408 µg/mL (range, 97 - 764 µg/mL) after the fifth 500 mg/m^2 infusion.

Subcutaneous Formulation (1600 mg)

SAWYER (BO25341)

MabThera at a fixed dose of 1600 mg was administered as a subcutaneous injection, in the abdomen, at 4-weekly intervals. Previously untreated patients with CD20+ CLL were randomized 1:1 to receive 6 cycles of MabThera SC (1st cycle MabThera IV at a dose of 375 mg/m^2 followed by 5 cycles of MabThera SC) or MabThera IV (1st cycle MabThera IV at a dose of 375 mg/m^2 followed by 5 cycles of MabThera IV at a dose of 500 mg/m^2) in combination with up to 6 cycles of FC chemotherapy administered every four weeks. The geometric mean C_{trough} values at Cycle 5 (pre-dose Cycle 6) were higher among the MabThera SC group than the MabThera IV group (97.5 µg/mL vs. 61.5 µg/mL, respectively). Similarly, the geometric mean AUC values at Cycle 6 were higher among the MabThera SC group than the MabThera IV group (4088 µg•day/mL vs. 3630 µg•day/mL, respectively).

Rheumatoid Arthritis

Following two intravenous infusions of rituximab at a dose of 1000 mg, two weeks apart, the mean terminal half-life was 20.8 days (range, 8.58 to 35.9 days), mean systemic clearance was 0.23 L/day (range, 0.091 to 0.67 L/day), and mean steady-state distribution volume was 4.6 L (range, 1.7 to 7.51 L). Population pharmacokinetic analysis of the same data gave similar mean values for systemic clearance and half-life, 0.26 L/day and 20.4 days, respectively. Population pharmacokinetic analysis revealed that BSA and gender were the most significant covariates to explain inter-individual variability in pharmacokinetic parameters. After adjusting for BSA, male subjects had a larger volume of distribution and a faster clearance than female subjects. The gender- related pharmacokinetic differences are not considered to be clinically relevant and dose adjustment is not required.

The pharmacokinetics of rituximab were assessed following two IV doses of 500 mg and 1000 mg on Days 1 and 15 in four studies. In all these studies, rituximab pharmacokinetics were dose proportional over the limited dose range studied. Mean C_{max} for serum rituximab following first infusion ranged from 157 to 171 µg/mL for 2 x 500 mg dose and ranged from 298 to 341 µg/mL for 2 x 1000 mg dose. Following second infusion, mean C_{max} ranged from 183 to 198 µg/mL for the 2 × 500 mg dose and ranged from 355 to 404 µg/mL for the 2 × 1000 mg dose. Mean terminal elimination half-life ranged from 15 to 16.5 days for the 2 x 500 mg dose group and 17 to 21 days for the 2 × 1000 mg dose group. Mean C_{max} was 16 to 19% higher following second infusion compared to the first infusion for both doses.

The pharmacokinetics of rituximab were assessed following two IV doses of 500 mg and 1000 mg upon re-treatment in the second course. Mean C_{max} for serum rituximab following first infusion was 170 to 175 µg/mL for 2 x 500 mg dose and 317 to 370 µg/mL for 2 x 1000 mg dose. C_{max} following second infusion was 207 µg/mL for the 2 x 500 mg dose and ranged from 377 to 386 µg/mL for the 2 x 1000 mg dose. Mean terminal elimination half-life after the second infusion, following the second course, was 19 days for 2 x 500 mg dose and ranged from 21 to 22 days for the 2 x 1000 mg dose. PK parameters for rituximab were comparable over the two treatment courses.

The pharmacokinetic parameters in the anti-TNF inadequate responder population, following the same dosage regimen (2 x 1000 mg, IV, 2 weeks apart), were similar with a mean maximum serum concentration of 369 µg/mL and a mean terminal half-life of 19.2 days.

Pemphigus Vulgaris

The PK parameters in adult PV patients receiving MabThera IV 1000 mg at Days 1, 15, 168, and 182 are summarized in Table 31.

Table 31 Population PK in adult PV patients from PV Study 2

Parameter	Infusion Cycle	
	1st cycle of 1000 mg Day 1 and Day 15 N=67	2nd cycle of 1000 mg Day 168 and Day 182 N=67
Terminal Half-life (days) Median (Range)	21.1 (9.3-36.2)	26.2 (16.4-42.8)
Clearance (L/day) Mean (Range)	391 (159-1510)	247 (128-454)
Central Volume of Distribution (L) Mean (Range)	3.52 (2.48-5.22)	3.52 (2.48-5.22)

Following the first cycle of rituximab administration, the PK parameters of rituximab in patients with PV were similar to those in patients with GPA/MPA and patients with RA. Following the 2nd cycle of rituximab administration, rituximab clearance decreased by 28% while the central volume of distribution remained unchanged.

Adult and Pediatric Granulomatosis with Polyangiitis (Wegener's) (GPA) and Microscopic Polyangiitis (MPA)

The PK parameters in adult and pediatric patients with GPA/MPA receiving 375 mg/m^2 MabThera IV once weekly for four doses are summarized in Table 32.

Table 32 Population PK in pediatric patients (WA25615) and adult patients (U2639s/ITN021AI) with GPA/MPA [148, 202]

Parameter	Statistic	Study	
		Pediatric GPA/MPA (WA25615)	Adult GPA/MPA (U2639s/ITN021AI)
N	Number of Patients	25	97
Terminal Half-life	Median	22	23

(days)	(Range)	(11 to 42)	(9 to 49)
Clearance (L/day)	Mean (Range)	0.221 (0.0996 to 0.381)	0.313 (0.116 to 0.726)
Volume of Distribution (L)	Mean (Range)	2.27 (1.43 to 3.17)	4.50 (2.25 to 7.39)

The PK parameters of rituximab in adult GPA/MPA patients appear similar to what has been observed in RA patients (see section 3.2 Pharmacokinetic Properties, Distribution).

Based on a population pharmacokinetic analysis in pediatric patients with GPA /MPA, the PK parameters of rituximab were similar to those in adults with GPA/MPA, once taking into account the BSA effect on clearance and volume of distribution parameters.

3.2.3 Metabolism

No text.

3.2.4 Elimination

See section 3.2.2 Distribution.

3.2.5 Pharmacokinetics in Special Populations

Renal impairment

No pharmacokinetic data are available in patients with renal impairment.

Hepatic impairment

No pharmacokinetic data are available in patients with hepatic impairment.

Pediatrics

The effect of body surface area on the pharmacokinetics of rituximab IV was assessed in a population pharmacokinetic analysis which included 9 children (≥ 6 years to < 12 years) and 16 adolescents (12 to < 18 years) with GPA/MPA. BSA was a significant covariate on rituximab pharmacokinetics (see section 2.2.1 Special Dosage Instructions).

3.3 NONCLINICAL SAFETY

3.3.1 Carcinogenicity

No text.

3.3.2 Genotoxicity

No text.

3.3.3 Impairment of Fertility

No text.

3.3.4 Reproductive Toxicity

No text.

3.3.5 Other

Subcutaneous Formulation

The subcutaneous formulation contains recombinant human hyaluronidase (rHuPH20), an enzyme used to increase the dispersion and absorption of co-administered drugs when administered subcutaneously. Systemic absorption of rHuPH20 after subcutaneous administration is unlikely to occur. However, pharmacokinetic and toxicology studies in animals demonstrate reductions in foetal weight and increases in the number of resorptions following injection of rHuPH20 at maternal systemic exposure levels comparable to those that could occur after accidental bolus IV administration of a single vial of the MabThera SC formulation in humans, based on the most conservative assumptions possible. There is no evidence of dysmorphogenesis (i.e., teratogenesis) resulting from systemic exposure to rHuPH20.

4. PHARMACEUTICAL PARTICULARS

4.1 STORAGE

Intravenous and Subcutaneous Formulation

This medicine should not be used after the expiry date (EXP) shown on the pack.

Intravenous Formulation

Store vials at 2°C - 8°C (in a refrigerator). Do not freeze. Keep the container in the outer carton in order to protect from light.

After aseptic dilution in 0.9% aqueous saline solution

The prepared infusion solution of MabThera IV in 0.9% aqueous saline solution is physically and chemically stable for 30 days at 2°C - 8°C plus an additional 24 hours at room temperature.

After aseptic dilution in 5% aqueous dextrose solution

The prepared infusion solution of MabThera IV in 5% aqueous dextrose solution is physically and chemically stable for 24 hours at 2°C - 8°C plus an additional 12 hours at room temperature.

From a microbiological point of view, the prepared infusion solution should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the

responsibility of the user and would normally not be longer than 24 hours at 2°C - 8°C, unless dilution has taken place in controlled and validated aseptic conditions.

Subcutaneous Formulation

Store in a refrigerator (2°C - 8°C). Do not freeze. Keep the container in the outer carton in order to protect from light.

From a microbiological point of view, the product should be used immediately. If not used immediately, preparation should take place in controlled and validated aseptic conditions. In-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 48 hours at 2°C - 8°C and subsequent 8 hours at 30°C in diffuse daylight.

4.2 SPECIAL INSTRUCTIONS FOR USE, HANDLING AND DISPOSAL

Intravenous Formulation

Use sterile needle and syringe to prepare MabThera. Withdraw the required amount of MabThera under aseptic conditions and dilute to a calculated rituximab concentration of 1 – 4 mg/mL in an infusion bag containing sterile, non-pyrogenic 0.9%, aqueous saline solution or 5% aqueous dextrose solution. To mix the solution, gently invert the bag to avoid foaming. Care must be taken to ensure the sterility of prepared solutions. Since the medicinal product does not contain any anti-microbial preservative or bacteriostatic agents, aseptic technique must be observed. Parenteral medications should be inspected visually for particulate matter or discoloration prior to administration.

The prepared infusion solution of MabThera IV is physically and chemically stable for 24 hours at 2°C - 8°C and subsequently 12 hours at room temperature.

Incompatibilities

No incompatibilities between MabThera IV and polyvinyl chloride or polyethylene bags or infusion sets have been observed.

Subcutaneous Formulation

MabThera SC solution (once transferred from the vial into the syringe) is physically and chemically stable for 48 hours at 2°C - 8°C and subsequent 8 hours at 30°C in diffused daylight.

MabThera SC is provided in sterile, preservative-free, non-pyrogenic, single use vials. Use a sterile needle and syringe to prepare MabThera.

Incompatibilities

No incompatibilities between MabThera SC and polypropylene or polycarbonate syringe material or stainless steel transfer and injection needles have been observed.

Intravenous and Subcutaneous Formulation

Disposal of unused/expired medicines

The release of pharmaceuticals in the environment should be minimized. Medicines should not be disposed of via wastewater and disposal through household waste should be avoided. Use established “collection systems”, if available in your location.

The following points should be strictly adhered to regarding the use and disposal of syringes and other medicinal sharps:

- Needles and syringes should never be reused.
- Place all used needles and syringes into a sharps container (puncture-proof disposable container).

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

4.3 PACKS

IV

Vial of 10 mL (10 mg/mL)	2
Vial of 50 mL (10 mg/mL)	1

SC

Vial of 1400 mg/11.7 mL	1
Vial of 1600 mg/13.4 mL	1

Medicine: keep out of reach of children

Current at August 2022

IV vials

Made for F. Hoffmann-La Roche Ltd, Basel, Switzerland

by Roche Diagnostics GmbH, Mannheim, Germany

SC vials

Made in Switzerland by F.-Hoffmann-La Roche Ltd, Basel,

manufacturing site Kaiseraugst