EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

31 January 2019
EMA/206826/2019
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

MabThera

International non-proprietary name: rituximab

Procedure No. EMEA/H/C/000165/II/0150

Note

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

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List of abbreviations

ABSIS	autoimmune bullous skin disorder intensity score
ADA	anti-drug antibody/anti-rituximab antibody
AE	adverse event
AI	autoimmune
BMI	body mass index
BSA	body surface area
CI	confidence interval
CLL	chronic lymphocytic leukemia
CR	complete remission
CRF	case report forms
CRoff	CR off corticosteroid/prednisone therapy
CRon	CR on corticosteroid therapy
CSR	clinical study report
Dsg	desmoglein
ELISA	enzyme linked immunosorbent assay
FDA	US Food and Drug Administration
GI	gastrointestinal
GPA	granulomatosis polyangiitis
HLA	human leukocyte antigen
ICD	International Statistical Classification of Diseases and Related Health Problems, 10th revision, German modification
iDMC	independent data monitoring committee
IRR	infusion-related reaction
ITT	intent to treat
IV	intravenous
MMF	mycophenolate mofetil
MPA	microscopic polyangiitis
NHL	non-Hodgkin's lymphoma
PBRER	periodic benefit risk evaluation report
PDAI	pemphigus disease activity score
PF	pemphigus foliaceus
PML	progressive multifocal leukoencephalopathy
PR	partial remission
PK	pharmacokinetic
PT	preferred terms
PV	pemphigus vulgaris
PVAS	pemphigus vulgaris activity score
RA	rheumatoid arthritis
SAE	serious adverse event
SAP	statistical analysis plan
SCE	summary of clinical efficacy
SCS	summary of clinical safety
SE	standard error
SOC	system organ class
TPMT	thiopurine methyltransferase
UK	United Kingdom
US	United States
USPI	US Prescribing Information

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Roche Registration GmbH submitted to the European Medicines Agency on 2 March 2018 an application for a variation.

The following variation was requested:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include the treatment of patients with moderate to severe pemphigus vulgaris (PV) for MabThera; as a consequence, sections 4.1, 4.2, 4.3, 4.4, 4.8 and 5.1 of the SmPC are updated. The MAH provided data from a phase III, randomized, controlled, multicenter, open-label study (Study ML22196) evaluating rituximab treatment plus short-term, low dose prednisone treatment compared to long-term, standard dose prednisone treatment as first-line treatment in patients with moderate to severe pemphigus. The Package leaflet is updated accordingly. Minor corrections are also proposed for the sake of accuracy and clarity. An updated RMP (v19.1) is also included in this submission.

The requested variation proposed amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Information on paediatric requirements

Not applicable

Information relating to orphan market exclusivity

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

Scientific advice

The applicant did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Sinan B. Sarac Co-Rapporteur: Paula Boudewina van Hennik

Timetable	Actual dates
Submission date	2 March 2018
Start of procedure:	31 March 2018
CHMP Co-Rapporteur Assessment Report	24 May 2018
CHMP Rapporteur Assessment Report	28 May 2018
PRAC Rapporteur Assessment Report	28 May 2018
PRAC members comments	6 June 2018
Updated PRAC Rapporteur Assessment Report	8 June 2018
PRAC Outcome	14 June 2018
CHMP members comments	n/a
Updated CHMP Rapporteur(s) (Joint) Assessment Report	21 June 2018
Request for supplementary information (RSI)	28 June 2018
Submission of responses	14 September 2018
CHMP Rapporteur Assessment Report	18 October 2018
PRAC Rapporteur Assessment Report	18 October 2018
PRAC members comments	n/a
Updated PRAC Rapporteur Assessment Report	n/a
PRAC Outcome	31 October 2018
CHMP members comments	n/a
Updated CHMP Rapporteur Assessment Report	n/a
Request for supplementary information (RSI)	15 November 2018
CHMP Rapporteur Assessment Report	20 December 2018
PRAC Rapporteur Assessment Report	20 December 2019
PRAC members comments	n/a
Updated PRAC Rapporteur Assessment Report	n/a
PRAC Outcome	17 January 2019
CHMP members comments	
Updated CHMP Rapporteur Assessment Report	23 January 2019
CHMP Opinion	31 January 2019

2. Scientific discussion

2.1. Introduction

Pemphigus vulgaris (PV) is a rare, serious and life-threatening AI blistering disease affecting the mucosa and skin, and there is a high unmet medical need for safer and more effective treatment options. A comprehensive literature review of approximately 300 publications in PV conducted by the Applicant identified many small, uncontrolled studies and case reports in 788 patients that support the safe and effective use of rituximab in patients with severe or refractory PV.

Due to the rarity of pemphigus, few prospective clinical trials are available and these are limited by the low numbers of patients studied and treatment arms that do not demonstrate statistically significant differences. Corticosteroids and, in some European countries, azathioprine are the only EU-approved treatments for patients with PV. Systemic corticosteroids have been the mainstay of treatment for pemphigus patients since the 1950s based on limited and uncontrolled clinical data. Similarly, the use of adjuvant immunosuppressant therapy, such as azathioprine, which has been approved alone and in combination with systemic corticosteroids, for the treatment of PV in the European Union for over 15 years, has been established in treatment guidelines in Europe despite the scarcity of well-designed randomized controlled studies, and evidence that adjuvant therapies have only a minimal steroid-sparing effect.

Based on the literature, chronic and/or high dose corticosteroid therapy alone results in an estimated remission rate of <30%. Remission may be short lived. Serious and sometimes fatal AEs, resulting from immunosuppression due to long-term use of steroids, may occur. Despite widespread use, there is no consensus on whether unapproved steroid-sparing agents are beneficial due to the scarcity of well-designed randomized controlled studies. PV remains a serious life-threatening disease and given the unsatisfactory safety and efficacy profile of the existing approved therapies (corticosteroids and azathioprine), a major unmet medical need exists for safer and more effective novel, targeted mechanism-based treatment options for moderately to severely active PV.

Owing to its ability to deplete pathogenic B cells and reduce autoantibodies, rituximab has been successfully used for AI indications of RA and GPA/MPA. Pemphigus patients develop autoantibodies to desmosomal cadherins. The mechanism that initiates the formation of these autoantibodies is presumed to involve loss of B cell tolerance to these self-antigens. In PF, these autoantibodies target Dsg1; in PV, these autoantibodies target Dsg1 and Dsg3. Circulating B cells produce these autoantibodies which bind to keratinocytes, inhibit cell-cell adhesion, and cause blister formation and inflammation in the skin and mucous membrane. Beyond the reduction of autoantibodies contributing to disease, dysregulated B cells may further worsen the disease by secreting cytokines, co-stimulating T cells, and differentiating into memory B cells which contribute to persistent autoantibody production and relapsing disease.

In the last decade, there have been approximately 300 reports of rituximab use in 788 PV patients published as case reports and small uncontrolled clinical studies, especially in severe, recalcitrant disease. These publications report on the successful use of rituximab in severe and refractory pemphigus due to its B cell-depleting effect. Similar to RA and GPA/MPA, in PV patients treated with rituximab, it has been observed that profound peripheral B cell depletion occurs by 3 weeks and B cell reconstitution begins at approximately 6 months after rituximab treatment. In addition, a dramatic decrease in anti-Dsg1 and anti-Dsg3 IgG antibodies was observed after rituximab treatment in 8 of 12 patients who achieved CR and CR in these patients was associated with blockage of B cell maturation, repopulation with naïve B cells and transitional B cells, delayed reappearance of memory B cells, and disappearance of desmoglein-specific IgG + B cells.

The Sponsor of Study ML22196 is Rouen University Hospital, France (Charles Nicolle Hospital-CHU-Hôpitaux de Rouen). The Applicant provided the rituximab study drug and funding for the 12 month post-treatment follow-up period, but had no role in study design, study conduct, data collection, or publication of the results. Study database and supporting documents were transferred from the Sponsor to the Applicant in December 2016 after the study had been completed and database lock had occurred.

A MAH-sponsored double-blind, randomised, active-controlled Phase III Study WA29330 (PEMPHIX) is still ongoing.

The Applicant therefore seeks regulatory approval for rituximab in the following indication:

Rituximab is indicated for the treatment of adult patients with moderate to severe pemphigus vulgaris.

2.2. Non-clinical aspects

No new clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.2.1. Ecotoxicity / environmental risk assessment

The pharmacologically active substance in MabThera, Rituximab (CAS 174722–31–7), is a recombinant immunoglobulin-G monoclonal antibody with a molecular mass of approximately 145 kD.

As an unaltered protein, Rituximab is predicted to be metabolised by regular proteinolysis in the patient and biodegraded in sewage treatment, as shown for other monoclonal antibodies. Thus, Rituximab is unlikely to result in a significant risk to the environment and therefore it is submitted that it does not need a formal ERA according to the EMA 2006 Guideline (corr. 2). This is acceptable to the CHMP.

2.2.2. Conclusion on the non-clinical aspects

It is agreed that due to the nature of the product and based on the data submitted in this application Rituximab is unlikely to result in a significant risk to the environment.

2.3. Clinical aspects

2.3.1. Introduction

The application consists of the data from a single multi-centre randomised controlled open-label trial with a 24-month treatment period and a 12-month follow-up period, comparing RTX and short-term 'low'-dose corticosteroids with long-term standard-dose corticosteroids in patients with newly diagnosed pemphigus vulgaris (PV) or pemphigus foliaceus. Most patients (had pemphigus vulgaris and the analyses focus on this population (denoted as ITT-PV), which is in line with the requested indication for pemphigus vulgaris only.

After completion of the clinical trial and database lock the data were transferred in December 2016 by the Sponsor-Investigator (Rouen University Hospital in France) to the applicant and MAH of MabThera (Roche) and re-analysed by a third party (Everest Clinical Research). The applicant stated that the study objectives and method of analysis for the primary endpoint were prospectively defined in the initial protocol and the sponsor's Statistical Analysis Plan.

The applicant had provided the study drug and funding for the 12-month follow-up period, and stated that they had no role in study design, study conduct, data collection, or publication of the results.

Currently another confirmatory study sponsored by the applicant is ongoing. Study WA29330 is a randomized (1:1), double-blind, double-dummy, active-comparator, parallel-arm, multi-center, superiority trial to evaluate safety and efficacy of rituximab compared with mycophenolate mofetil (MMF) in achieving sustained clinical remission (off prednisone for at least 4 consecutive months) at week 52, in adult patients with moderate-to-severely active pemphigus vulgaris. The planned enrolment of 132 patients in Study WA29330 was completed and primary analysis results are anticipated to be available Q4 2018/Q1 2019.

GCP

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

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

2.3.2. Pharmacokinetics

No pharmacokinetic or immunogenicity assessments were prospectively planned by the sponsor as part of the study ML22196 protocol or schedule of assessments. The applicant evaluated the frozen sera collected from rituximab-dosed patients and determined that it was not feasible to perform population pharmacokinetic analyses from the samples available from this study; most of the samples were outside the stability window based on available pharmacokinetic sample stability data, resulting in a very limited number of patient samples for which concentrations could be accurately quantified for inclusion in a population pharmacokinetic analysis (3.5 years). In addition, the information required for population pharmacokinetic analysis such as the actual date and time of blood sampling, the exact dose of rituximab administered (overall, in case of dosing interruption and/or relapse), and the actual date and time of drug administration were not collected on the patient Case Report Forms.

Rituximab concentrations were only measured in samples used for the measurement of serum anti-drug antibodies (ADAs), to help in the interpretation of the ADA data. No concentration data were provided.

Frozen serum samples were within the established stability for anti-drug antibody (ADA) analysis (7 years, 10 months), and the applicant assessed immunogenicity in the pemphigus vulgaris patient population.

For the analysis of rituximab concentrations in pemphigus vulgaris patient serum samples, validated ELISA was used. The calibration curve range was 2.5 - 160 ng/ml. The minimum dilution for neat human serum samples is 1/100, resulting in a minimum quantifiable concentration of 500 ng/ml. The accuracy and the precision were within acceptable ranges. No hook effect was observed (by using a high rituximab concentration level) and accuracy and linearity of dilution was determined to be acceptable. Stability of neat human serum samples was evaluated and within range for multiple freeze/thaw cycles, for 24 hours at room temperature, after long term storage at −20°C for four months and after long term storage at −60°C or below for three years and six months.

An (updated) anti-rituximab antibody assay was developed with acceptable accuracy and precision. The relative sensitivity of the method for the evaluated positive control (rabbit polyclonal antirituximab antibodies) was approximately 1.42 ng/ml serum. Above this detection threshold, the assay can tolerate an approximate 590-fold excess of rituximab over anti-rituximab antibodies (evaluated for the positive control antibody during assay validation).

A patient was considered to have an ADA positive result when the baseline sample (i.e. prior to the first rituximab administration in the study) was negative or missing, and at least one sample post-baseline was positive and was classified as “treatment-induced”. In patients where the baseline sample was positive, the patient was classified as “treatment-enhanced”, when at least one post baseline sample had an increase in titer of ≥0.6. In cases where the baseline sample was positive, but the post baseline samples increased by <0.6, patients were classified as “treatment unaffected”.

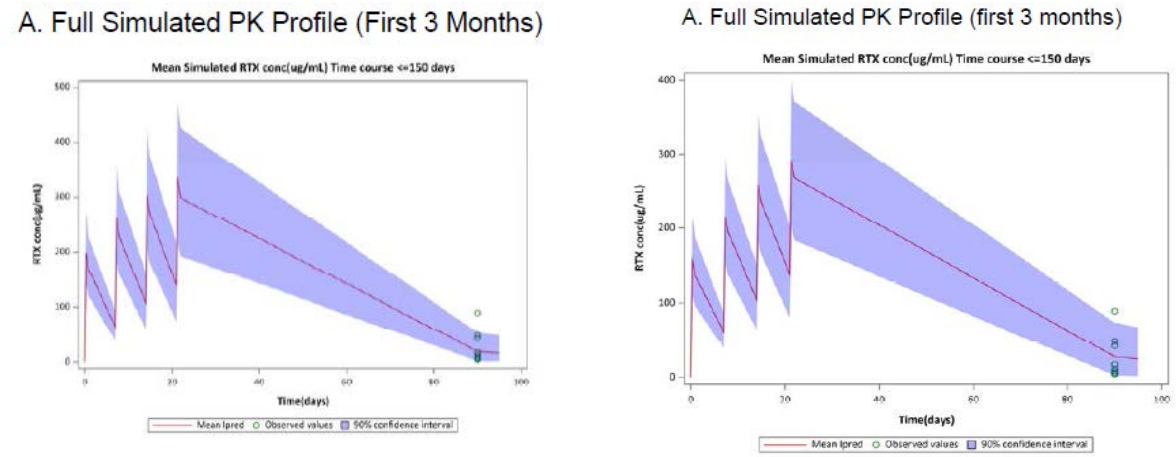
Baseline and at least one post-baseline sample were evaluable in 34 of the 38 pemphigus vulgaris patients in the rituximab + prednisone arm. Fourteen of the 34 patients (41%) were considered treatment-induced and 5 of 34 (15%) were considered treatment-enhanced. Therefore, the incidence of treatment-induced/enhanced in pemphigus vulgaris patients was 19 of 34 patients (55.9%). ADAs were generally transitory, with positive titers ranging from 1 to 4.31.

Rituximab concentrations were reported in one publication in the pemphigus vulgaris patient population (Schmidt et al. 2009). The pharmacokinetics of rituximab was characterized in 11 patients (6 male and 5 female, aged 27 - 70 years) with severe pemphigus vulgaris who were resistant to at least one previous therapy, not including rituximab. Rituximab was administered by infusions at a dose of 375 mg/m^2 at weekly intervals for a total of four doses. This is the same dose as recommended for patients with polyangiitis/microscopic polyangiitis patients. Patients also received immunosuppressant therapies

including azathioprine, corticosteroids, and mycophenolate mofetil. In serum samples collected 3 months after the first rituximab infusion, the mean (s.d.) rituximab concentration was 22.9 (24.6) µg/ml and ranged from 4.8 to 89.2 µg/ml.

Using population pharmacokinetic analysis models previous developed for rheumatoid arthritis patients and granulomatosis with polyangiitis/microscopic polyangiitis patients, the rituximab concentrations at 3 months after first infusion from this publication were in agreement with those predicted for rheumatoid arthritis patients and granulomatosis with polyangiitis/microscopic polyangiitis patients (see figures below).

Figure PK 1. Comparison of simulated pharmacokinetic profiles and observed data (day 90) in pemphigus vulgaris patients who received 4 i.v. infusions of rituximab 375 mg/m^2; popPK model in rheumatoid arthritis patients (left figure) and polyangiitis/microscopic polyangiitis patients (right figure).



2.3.3. Pharmacodynamics

Mechanism of action

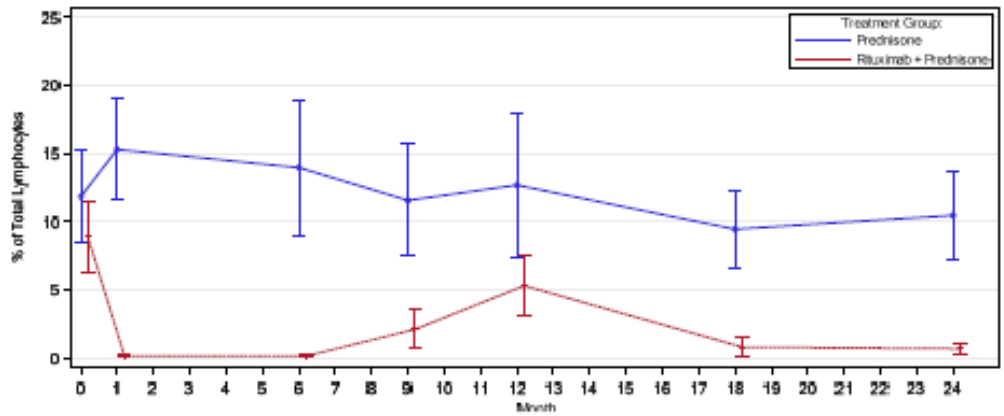
Rituximab is a chimeric murine/human monoclonal antibody that binds to B-lymphocyte antigen (CD20), a transmembrane protein present on B lymphocytes. The binding of rituximab to CD20 on B-lymphocytes promotes B cell lysis via a number of different possible mechanisms, including antibody-dependent cellular cytotoxicity, complement-dependent cytotoxicity, and induction of apoptosis.

Primary and secondary pharmacology

In study ML22196, pharmacodynamics measurements, i.e. level of CD19+ B-cells as a marker for the target CD20+ cells, and desmoglein (Dsg) 1 and 3 antibody titres, were performed for the first 37 patients. In the Safety-PV sample, pharmacodynamics measurements were available for n=16 in the rituximab group and 15 in the corticosteroid-only group.

One month after baseline, after two 1000 mg infusions in the rituximab group, the percentage of CD19+ B lymphocytes (of total lymphocytes) was on average 0.2% in the rituximab group and 14% in the corticosteroid-only group. It appears that the percentage of CD19+ B lymphocytes increases towards month 12, to approach baseline levels (Figure 6 below). At month 24, the percentage of CD19+ positive B lymphocytes was still low in the patients (n=15) from the rituximab treated group.

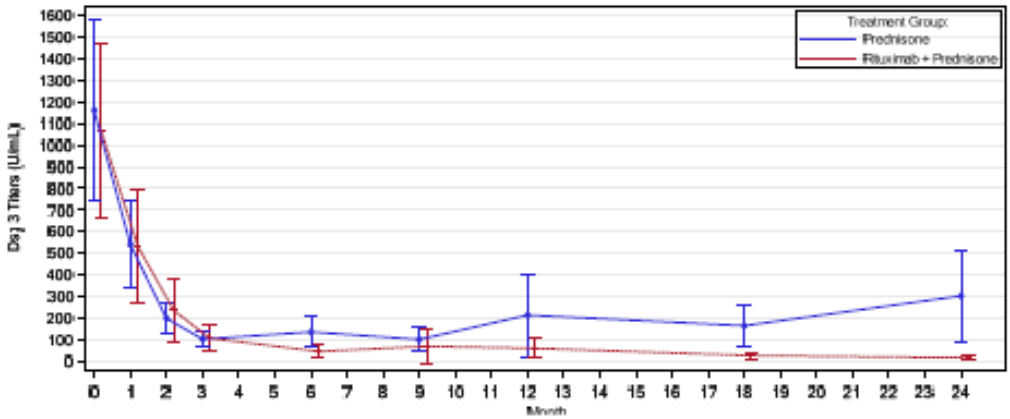
Figure 6 Mean (95% CI) CD-19+ Percentages by Visit (Safety)



Total lymphocytes include B and T cells. CI = confidence interval
Source: fpd004se

The baseline titres of anti-Dsg1 and anti-Dsg3 (Figure 8) decreased within 3 months to similar low levels in both groups (Figure 8). In the corticosteroid-only group, the titres of anti-Dsg3 started to increase again after 12 months, although they did not return to baseline level in 24 months. Anti-Dsg1 titres remained low over 24 months in both groups (not shown).

Figure 8 Dsg-3 Mean Titers (95% CI) by Visit (Safety PV)



CI = confidence interval
Source: fim002se

The pharmacodynamics results regarding sustained B-cell depletion and regarding sustained reduction of anti-desmoglein 1 and 3 are considered to be supportive for the mode-of-action of rituximab in pemphigus vulgaris. Anti-desmoglein 1 and 3 play a key role in the pathogenesis of pemphigus vulgaris.

There was no major difference between Rituximab arm (Rituximab + Low-Dose Prednisone) and High-Dose Prednisone treatment groups regarding the reduction of anti-desmoglein in the first 12 months of therapy. It is noted that high-Dose Prednisone treatment is known to be effective in PV. After 12 months, Rituximab + Low-Dose Prednisone was superior in reducing Dsg-3 titers. Although sample size for these measurements was low (N=37), sample size was pre-planned and seen the clear effect it is considered unlikely that a larger sample would change the results.

It is noted that mean percentages of CD19+ B cell may be a suboptimal presentation because distributions are expected to be skewed. Percentage of patients below detection limit over time (baseline, months 3, 6, 12, 18 and 24) could have been an alternative. Further, the number of patients in the corticosteroid group

is very small. As the effect of rituximab on B-cells in auto-immune diseases is well established, the issue is not pursued.

2.3.4. PK/PD modelling

No PK/PD modelling has been applied.

2.3.5. Discussion on clinical pharmacology

The pharmacodynamics results regarding sustained B-cell depletion and regarding sustained reduction of anti-desmoglein 1 and 3 are considered to be supportive for the mode-of-action of rituximab in pemphigus vulgaris. Anti-desmoglein 1 and 3 play a key role in the pathogenesis of pemphigus vulgaris.

No pharmacokinetic data have been obtained in the submitted studies. In literature one study was described in this patient group, in which pharmacokinetic data was obtained 90 days after the first rituximab infusion.

Using the previous developed popPK models for rheumatoid arthritis (RA) patients and granulomatosis with polyangiitis/microscopic polyangiitis patients (GPA/MPA) did not indicate that the serum concentrations at day 90 in pemphigus vulgaris patients were different than those predicted in RA patients and GPA/MPA patients. Although these results may be expected, being all three autoimmune populations, it should be noted that the data in pemphigus vulgaris patients is very limited.

The majority of the patients developed ADAs (HACA), but seemed not to have a negative impact on efficacy (see clinical assessment).

Both rituximab as the comparator High-Dose Prednisone induced the reduction of auto-antibodies anti-desmoglein 1 and 3 to similar extent in the first 12 months of treatment. After 12 months, the reduction of these auto-antibodies was better maintained with rituximab, than with High-Dose Prednisone.

2.3.6. Conclusions on clinical pharmacology

No concerns have been identified with regard to the clinical pharmacology.

2.4. Clinical efficacy

Introduction

The basis of this application is the pivotal study, ML22196, where newly diagnosed patients with moderate to severe pemphigus are randomized to rituximab + low-dose corticosteroids (CS) or high-dose CS.

The goal of treatment is rapid disease control, thus, systemic CS have played a central role in the first-line. CS has been backbone of therapy in patients with pemphigus vulgaris (PV), and is usually very effective with regards to disease control. However, systemic CS comes at a cost, since side effects are common. Thus, in an attempt to reduce the exposure to CS, other non-steroidal immune-modulatory agents, such as azathioprine and mycophenolate mofetil, have been used in combination with (low-dose) CS. However, despite the well-known use of CS sparring agents in the clinical setting, it is acknowledged that there has not been any prospective randomized clinical trial, where CS + a CS sparring agent showed positive efficacy.

2.4.1. Dose response study(ies)

Formal dose-response studies were not conducted but refer to the previous studies conducted in patients with RA. This is endorsed.

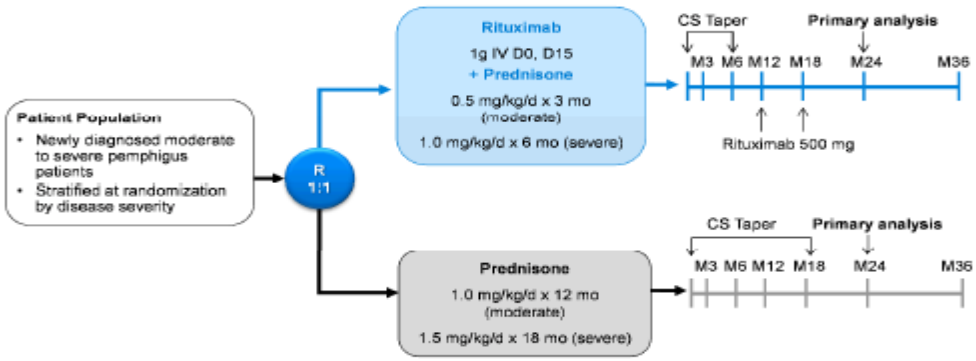
The choice of the initial rituximab dose administered at 2 x 1000 mg IV, 2 weeks apart, was based on findings demonstrated in patients with RA where this regimen sustained peripheral B-cell depletion for approximately 6 to 9 months. The same has also been reported in PV patients treated with rituximab, where it was observed that B cell reconstitution begins at approximately 6 months after rituximab treatment (Mouquet et al. 2008).

Maintenance doses of 500 mg IV at 12 months (M12) and 18 months (M18) after the initial treatment was based on the Principal Investigator's previous published study in which the rate of relapse was observed to be approximately 30% after two years; with patients relapsing during the second year (mean (SD) time to relapse: 18.9 ± 7.9 months) (Joly et al. 2007). The two additional infusions at M12 and M18 were expected to prevent relapses during the second year of treatment. The Principal Investigator acknowledged that the 500 mg dose of rituximab used for maintenance had not been formally studied although it was similar to the maintenance dose used in ANCA associated vasculitis (Guillevin et al. 2014). Patients could receive 1000 mg IV rituximab at the time of relapse (but no earlier than 16 weeks after the previous infusion), and the scheduled maintenance rituximab dose withheld, depending on the timing of the relapse.

2.4.2. Main study – Study ML22196

Title of Study: Comparison of Treatment with Anti-CD20 Monoclonal Antibody Rituximab (Mabthera®) in Combination with Short-Term Systemic Corticosteroid Therapy Compared to Long-Term Systemic Corticosteroid Therapy in Patients with Pemphigus

Figure 1 Study Design for ML22196



CS = corticosteroid; D = day; IV = intravenous; M = month; mo = month; R = randomized

Methods

Study participants

Inclusion Criteria

1) Patients between ≥18 and ≤80 years of age.

2) Written consent obtained from the patient (or a family member if the patient was unable to provide consent).

3) For women of childbearing potential, an effective method of contraception (e.g. intrauterine device, oral contraceptive pill) was required during treatment and for a year following discontinuation of rituximab treatment.

4) Newly diagnosed cases of PV or PF diagnosed based on all of the following items:

- Compatible or suggestive clinical signs (Martel and Joly 2001).

- Histologic examination showing intraepidermal bullae including suprabasal or subcorneal detachment, in the presence of acantholytic cells.
- Direct immunofluorescence showing deposits of IgG and/or C3 on the keratinocyte cell membranes (mesh pattern).
- Patients solely treated with topical corticosteroid therapy (without systemic corticosteroid therapy or immunosuppressants) or having received less than one month of systemic corticosteroid therapy at a dose of ≤0.5 mg/kg/day prior to being diagnosed.

  Note: the recent cases of pemphigus treated prior to the diagnosis by non-specific corticosteroid therapy (≤0.5 mg/kg/day) proven ineffective against pemphigus were not intentionally excluded because the practice of a short “corticosteroid therapy trial” is quite common for undiagnosed oral erosions.

5) Current immunization status. The investigators confirmed the immunization status of all eligible patients and followed the national guidelines for the immunization plan in adults, ensuring a 28-day period between any vaccination and the first administration of rituximab.

Additionally, the following were considered as moderate pemphigus:

a) Patients with non-severe oral involvement only based on Harman's criteria

b) Patients with non-severe skin involvement only based on Harman's criteria.

c) Patients with mucocutaneous involvement including minimal skin involvement (<5% of the body surface) and non-severe mucosal involvement based on Harman's criteria.

The following were considered as severe pemphigus:

a) Patients with mucocutaneous involvement and significant skin involvement (>5% of the body surface)

b) Patients with only mucosal involvement affecting at least two sites (e.g., oral and genital mucosa, oral and anal mucosa, oral and ear, nose and throat mucosa)

c) Patients with oral mucosal involvement only AND:

– Weight loss of ≥3 kg related to dysphagia,

– Severe mucosal involvement based on Harman's criteria:

  - o Presence of at least 10 small discrete erosions, or
  - o Confluent erosions of the oral mucosa, or
  - o Generalized desquamative gingivitis with discrete erosions at other oral sites.

d) Pemphigus with only skin involvement considered severe based on Harman's criteria:

– Presence of at least 20 erosive lesions or squamous/crusting lesions or bullous lesions, or

– Extensive, confluent erosive lesions or squamous/crusting lesions.

Exclusion Criteria

1) Previous pemphigus that has already been treated.

2) Pregnant or lactating woman.

3) Known hypersensitivity to any one of the product compounds or to murine proteins, or previous history of allergic reaction to humanized monoclonal antibodies.

4) Unstable angina or advanced ischemic heart disease (recent extensive infarction <3 months or post-MI cardiac failure)

5) Severe heart failure (New York Heart Association [NYHA] class III or IV), or severe, uncontrolled heart disease

6) Poorly controlled arrhythmia

7) Patients younger than 18 years of age or older than 80 years of age

8) Use of an immunosuppressant medication in the month prior to study enrollment.

9) Patients diagnosed with hepatitis B, or active or inactive hepatitis C. However, patients with hepatitis B antibodies resulting from a vaccination can be included.

10) Human immunodeficiency virus (HIV)-seropositive patient.

11) Bacterial, viral, fungal (excluding nail edge fungus) or mycobacterial infection, any other progressive infection, any significant event of infection requiring hospitalization or IV antibiotic treatment during the four weeks prior to screening, or an oral antibiotic treatment less than two weeks prior to the administration of rituximab.

12) History of deep tissue infection (fasciitis, deep-seated abscess, osteomyelitis, septic arthritis) in the year prior to the administration of rituximab.

13) Patients who have not provided their consent or who cannot be monitored regularly.

14) Active primary or secondary immune deficiency.

15) History of chronic or recurrent severe infection or any other underlying condition which predisposes the patient to severe infections.

16) Administration of a live vaccine in the 4 weeks prior to the administration of rituximab

17) Patients who have received immunosuppressive therapy (such as cyclosporine, mycophenolate mofetil, cyclophosphamide, azathioprine) or any other treatment that could potentially affect pemphigus lesions (disulone, IVIG, other biotherapies, plasma exchanges) in the month prior to enrollment in the trial.

18) Karnofsky index <50%.

19) Previous treatment with rituximab or any other treatment leading to severe lymphocyte depletion (e.g., MabCampath).

20) Previous treatment with lymphocyte trafficking inhibitors (e.g., Tysabri).

21) Known severe chronic obstructive pulmonary disease (forced expiratory volume in 1 second □50% or grade 3 functional dyspnea)

Additionally, patients with paraneoplastic pemphigus were excluded from this study because of their very different disease progression and their prognosis depending strongly on the type of associated malignant tumor.

Treatments

For purpose of this study, rituximab was supplied and distributed by the applicant to the hospitals' pharmacies and was dispensed for the study patient through the pharmacy. Prednisone was obtained commercially by the patients themselves. The use of RTX in the study is identical to the use proposed in the SmPC for this indication. The aim of initial prednisone therapy in combination with rituximab was to control the patients' lesions until rituximab took effect.

After start in one of the two treatment arms the patients were assessed every 7 days to evaluate whether disease activity was 'in control'. This was defined according to the Consensus Statement on pemphigus endpoints [Murrell 2008] as: "new lesions cease to form and established lesions begin to heal". If disease activity was deemed 'in control' tapering was started [Murrell 2008] according to a predefined schedule. If after 4 weeks disease activity was not 'in control' the dose of corticosteroids remained the same up to another 4 weeks in the RTX arm or if disease activity was 'moderate'. Only in patients with 'severe' pemphigus who were in the corticosteroid arm the dose was increased to 2 mg/kg/day for up to another 4 weeks. If disease activity was severe and still uncontrolled after 8 weeks in any of the treatment arms, this was considered treatment failure, but the patient remained in the study for follow-up. If disease activity was moderate and still uncontrolled after 8 weeks, patients were treated as having 'severe' pemphigus.

Treatment with RTX consisted of two intravenous infusions of 1000 mg at day 1 (baseline) and day 15, administered at the hospital. Premedication with paradiphenhydramine antihistamine, paracetamol, and IV methylprednisolone was applied before each infusion. The third and fourth 'maintenance' infusions had a dose of 500 mg and were administered at 12 and 18 months after baseline (also see figure 1 above). In case of relapse, patients could receive 1000 mg RTX if the last infusion was longer than 16 weeks ago, and the next 'maintenance dose was then omitted.

The rationale for the initial RTX dosing (1000 mg 2 weeks apart) was based on the findings in patients with Rheumatoid Arthritis, where this dosing leads to B-cell depletion that is sustained for 6-9 months. This has also been found in a small (N=21) cohort of patients with pemphigus treated with RTX [Mouquet 2008]. These patients were treated with RTX in one cycle of four weekly infusions at a dosage of 375mg/m2 of body surface area, similar as in ANCA-positive vasculitis [Mabthera SmPC]. The rationale for the need of a 'maintenance' dose was based on the observation that about 30% of patients with pemphigus relapse after 2 years [Joly 2007]. The dose of 500 mg was supposed to prevent relapses but had not been studied in a dose-finding study, it had been applied in a similar way in ANCA-positive vasculitis [Guillevin 2014].

Treatment with prednisone was stratified according to disease severity and according to treatment group (Table 1). Tapering of corticosteroids for severe patients in the prednisone group will last 18 months in total, and for moderate patients in the RTX+prednisone group tapering will last 3 months in total (Table 1). The tapering schedule in the RTX group was based on earlier experience in the uncontrolled study of pemphigus patients (N=21) treated with RTX [Joly 2007]. Treatment with 'high dose' corticosteroids followed by slow tapering as soon disease activity is under control is regarded as standard of care [Murrell 2008].

Table 1

Scheduled Oral Corticosteroid Treatment

Severe Pemphigus				Moderate Pemphigus			
Prednisone Arm[a]		RTX+Prednisone Arm[b]		Prednisone Arm[c]		RTX+Prednisone Arm[d]	
Dose of Prednisone	No. of Months	Dose of Prednisone	No. of Months	Dose of Prednisone	No. of Months	Dose of Prednisone	No. of Months
1.5 mg/kg/d	1 month	1.0 mg/kg/d	1 month	1.0 mg/kg/d	1 month	0.5 mg/kg/d	1 month
1.25 mg/kg/d	1 month	0.75 mg/kg/d	1 month	0.75 mg/kg/d	1 month	0.3 mg/kg/d	1 month
1.0 mg/kg/d	1 month	0.5 mg/kg/d	1 month	0.5 mg/kg/d	2 months	0.2 mg/kg/d	1 month
0.75 mg/kg/d	1 month	0.3 mg/kg/d	1 month	0.3 mg/kg/d	2 months	-	-
0.5 mg/kg/d	3 months	0.2 mg/kg/d	1 month	0.2 mg/kg/d	3 months	-	-
0.3 mg/kg/d	3 months	0.1 mg/kg/d	1 month	0.1 mg/kg/d	3 months	-	-
0.2 mg/kg/d	4 months	-	-	-	-	-	-
0.1 mg/kg/d	4 months	-	-	-	-	-	-

RTX=rituximab

Source: based on Protocol v14 Section VI.4

[a] prednisone tapered over 18 months.

[b] prednisone tapered over 6 months.

[c] prednisone tapered over 12 months.

[d] prednisone tapered over 3 months.

Treatment of relapses was different in the two treatment groups.

Patients in the RTX and prednisone group received one infusion of RTX 1000 mg and prednisone was resumed or the prednisone dose was escalated. Subsequent infusions could occur no sooner than 16 weeks following the previous infusion and the next scheduled 'maintenance' infusion was left out. For example, if relapse occurred during the steroid taper or if relapse occurred after discontinuation of prednisone and before month 12, the patient received 1000 mg RTX at the time of relapse and the scheduled month 18 infusion of 500 mg RTX, but no infusion at month 12. If for example relapse occurred after discontinuation of prednisone and between month 12 and month 18, 1000 mg RTX was given at the time of relapse (no infusion at month 18), and if relapse occurred after month 18, the patient was treated with RTX 1000 mg at the time of relapse. In the event that a patient experienced more than one relapse, only the first relapse was treated with RTX.

Patients in the prednisone-only treated group resumed or escalated their prednisone dose. If relapse occurred during the prednisone taper, the prednisone dose was increased to a prior dose level that permitted disease control. If relapse occurred after prednisone withdrawal, prednisone was resumed at a dose of 0.3 mg/kg/day or 0.5 mg/kg/day depending on the severity of the relapse.

Relapse was defined as the appearance of 3 or more 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 [Murrell 2008]. Presence of relapse was determined after physical examination at a study visit.

Objectives

The protocol specified study objectives were:

1) To demonstrate that it was possible to control, and then to heal, the mucocutaneous lesions of patients with pemphigus vulgaris or pemphigus foliaceus, in spite of short-term systemic corticosteroid therapy, as a result of the use of rituximab.

2) To demonstrate that initial treatment with rituximab, repeated after 12 months and 18 months, helped achieve prolonged control of the mucocutaneous lesions caused by pemphigus, making it possible for a larger number of patients to achieve complete remission without corticosteroid therapy at 24 months and 36 months after the start of treatment, compared to a standard regimen of systemic corticosteroid therapy.

3) To demonstrate that the rituximab + prednisone treatment regimen was well tolerated with fewer side effects of systemic corticosteroid therapy. An extended follow-up period (up to 10 years) was to be carried out to ensure the long-term absence of side effects (e.g., lymphoma, progressive multifocal leukoencephalopathy [PML]).

4) To monitor the changes in biological and immunological parameters during treatment, namely those related to activation of B lymphocytes specifically directed against desmogleins 1 and 3. In particular: the titer, isotype, and specificity of anti- Dsg-1 and anti-Dsg-3 antibodies, the total number of B lymphocytes and the number of Dsg-1-specific B lymphocytes, Dsg-3-specific B lymphocytes, B cell repertoire, Dsg-1-specific B-cell repertoire, and Dsg-3-specific B-cell repertoire were to be monitored.

Any differences between the protocol-specified objectives and those included in the Applicant's analyses and any objectives not carried out are presented in the section *"Conduct of the study".*

Outcomes/endpoints

Primary Endpoint

The primary endpoint was the evaluation of complete remission (complete epithelialization and absence of new and/or established lesions) at Month 24 without CS therapy for at least two months ("complete remission off therapy" according to the "Consensus Treatment Definitions of Disease Endpoints and Therapeutic Responses for Pemphigus" [Murrell et al. 2008]).

Secondary Endpoints

- "Severe" and "moderate" relapses at Month 24. Relapse defined as 3 or more new lesions per month that do not heal spontaneously within a week or extension of established lesions in a patient who has achieved disease control. The definitions of "severe" and "moderate" relapse correspond to the protocol definitions of severe and moderate pemphigus, but in addition, if a relapse remained uncontrolled despite 4 weeks of prednisone dose increases to 0.5 mg/kg/d, the relapse was considered severe.
- Complete remission at Month 24 with minimal CS treatment ("Complete remission on minimal therapy," defined according to the Consensus Statement (Murrell et al. 2008) as a dose of prednisone ≤ 10 mg/day).
- Total mean cumulative dose of prednisone up to Month 24.
- The mean duration of complete remission (healing of the mucocutaneous lesions) without general corticosteroid therapy at Month 24.
- The number of SAEs, including death, attributable to the corticosteroid therapy and/or rituximab.
- Quality-of-life scores (Skindex-France [Chren et al. 1997, Leplege et al. 2003] herein referred to as "Skindex") and Dermatology Life Quality Index (DLQI) [Basra et al. 2015]) at baseline (start of treatment) and Months 3, 6, 9, 12, 18 and 24. Patient reported outcomes of health-related quality of life were assessed using the Skindex- France and DLQI Skin Diseases, both of which are validated and reliable patient self-reported measures available in French that measure the impact of skin disease on the psychological well-being, social functioning and everyday activities of the patients. The recall period for the Skindex-France is the previous week and consists of eight scales, which address the following: cognitive effects, social effects, depression, fear, embarrassment, anger, physical discomfort, and physical limitations. The DLQI refers to the past 7 days and includes 10 questions addressing symptoms and feelings, daily activities, leisure, work and school, personal relationships, and treatment. A lower score for both the Skindex-France and DLQI indicates better quality of life.

Additional Endpoints

The following additional pharmacodynamic, safety and efficacy endpoints, including exploratory endpoints, were evaluated:

- Percentages of CD-19+ peripheral B-lymphocytes at baseline and post-baseline study visits in the first 37 patients randomized in the study.
- Retrospective anti-drug antibody (ADA) measurements at baseline, D180, D365, and D545 study visits in patients treated with rituximab + prednisone.
- Measurements of anti-Dsg-1 and –Dsg-3 pathogenic antibodies at baseline and post-baseline study visits.
- Non-serious AEs related to trial drugs with information collected in the study CRFs, the reported grade of intensity (Common terminology criteria for adverse events [CTCAE] v4) and the timing.
- Numbers of relapses (either "severe" or "moderate") at Month 36 (± 4 months), for patients who achieved complete remission off prednisone therapy at Month 24 (primary endpoint).

Data management

CRFs were used for the prospective data collection. A Clinical Research Associate delegated by the sponsor-investigator (CHU Rouen) performed monitoring which included validation of 100% of critical data in all patients. Due diligence site visits of the Sponsor site and select investigator sites (for sites with high patient enrollment) were conducted by the Applicant in 2017. Overall, the findings at the site visits provided supportive evidence that the study was conducted according to GCP.

Sample size

The number of patients estimated for inclusion in the study by the Sponsor was 45 patients per treatment arm, for a total number of 90 patients. This number was calculated according to the primary assessment criterion (number of patients in complete remission, tapered off any CS treatment for at least 3 months, during the evaluation at M24) as described in the Protocol v3.

Randomisation

Randomization was centralized and performed by the Biostatistical Unit at the Rouen University Hospital. After determining eligibility (verifying inclusion criteria and signing the consent form), the patients were randomized 1:1 to receive one of the two treatments (rituximab + prednisone or prednisone) and were stratified by severity of pemphigus (moderate or severe). Within each strata (moderate or severe), randomization to each treatment arm was conducted using permuted blocks of size 4.

Blinding (masking)

Not applicable; this was an open-label study.

Statistical methods

Analysis populations

The intention-to-treat population consisted of all randomized patients, even if no study treatment was received. The primary population for efficacy was the ITT population of all patients being diagnosed as having pemphigus vulgaris (ITT-PV). Patients with pemphigus foliaceus (PF) were analysed within the total ITT population for the primary outcome only. The safety population consisted of all (PV and PF) patients who were treated with either rituximab or protocol-specified prednisone treatment.

The primary analysis of the primary endpoint is a chi square test (or Fisher exact test in case expected cell frequencies are below 5). The Sponsors regarded patients who withdrew due to inefficacy of treatment, to a serious side event threatening the vital prognosis, enrolled by mistake and thus excluded, lost-to-follow-up, or died during the study, as treatment failures. The Applicant regarded patients without an assessment at month 24 for any reason and patients who withdrew early even if they had follow-up data at month 24 as

treatment failures. The Applicant added a Cochran-Mantel-Haenszel test for gender difference and a log binomial regression to adjust for gender and PDAI.

An analysis using the original definition (complete remission without prednisone therapy for at least three months) was performed as well.

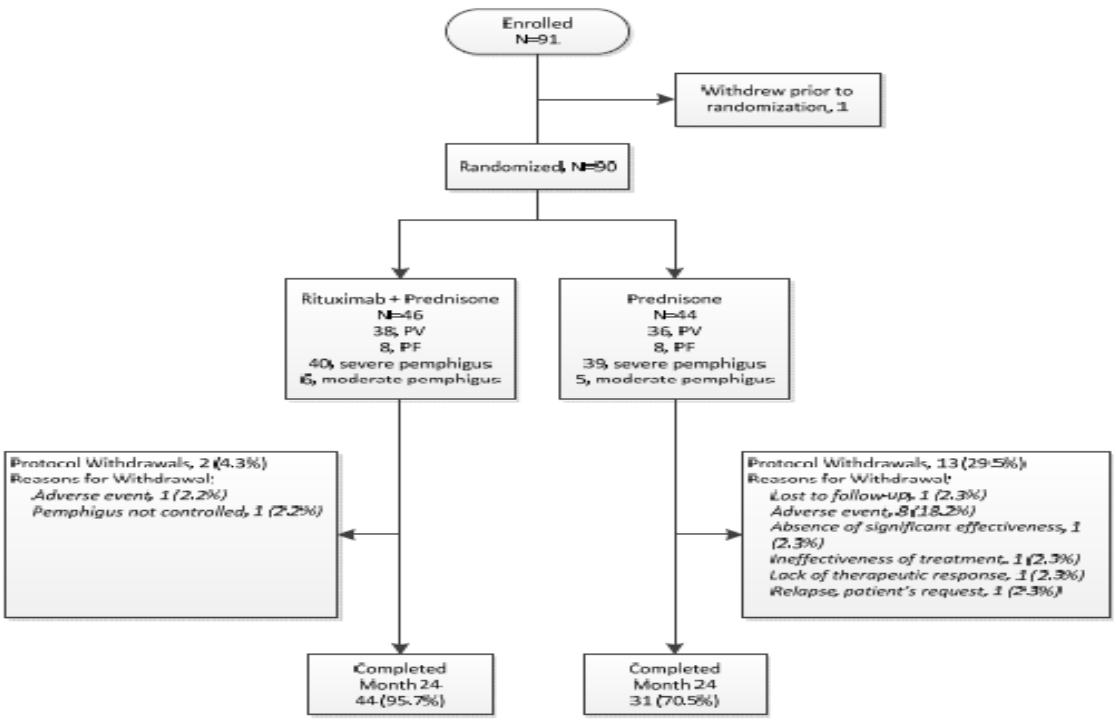
Continuous outcomes were analysed using a t-test (if normality was not violated) or a Mann-Whitney U test otherwise. Chi square test (or Fisher exact test in case expected cell frequencies are below 5)were used for binary variables.

For each patient in complete remission without oral corticosteroid therapy at Month 24, the average period during which the patient was in complete remission off corticosteroid therapy will be evaluated. Only data where the duration is at least 2 months will be analysed. This will be confirmed through either a yes answer for the CRF item “In complete remission and no longer receiving oral corticosteroid therapy for 3 months”, or by confirming that patient is in remission and no longer receiving prednisone at both Month 22 and Month 24 visits. The average period will also be assessed for patients off corticosteroid therapy for 3 months, using only the CRF item.
To this end, the time duration will be calculated by using, as date of origin: the date of complete remission without corticosteroid therapy, and as end date, the last date of visit during which no relapse was noted without intake of corticosteroid therapy. Since prednisone dose is not reported at Day 1, the dose reported at Day 7 will be assumed to apply from Day 1 to the day before Day 7. Similarly, the dose reported at subsequent visits will be assumed to apply from the previous visit to the day before the reporting visit. For missing dose, the last previous non-missing dose will be carried forward (LOCF method), except after the last reported nonzero dose.

Results

Participant flow

Figure 2 Patient Disposition – All Patients



In the ITT sample up to 24 months, there were n=2 (4%) withdrawals in the rituximab treatment group and n=13 (30%) withdrawals in the corticosteroid-only treatment group. Most of the withdrawals in the latter group were because of adverse events (n=8) or because of lack of effectiveness/relapse (n=4). The visit at month 36 (figure 1) was added by amendment, when a number of patients already had passed month 36. Month 36 visits could be assessed in 71% of patients and was assessed post-hoc 22% and remained missing in 7% (Table 2).

Table 2

Summary of Analysis Populations in Study ML22196

	Rituximab + Prednisone (N=46)	Prednisone (N=44)
Intent-to-treat [a]	46 (100.0%)	44 (100.0%)
Safety [a]	46 (100.0%)	44 (100.0%)
Received rituximab [a]	46 (100.0%)	0
Received prednisone [a]	0	44 (100.0%)
Intent-to-treat PV [b]	38 (82.6%)	36 (81.8%)
Safety PV [b]	38 (82.6%)	36 (81.8%)
Received rituximab [b]	38 (82.6%)	0
Received prednisone [b]	0	36 (81.8%)

PV=pemphigus vulgaris
[a] Patients with a diagnosis of PV or pemphigus foliaceus
[b] Patients with a diagnosis of PV
Source: ML22196 CSR Table 8

In the ITT-PV sample, n=38 patients were allocated to the rituximab group and n=36 were allocated to the corticosteroid-only group. In the rituximab group, one patient withdrew from treatment (because of pregnancy), but all n=38 patients completed the month 24 visit. In the corticosteroid-only group, n=12 (33%) patients withdrew from treatment, while n=30 (83%) completed the month 24 visit. The number and reasons for withdrawal in the ITT-PV sample are shown in Table 3.

Table 3

Reasons for Protocol Withdrawal (ITT-PV Population)

	Rituximab + Prednisone (N=38)	Prednisone (N=36)	All Patients (N=74)
Protocol Withdrawal[a]	1 (2.6%)	12 (33.3%)	13 (17.6%)
Reason:			
Death	0 (0.0%)	0 (0.0%)	0 (0.0%)
Lost To Follow-Up	0 (0.0%)	1 (2.8%)	1 (1.4%)
Withdrew Consent	0 (0.0%)	0 (0.0%)	0 (0.0%)
Adverse Event	1 (2.6%)	7 (19.4%)	8 (10.8%)
Protocol Deviation	0 (0.0%)	0 (0.0%)	0 (0.0%)
Patient Non-compliance	0 (0.0%)	0 (0.0%)	0 (0.0%)
Other	0 (0.0%)	4 (11.1%)	4 (5.4%)
Absence Of Significative Effectiveness	0 (0.0%)	1 (2.8%)	1 (1.4%)
Ineffectiveness Of Treatment Patient Put On Mabthera At The End Of Study	0 (0.0%)	1 (2.8%)	1 (1.4%)
Lack Of Therapeutic Response. PV Not Controlled By Simple Corticotherapy	0 (0.0%)	1 (2.8%)	1 (1.4%)
Relapse Patient's Wish For Another Treatment	0 (0.0%)	1 (2.8%)	1 (1.4%)

Abbreviations: CRF = Case report form.
Percentages are based on N.
[a] Reason is that reported on the CRF assessed as the primary reason for protocol withdrawal.
Protocol withdrawal is withdrawal from protocol-specified treatment. Most such patients continue to have study assessments.
Modified from tds004it

First Patient Entered: 15 May 2010

Last Patient Entered: 07 December 2012

LPLV: 22 March 2016

The Principal Investigator was Prof. Pascal Joly. Twentyfive other primary investigators belonging to the Bullous Group of the French Dermatology Society enrolled patients. France (26 centers)

Conduct of the study

Protocol Amendments

There were a total of 13 protocol amendments; the first 2 amendments occurred before the first patient was enrolled under Protocol v3. Table 4 lists major changes to the protocol. In protocol v12 dated 31 March 2014, clinical follow-up was extended to 36 months; Due to the fact that the extension of clinical follow-up took place late in the study (M24 LPLV for the primary endpoint was 04 December 2014), the additional visit was not done at M36 for all patients. Some patients had a follow-up visit after M36 which recorded their clinical status at the time of the visit, and their clinical status at M36 was retrospectively assessed. Extended follow-up of 10 years, which was included in the objectives in Protocol v14, was not performed.

Of importance, in Protocol v13 dated 25 June 2015, the definition of complete remission off prednisone was modified to reflect the updated clinical guidelines on duration of complete remission off of CS (Murrell et al. 2008). Thus, the primary efficacy endpoint was changed from CRoff CS for at least 3 months at M24 to CRoff CS for at least 2 months at M24.

Protocol-Specified Study Objectives

The protocol specified objectives included the intent to monitor changes in biological and immunological parameters during treatment, namely those related to activation of B lymphocytes specifically directed against Dsg-1 and Dsg-3. This objective was considered to be exploratory by the Applicant and for the purposes of this CSR analyses were limited to Dsg-1 and Dsg-3 antibody levels.

Comparison of Protocol-Specified and DAP-Specified Study Endpoints and Analyses

A number of secondary endpoints were specified in the Sponsor's Protocol v14.

The key changes were:

- Quality of life (QoL) was assessed at additional timepoints compared to those specified in the Protocol v14. QoL was assessed with Skindex-France and DLQI at Months 3, 6, 9, 12, 18 and 24. The following protocol-specified secondary endpoints were not included in the Applicant's analyses:
- The number of patients with complete healing of their mucocutaneous lesions six months after the start of treatment.
- The number of patients with incomplete remission off treatment at M24.
- The number of patients in complete remission, who continued on minimal corticosteroid therapy (prednisone □□10 mg/day) at M36 (+/- 4 months), or received multiple courses of corticosteroid therapy following one or more relapses.
- The number of patients in complete remission off treatment at M36 (+/- 4 months). The Applicant also performed analyses of the following additional endpoints not included in the protocol (Applicant DAP):
- Pharmacodynamic counts and percentages of CD-19+ B-Lymphocytes at Baseline and post-Baseline study visits.
- Retrospective measurements of ADA at Baseline, D180, D365, and D545 study visits.
- Measurements of anti-Dsg-1 and -Dsg-3 antibodies at Baseline and post-Baseline study visits.

- For side effects (AEs related to trial drugs with information collected in the study CRFs), the reported grade of intensity (CTCAE version 4) and the timing.
- Numbers of relapses (either “severe” or “moderate”) at M36 (± 4 months), for patients who achieved complete remission off CS therapy for at least 2 months at M24.

The Applicant also presented an analysis of selected AEs of rituximab (infections and IRRs) and infections. Additionally, the primary analysis was stratified by gender to assess gender effect on response; this was not part of the sponsor's analysis plan.

Differences in Analysis between the Sponsor SAP and the Applicant DAP

The Sponsor’s SAP v3 states that all analyses will be performed for the ITT population. In the Applicant’s DAP, all analyses were performed for the PV population; only selected analyses were done for the ITT population.

Table 4

Summary of Select Key Changes to the Protocol

Document, Version, Date	Summary of Key Change	Rationale for Change
Protocol, v 03 29 January 2009 The first protocol version submitted to the French Health Authority	Updated Investigator information pertaining to monitoring neurological symptoms for possible PML	Specifications requested by AFFSAPS
	Added prohibition of any use of live vaccine during and post-study	Specifications requested by AFFSAPS
	Added treatment information for mild, moderate, and severe infusion reactions.	Specifications requested by AFFSAPS
	Exclusion criteria were modified to include history of allergic reaction to monoclonal antibodies, class III NYHA heart failure, hepatitis B or C, infections requiring hospitalization or antibiotic treatment within 4 weeks prior to study, history of deep tissue infection within 1 year prior to study, active primary or secondary immune deficiency, history of chronic or recurrent infection, administration of live vaccine with 4 weeks prior to study, previous treatment with Rituximab or any treatment leading to severe lymphocyte depletion, previous treatment with lymphocyte trafficking inhibitors, and severe chronic obstructive pulmonary disease	Specifications requested by AFFSAPS
	Immunization status added to inclusion criteria 5.	Specifications requested by AFFSAPS
Protocol, v 04 18 May 2009	The duration of the first and second Rituximab infusions were changed from 2 hours 15 minutes to 4 hours 30 minutes	Increased initial dosage required a longer infusion period
	The dosage for the first and second Rituximab infusions were changed from two 500 mg infusions to two 1000mg infusions	Notification of the new dosage of the initial treatment, changing from 2x500 mg to 2x1000 mg of rituximab
Protocol, v 06 20 January 2010	Added that pregnancy test should be performed before any administration of rituximab	To update that pregnancy test should not be only at the start of the protocol.

Summary of Select Key Changes to the Protocol (cont.)

Document, Version, Date	Summary of Key Change	Rationale for Change
Protocol, v. 07 13 July 2010	Inclusion criterion amended to read "patient having received less than one month of systemic corticosteroid therapy at a dose ≤ 0.5 mg/kg/d or local corticosteroid therapy prior to the disease being diagnosed"	Cases of pemphigus treated prior to the diagnosis by non-specific corticosteroid therapy (≤0.5 mg/kg/day) proven ineffective against pemphigus were not intentionally excluded, because the practice of a short "corticosteroid therapy trial" is common for undiagnosed oral erosions.
Protocol, v 09 16 June 2011	Patient information sheets amended to include "four cases of fatal reactions occurring during or after the infusion and leading to death have been reported in patients treated for rheumatoid arthritis. Two of these patients had underlying heart disease. These fatal reactions are rare, given the number of prescriptions for Rituximab since its marketing"	Safety information provided by the Applicant
Protocol, v 11 03 January 2013	Updated patient safety information: The description of exceptional cases of severe skin reactions (toxic epidermal necrolysis (TEN) or Stevens-Johnson syndrome (SJS)) after a variable period from several hours up to 4 months after the first infusion, must lead to the patient being closely monitored. Investigators must inform patients that they must immediately contact a physician if they notice a significant change in vision, problems with balance or movement coordination, or experience any confusion	Safety information provided by the Applicant

Summary of Select Key Changes to the Protocol (cont.)

Document, Version, Date	Summary of Key Change	Rationale for Change
	Long-term pharmacovigilance data: In light of the description of exceptional cases of lymphoma or PML (in lupus patients only), of severe skin reactions in patients with auto-immune diseases, follow-up of the patients in the trial will be conducted by telephone up to 10 years after treatment in order to ensure that there are no long-term side effects. In the latter case, severe skin reactions called Lyell's syndrome and Stevens-Johnson syndrome cause epidermal necrosis, a detachment of the skin, similar in appearance to the skin of burn victims, as well as oral, genital, or ocular erosions. These reactions are severe and could be fatal in some cases. The mechanism of these reactions is unknown, but the occurrence of such a reaction would naturally warrant immediate discontinuation of study medication.	Safety information provided by the Applicant
Protocol, v 12 31 March 2014	"In addition, some cases of viral hepatitis, some of which are severe or fatal, have occurred in patients treated with rituximab for lymphoma (cancer of the ganglia) or polyarthritis. These cases are most probably linked to a reactivation of the hepatitis B virus by rituximab in combination with chemotherapy (in patients with lymphoma) and/or cortisone (in patients with polyarthritis). None of these cases has been described in patients treated for pemphigus with Rituximab. It is therefore recommended for patients, having had viral hepatitis in their lives that was linked to the hepatitis B virus, to have their blood screened, and if there are signs of reactivation of this hepatitis B virus, to consult with a liver specialist to be treated in compliance with current recommendations. Telephone monitoring for a period of 10 years was to be scheduled to ensure good long-term tolerance to treatment which you have received during this study."	Safety information provided by the Applicant and request for study extension

Summary of Select Key Changes to the Protocol (cont.)

Document, Version, Date	Summary of Key Change	Rationale for Change
	Added Secondary Endpoints The number of patients in complete remission, who continue minimal corticosteroid therapy (Prednisone </= 10 mg/day) at M36 (+/- 4 months), or are receiving corticosteroid therapy following one or more relapses. The number of patients in complete remission off treatment at M36 (+/- 4 months).	
	Clinical follow-up extended to 36 months	Safety information provided by the Applicant and Sponsor request for study extension
Protocol, v. 13 25 June 2015	The primary endpoint was changed from "Evaluate the number of patients in complete remission during the M24 evaluation who have not received systemic corticosteroid therapy for at least three months" to "Evaluate the number of patients in complete remission during the M24 evaluation who have not received systemic corticosteroid therapy for at least two months"	Update to Clinical Guidelines (Murrell et al. 2008)

AFFSAPS = Agence Française de Sécurité Sanitaire des Produits de Santé

Protocol v1 was a working copy. Protocol v2 was the version that received a favorable recommendation from the Committee for the Protection of Persons 18 December 2008. Protocol v5, v8, and v10 had administrative changes only; Protocol v14 is the final version.

Major Protocol deviations

Major protocol deviations were defined by the sponsor as mistakes or technical deviations which could lead to danger for patients and could affect the integrity of the results of the study. In the ITT population, 197 major protocol deviations were reported in 77 patients (86%). Sponsor definitions were not reclassified or adjudicated by the Applicant, although upon review, many of the deviations categorized by the Sponsor as 'major' did not meet the Applicant's standard definition for a major protocol deviation. The Applicant's definition of a major protocol deviation is one that has the potential to impact patient safety, the efficacy of the treatment regimen, or the study analysis. Applicant review of the Sponsor's 'major protocol deviations' concluded that these deviations as collected and classified by the Sponsor did not have an impact on the overall interpretation of efficacy and safety results. No protocol deviations led to withdrawal of patients from the study. Per-protocol analysis was not performed for this study.

The major deviations observed in the ITT population were primarily procedural (e.g., ICF updates/versions not signed at the correct time [however, original ICFs were signed], information updates not signed, not dated, or lost) or medication-related (e.g., prednisone dose increases/decreases not per protocol guidance at some study visits). In the ITT-PV population, the deviations were balanced across the arms with 159 major protocol deviations being reported in 63 patients; 75 deviations in 32 patients in the rituximab + prednisone arm and 84 deviations in 31 patients in the prednisone arm.

The major deviations observed in the ITT PV population were similar to those seen in the ITT population.

To further investigate the potential significance of these protocol deviations, the Applicant undertook site visits at 8 of 25 centers, including the center with the most major protocol deviations. Review of the site visit findings indicate that the study centers addressed the issues identified during the site visits and confirmed that the findings observed did not have an impact on data integrity.

Table 5

Roche Rituximab (ML22196)

Table DS005IT: Major Protocol Deviations by Treatment
Analysis Set: Intent to Treat PV

	Rituximab + Prednisone (N = 38) n (%)	Prednisone (N = 36) n (%)
deviation on inclusion criterion	0 (0.0%)	1 (2.8%)
deviation on pharmacovigilance	2 (5.3%)	4 (11.1%)
information letter/consent not found	2 (5.3%)	1 (2.8%)
information letter/consent not signed	14 (36.8%)	1 (2.8%)
information letter/consent to enrollment not appropriate	12 (31.6%)	11 (30.6%)
information letter/consent to enrollment not signed by investigator	0 (0.0%)	1 (2.8%)
information letter/consent to enrollment signature not appropriate	0 (0.0%)	1 (2.8%)
pharmacy technical deviation	1 (2.6%)	0 (0.0%)
technical deviation on record at site	3 (7.9%)	3 (8.3%)
trial treatment not followed	17 (44.7%)	26 (72.2%)

Baseline data

Table 6

Demographic Data (ITT-PV Population)

	Rituximab + Prednisone (N=38)	Prednisone (N=36)	All Patients (N=74)
Baseline Age (years)			
n	38	36	74
Mean	54.7	51.8	53.3
SD	16.15	13.39	14.84
Median	55.0	49.0	51.5
Q1, Q3	42.0, 68.0	42.5, 63.5	42.0, 67.0
Min, Max	25, 79	30, 79	25, 79
Age Category			
n	38	36	74
<25 years	0 (0.0%)	0 (0.0%)	0 (0.0%)
25-35 years	5 (13.2%)	4 (11.1%)	9 (12.2%)
35-45 years	5 (13.2%)	7 (19.4%)	12 (16.2%)
45-65 years	15 (39.5%)	17 (47.2%)	32 (43.2%)
>=65 years	13 (34.2%)	8 (22.2%)	21 (28.4%)
Gender			
n	38	36	74
Male	11 (28.9%)	21 (58.3%)	32 (43.2%)
Female	27 (71.1%)	15 (41.7%)	42 (56.8%)
Baseline Height (cm)			
n	38	36	74
Mean	162.0	170.7	166.2
SD	10.35	8.54	10.41
Median	161.0	172.5	165.0
Q1, Q3	155.0, 168.0	162.5, 178.0	160.0, 175.0
Min, Max	124, 182	155, 185	124, 185
Baseline Weight (kg)			
n	38	36	74
Mean	68.3	75.2	71.7
SD	21.26	18.65	20.28
Median	63.0	74.5	69.5
Q1, Q3	58.0, 74.0	64.0, 85.0	59.0, 80.0
Min, Max	43, 177	43, 155	43, 177
Baseline BMI (kg/m^2)			
n	38	36	74
Mean	27.0	25.7	26.4
SD	10.26	5.13	11.45
Median	25.4	25.3	25.3
Q1, Q3	21.6, 27.4	22.5, 27.8	22.0, 27.4
Min, Max	15, 115	17, 46	15, 115
Baseline BSA (m^2)			
n	38	36	74
Mean	1.7	1.9	1.8
SD	0.21	0.25	0.24
Median	1.7	1.9	1.8
Q1, Q3	1.6, 1.8	1.7, 2.0	1.6, 1.9
Min, Max	1, 2	1, 2	1, 2

Abbreviations: SD = Standard deviation, Q1, Q3 = 1st and 3rd quartiles, cm = Centimeter, kg = Kilogram, BMI = Body mass index, BSA = Body surface area, m = Meter.
BMI and BSA are calculated from weight and height.
n = number of patients with a non-missing value. Percentages are based on n.

Modified from tdm001it

Table 7

Baseline Disease Characteristics (ITT-PV Population)

	Rituximab + Prednisone (N=20)	Prednisone (N=16)	All Patients (N=74)
Clinical Disease Type			
n	20	16	74
Pemphigus Vulgaris	20 (100.0%)	16 (100.0%)	74 (100.0%)
Histological Disease Type [a]			
n	20	16	74
Pemphigus Vulgaris	17 (97.4%)	16 (100.0%)	72 (98.6%)
Disease Severity			
Moderate	5 (13.2%)	3 (8.3%)	8 (10.8%)
Skin and Mucosa	2 (5.3%)	3 (8.3%)	5 (6.8%)
Skin Only	2 (5.3%)	0 (0.0%)	2 (2.7%)
Mucosa Only	1 (2.6%)	0 (0.0%)	1 (1.4%)
Oral Only	0 (0.0%)	0 (0.0%)	0 (0.0%)
Severe	33 (86.8%)	33 (91.7%)	66 (89.2%)
Skin and Mucosa	24 (63.2%)	25 (69.4%)	49 (66.2%)
Skin Only	0 (0.0%)	0 (0.0%)	0 (0.0%)
Mucosa Only	9 (23.7%)	8 (22.2%)	17 (23.0%)
Mucosal Involvement at 2 or More Sites	12 (31.6%)	9 (25.0%)	21 (28.4%)
Oral Only	4 (10.5%)	5 (13.9%)	9 (12.2%)
Duration of Skin Lesions (Days)			
n	20	16	74
Mean	111.9	94.4	103.1
SD	274.29	134.09	216.38
Median	30.5	50.0	44.0
Q1, Q3	0.0, 106.0	8.5, 108.0	1.0, 106.0
Min, Max	0, 1090	0, 422	0, 1090
Duration of Mucosal Lesions (Days)			
n	20	16	74
Mean	138.7	115.4	127.4
SD	191.82	130.10	160.46
Median	109.0	84.0	94.0
Q1, Q3	30.0, 184.0	42.0, 122.5	29.0, 166.0
Min, Max	0, 871	1, 491	0, 691
Skin Lesions on			
Head and Neck	13 (60.5%)	26 (72.2%)	49 (66.2%)
Anterior Trunk	22 (57.9%)	22 (61.1%)	44 (59.5%)
Posterior Trunk	18 (47.4%)	21 (58.3%)	39 (52.7%)
Upper Limbs (not hands)	12 (31.6%)	17 (47.2%)	29 (39.2%)
Lower Limbs (not hands)	10 (26.3%)	15 (41.7%)	25 (33.8%)
Hands and Feet	4 (11.1%)	4 (11.1%)	11 (14.2%)
> 5% of Body Surface	9 (23.7%)	12 (33.3%)	21 (28.4%)
<= 5% of Body Surface	2 (5.3%)	3 (8.3%)	5 (6.8%)
Mucosal Lesions Which are			
At More Than One Site	12 (31.6%)	9 (25.0%)	21 (28.4%)
Oral	35 (92.1%)	36 (100.0%)	71 (95.9%)
Oral - Not Dysphagia	8 (21.1%)	8 (22.2%)	16 (21.6%)
Oral - Dysphagia	27 (71.1%)	28 (77.8%)	55 (74.3%)
Oral - Dysphagia with Weight Loss >= 3 kg	25 (65.8%)	21 (58.3%)	46 (62.2%)
Genital	15 (39.5%)	16 (44.4%)	31 (41.9%)
Other	22 (57.9%)	20 (55.6%)	42 (56.8%)
Karnofsky Index (%)			
n	20	16	74
Mean	90.5	91.9	91.4
SD	13.02	12.38	13.07
Median	100.0	100.0	100.0
Q1, Q3	80.0, 100.0	80.0, 100.0	80.0, 100.0
Min, Max	60, 100	60, 100	60, 100
PDAI			
n	20	25	72
Mean	34.1	46.6	40.1
SD	19.51	23.61	27.39
Median	26.0	38.0	28.0
Q1, Q3	14.0, 40.5	26.5, 62.5	19.0, 57.5
Min, Max	9, 101	7, 106	9, 101

Abbreviations: SD = Standard deviation, Q1, Q3 = 1st and 3rd quartiles, mmHg = Millimeters of mercury, PDAI = Pemphigus disease area index.
n = number of patients with a non-missing value.
Percentages are based on n.
[a] Histological disease type could not be assessed for one patient due to concurrent infection. Another patient had pemphigus foliaceus selected as well as pemphigus vulgaris.
Severe and Moderate defined as per Harman's criteria.

Modified from tpe001it

Overall, 74 patients (82.2%) had a diagnosis of PV and 16 patients had a diagnosis of PF (Table 8). Baseline characteristics for the ITT population are presented in Table 8. Baseline disease history is presented in ldm003it which can be found in the submitted dataset

Table 8

Baseline Disease Characteristics (ITT Population)

	Rituximab + Prednisone (N=46)	Prednisone (N=44)	All Patients (N=90)
Clinical Disease Type			
n	46	44	90
Pemphigus Vulgaris	38 (82.6%)	36 (81.8%)	74 (82.2%)
Pemphigus Foliaceus	8 (17.4%)	8 (18.2%)	16 (17.8%)
Histological Disease Type			
n	46	44	90
Pemphigus Vulgaris	37 (80.4%)	36 (81.8%)	73 (81.1%)
Pemphigus Foliaceus	8 (17.4%)	8 (18.2%)	16 (17.8%)
Undetermined	1 (2.2%)	1 (2.3%)	2 (2.2%)
Disease Severity [a]			
Moderate	6 (13.0%)	5 (11.4%)	11 (12.2%)
Skin and Mucosa	2 (4.3%)	3 (6.8%)	5 (5.6%)
Skin Only	3 (6.5%)	2 (4.5%)	5 (5.6%)
Mucosa Only	1 (2.2%)	0 (0.0%)	1 (1.1%)
Oral Only	0 (0.0%)	0 (0.0%)	0 (0.0%)
Severe	40 (87.0%)	39 (88.6%)	79 (87.8%)
Skin and Mucosa	24 (52.2%)	25 (56.8%)	49 (54.4%)
Skin Only	7 (15.2%)	6 (13.6%)	13 (14.4%)
Mucosa Only	9 (19.6%)	8 (18.2%)	17 (18.9%)
Mucosal Involvement at 2 or More Sites	12 (26.1%)	9 (20.5%)	21 (23.3%)
Oral Only	4 (8.7%)	5 (11.4%)	9 (10.0%)
Duration of Skin Lesions (Days)			
n	46	44	90
Mean	177.8	128.0	153.2
SD	312.09	174.08	253.94
Median	67.5	61.5	61.5
Q1, Q3	8.0, 174.0	10.5, 156.0	12.0, 166.0
Min, Max	0, 1890	0, 765	0, 1890
Duration of Mucosal Lesions (Days)			
n	46	44	90
Mean	114.6	94.4	104.7
SD	130.87	128.71	177.90
Median	55.5	36.0	64.5
Q1, Q3	15.0, 166.0	16.5, 113.5	16.0, 134.0
Min, Max	0, 571	0, 691	0, 691
Skin Lesions on			
Head and Neck	29 (63.0%)	32 (72.7%)	61 (67.8%)
Anterior Trunk	30 (65.2%)	29 (65.9%)	59 (65.6%)
Posterior Trunk	26 (56.5%)	28 (63.6%)	54 (60.0%)
Upper Limbs (not hands)	18 (39.1%)	24 (54.5%)	42 (46.7%)
Lower Limbs (not hands)	13 (28.3%)	21 (47.7%)	34 (37.8%)
Hands and Feet	9 (19.6%)	7 (15.9%)	16 (17.8%)
> 5% of Body Surface	15 (32.6%)	17 (38.6%)	32 (35.6%)
<= 5% of Body Surface	2 (4.3%)	4 (9.1%)	6 (6.7%)
Mucosal Lesions Which are			
At More Than One Site	12 (26.1%)	9 (20.5%)	21 (23.3%)
Oral	35 (76.1%)	36 (81.8%)	71 (78.9%)
Oral - Non Dysphagia	9 (19.6%)	8 (18.2%)	17 (18.9%)
Oral - Dysphagia	27 (58.7%)	28 (63.6%)	55 (61.1%)
Oral - Dysphagia with Weight Loss >= 3 kg	25 (54.3%)	21 (47.7%)	46 (51.1%)
Genital	15 (32.6%)	16 (36.4%)	31 (34.4%)
Other	22 (47.8%)	20 (45.5%)	42 (46.7%)
Karnofsky Index (%)			
n	46	44	90
Mean	91.5	92.5	92.0
SD	13.32	11.44	12.38
Median	100.0	100.0	100.0
Q1, Q3	90.0, 100.0	90.0, 100.0	90.0, 100.0
Min, Max	50, 100	60, 100	50, 100
PDAI			
n	46	42	88
Mean	33.5	46.0	39.5
SD	23.07	22.72	24.69
Median	24.0	47.0	33.5
Q1, Q3	14.0, 40.5	26.5, 62.0	20.0, 56.0
Min, Max	9, 131	7, 106	9, 131

Abbreviations: SD = Standard deviation, Q1, Q3 = 1st and 3rd quartiles, mmHg = Millimeters of mercury, PDAI = Pemphigus disease area index.
n = number of patients with a non-missing value.
Percentages are based on n.
[a] Severe and Moderate defined as per Harman's criteria. Details in the protocol. These percentages based on N.

Modified from tpe002it

Numbers analysed

Table 9

Summary of Analysis Populations (ITT Population)

	Rituximab + Prednisone (N=46)	Prednisone (N=44)	All Patients (N=90)
Included in INTENT-TO-TREAT (ITT)	46 (100.0%)	44 (100.0%)	90 (100.0%)
Included in SAFETY	46 (100.0%)	44 (100.0%)	90 (100.0%)
Received rituximab	46	0	46
Received only prednisone	0	44	44
Included in INTENT-TO-TREAT PV	38 (82.6%)	36 (81.8%)	74 (82.2%)
Included in SAFETY PV	38 (82.6%)	36 (81.8%)	74 (82.2%)
Received rituximab	38	0	38
Received only prednisone	0	36	36

Abbreviations: PV = Pemphigus vulgaris.

Modified from tde0003t

Outcomes and estimation

Table 10

Overview of Efficacy in the ITT-PV Population

	Rituximab + Prednisone N=38	Prednisone N=36
Primary Endpoint		
CRoff prednisone ≥2 months at M24		
Number of responders (n [%])	34 (89.5%)	10 (27.8%)
Difference in response rates (p-value[a])	<0.0001	
CRoff prednisone ≥ 3 months at M24[b]		
Number of responders (n [%])	34 (89.5%)	9 (25.0%)
Difference in response rates (p-value)	<0.0001	
Secondary Endpoints[c]		
Severe and Moderate Relapses at M24		
Number of patients who had at least one Severe/Moderate Relapse at M24 (n [%])	9 (23.7%)	18 (50.0%)
CR at M24 on Minimal Prednisone Treatment		
Number of patients (n [%])	34 (89.5%)	12 (33.3%)
Total Cumulative Dose of Prednisone at M24		
Mean cumulative dose (SD) (mg)	7356.4 (5736.59)	21,845.3 (11,755.81)
Median cumulative dose (min, max) (mg)	5799.5 (2304, 29303)	20520 (2409, 60565)
Duration of CRoff prednisone at M24 in responders		
Number of responders	34	10
Median duration of CRoff prednisone ≥ 2 months at M24 (min, max)(days)	498.5 (91, 609)	125.0 (56, 680)
PRO/Quality of Life		
Mean Skindex-France score at M24 (mean [SD] change from baseline)	12.3 (-40.5)	21.5 (-37.5)
Mean DLQI score at M24 (mean [SD] change from baseline)	1.7 (-7.9)	3.6 (-7.4)

CR = complete remission; CRoff = complete remission off prednisone therapy; DLQI = Dermatology Quality of Life Index; ITT = intent-to-treat; M = month; PRO = patient-reported outcomes

[a] p-value is from Fisher's exact test with mid-p correction

[b] Original primary endpoint was CRoff prednisone ≥ 3months at M24 collected on the case report forms and updated to CRoff prednisone ≥ 2 months at M24 to reflect published clinical guidelines (Murrell et al. 2008).

[c] No adjustment for multiplicity was made for secondary endpoints.

Primary endpoint (CR off prednisone therapy for 2 months or more at month 24)

At M24, the proportion of PV patients with CRoff prednisone for 2 months or more was statistically significantly higher in the rituximab + prednisone arm than in the prednisone arm (34 patients [89.5%] vs. 10 patients [27.8%], p-value <0.0001). The unadjusted risk ratio comparing the rituximab + prednisone arm to the prednisone arm was 3.2 (95% CI 1.9, 5.5; p-value <0.0001). Similar risk ratios were obtained when adjusted for gender and baseline PDAI scores in a log-binomial model (3.2 [95% CI 1.9, 5.6; p-value 0.0001] and 3.0 [95% CI 1.7, 5.2; p-value 0.0001], respectively).

Results from logistic regression models are presented. The unadjusted odds ratio was 22.1 (95% CI 6.2, 78.5; p-value <0.0001). After adjusting for gender, the odds ratio was 23.0 (95% CI 6.1, 87.3; p-value 0.0001) and after adjusting for baseline PDAI score, the odds ratio was 19.6 (95% CI 5.4, 70.5; p-value <0.0001).Gender breakdown of the primary endpoint by treatment arm was as follows: 90.9% and 28.6% for males; and 88.9% and 26.7% for females between rituximab + prednisone and prednisone arms, respectively.

Secondary outcomes

An overview of the results on secondary outcomes is provided in table 11. All between-group differences in secondary outcomes were in favour of the rituximab treated group.

Table 11

Overview of Efficacy Endpoints in Patients with Pemphigus (ITT-PV Population Study ML22196)

	Rituximab + Prednisone N=38	Prednisone N=36
Primary Endpoint		
CRoff ≥2 months at M24		
Number of responders (n [%])	34 (89.5%)	10 (27.8%)
Difference in response rates (p-value [a])	<0.0001	
CRoff ≥ 3 months at M24 [b]		
Number of responders (n [%])	34 (89.5%)	9 (25.0%)
Secondary Endpoints [c]		
Severe and Moderate Relapses at M24		
Number of patients who had at least one Severe/Moderate Relapse at M24 (n [%])	9 (23.7%)	18 (50.0%)
CR at M24 on Minimal Prednisone Treatment		
Number of patients (n [%])	34 (89.5%)	12 (33.3%)
Total Mean Cumulative Dose of Prednisone at M24		
Mean cumulative dose (SD) (mg)	7356.4 (5736.59)	21845.3 (11,755.81)
Median cumulative dose (min, max) (mg)	5799.5 (2304, 29303)	20520 (2409, 60,565)
Duration of CRoff at M24 in responders		
Number of responders	34	10
Median duration of CRoff≥2 months at M24 in days (Q1, Q3)	498.5 (91, 609)	125.0 (56, 680)
PRO/Quality of Life		
Mean Skindex-France score at M24 (mean [SD] change from baseline)	12.3 (–40.5)	21.5 (–37.5)
Mean DLQI score at M24 (mean [SD] change from baseline)	1.7 (–7.9)	3.6 (–7.4)

CR = complete remission; CRF=case report form; CRoff = complete remission off prednisone therapy; DLQI = Dermatology Quality of Life Index; ITT = intent-to-treat; M = month; Max=maximum; Min=minimum; PRO=patient-reported outcome; Q1=lower quartile; Q3=upper quartile; SD=standard deviation.

[a] p-value is from Fisher's exact test with mid-p correction

[b] Original primary endpoint was CRoff ≥ 3months at M24 and updated to CRoff ≥ 2 months at M24 to reflect published clinical guidelines (Murrell et al. 2008). CRoff ≥ 3 months was the original protocol specified primary endpoint and collected on the CRFs.

[c] No adjustment for multiplicity was made for secondary endpoints.

Source: ML22196 CSR Table 12

The duration of remission while off corticosteroids (in patients who were responders at month 24) was longer in the rituximab group as compared to the corticosteroid-only treated group.

At 24 months, the proportion of patients in clinical remission while receiving a minimal dose of prednisone (⩽10 mg/day) in the rituximab group was identical to the proportion of patients off corticosteroids, but in the corticosteroid-only group there were 2 patients more as compared to the primary outcome (off corticosteroids).

In the rituximab treated group, the number of patients having had severe/moderate relapses up to month

24 was smaller than in the corticosteroid-only group (Table 12). Also, the number of patients having had more than one relapse was larger in the corticosteroid-only treated group.

Table 12

Number of Relapses per Patient at Month 24 (ITT-PV Population, Study ML22196)

	Rituximab + Prednisone (N = 38)	Prednisone (N = 36)
Severe/moderate relapses per patient by M24, n (%)		
0	29 (76.3%)	18 (50.0%)
	p=0.0163	
1	7 (18.4%)	11 (30.6%)
2	2 (5.3%)	6 (16.7%)
3	0 (0.0%)	1 (2.8%)
>3	0 (0.0%)	0 (0.0%)

ITT=intent to treat; M=month; PV=pemphigus vulgaris

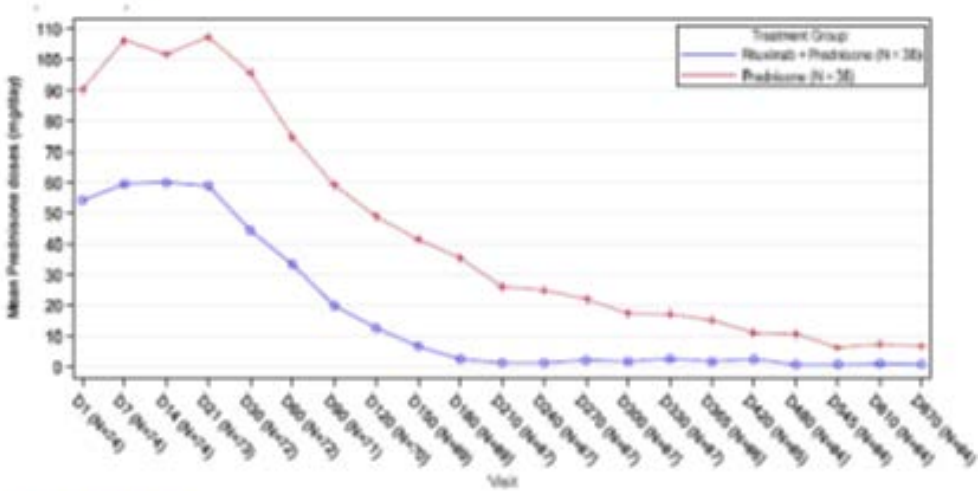
Note: p-values were calculated from Fisher's exact test with mid-p correction.

Source: ML22196 CSR Table 18

The cumulative dose of prednisone used in the rituximab treated group was about 30% of the cumulative dose used in the corticosteroid-only group (Figure 13).

Table 13

Mean Prednisone Dose (mg/day) Over Time (Safety PV Population)



Source: fex003se

In the period between month 24 and month 36, there were 11 patients with a relapse in the corticosteroid-only treated group. There were two patients in the rituximab group who had a relapse, one of them had been in remission (CRoff) at month 24 (Table 14). There were 94% (32/34) of patients who maintained CRoff in the rituximab group and 60% (6/10) who maintained CRoff in the corticosteroid-only group.

Table 14

Summary of Number of Patients Who Achieved CRoff at Month 24 but Relapsed at Month 36 (ITT-PV Population, Study ML22196)

	Rituximab + Prednisone (N=38)	Prednisone (N=36)
Achieved primary outcome (CRoff at Month 24)	34	10
Severe/moderate relapse at Month 36	1 (2.9%)	4 (40.0%)
Severe/moderate skin relapse at Month 36	1 (2.9%)	2 (20.0%)
Severe/moderate mucosal relapse at Month 36	0	0
Severe/moderate mucocutaneous relapse at Month 36	0	2 (20.0%)

CRoff=complete response off prednisone therapy; ITT=intent-to-treat; PV=pemphigus vulgaris.

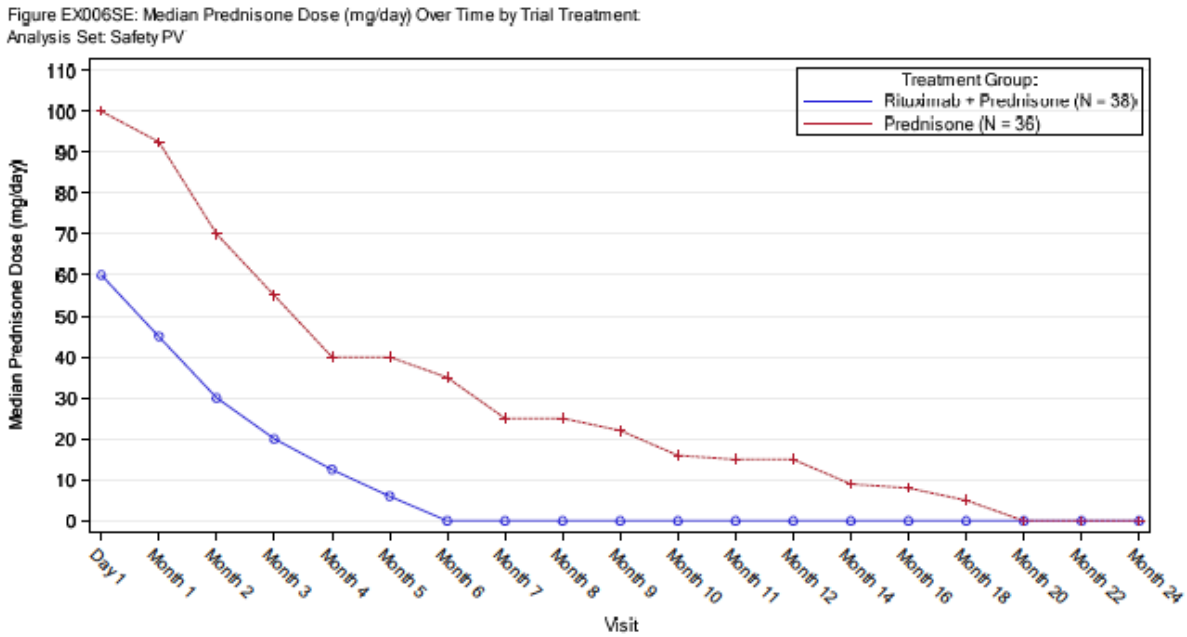
Notes: Includes relapse events reported during Month 36 or post-Month 36 visit, occurring up to Month 40 from randomization. If there was more than one relapse for a patient, only the last relapse was included in this table.

Includes patients with no data after Month 24 who were confirmed to be relapse-free.

Percentages are based on n (number of patients achieving primary endpoint).

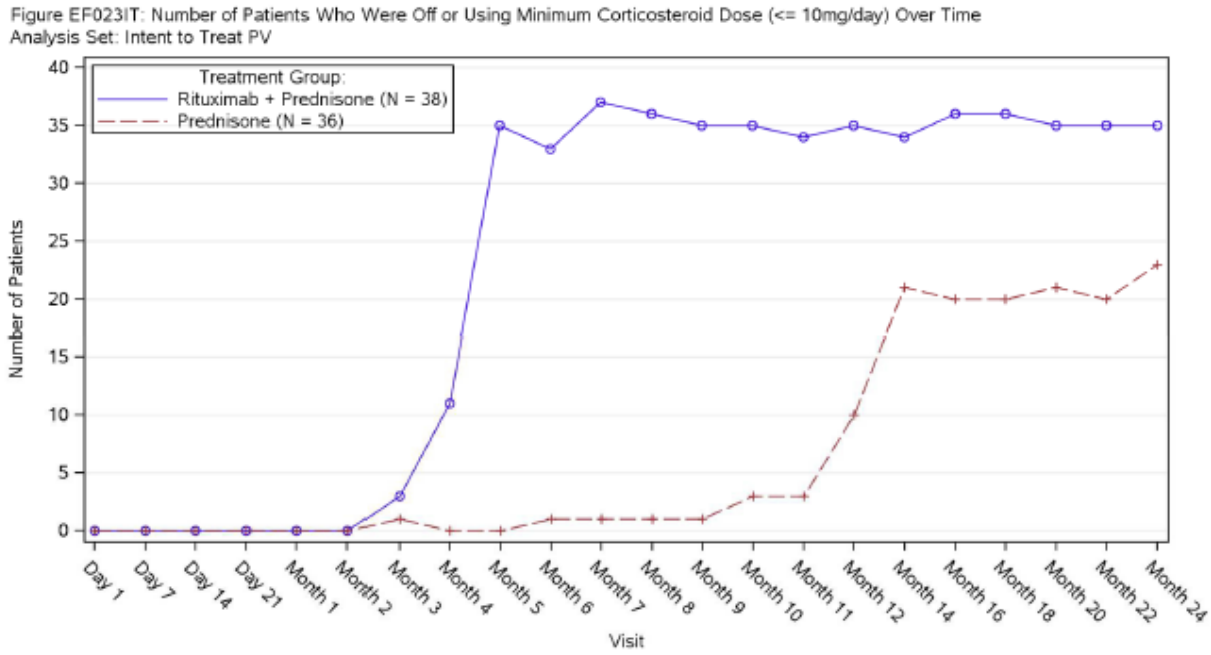
Source: ML22196 CSR Table 21, ML22196 CSR Table EF014IT

Figure 2 Median Prednisone Dose (mg/day) Over Time by Trial Treatment



Source: EX001SE

Figure 3 Number of Patients Who Were off or Using Minimum Corticosteroid Dose (<=10 mg/day) Over Time



Source Table: EX001SE

Secondary endpoint: QoL

- Completion rates for the Skindex questionnaire were >70% in the rituximab + prednisone arm and >55% in the prednisone arm. Completion rates for the DLQI questionnaire were >85%in the rituximab + prednisone arm and >70%in the prednisone arm.
- Patients in both arms reported an improvement in Skindex-France scores from baseline to M3 and this improvement was maintained until M24.
- Patients in both arms reported a clinically meaningful improvement in DLQI scores from baseline to M3 and this improvement was maintained until M24.

Skindex-France

The total Skindex-France score is calculated on a scale of 0 to 100 where higher scores mean greater impairment of the patient's health-related QoL. Completion rates for the Skindex questionnaire were >70% in the rituximab + prednisone arm and >55% in the prednisone arm (Table 15).

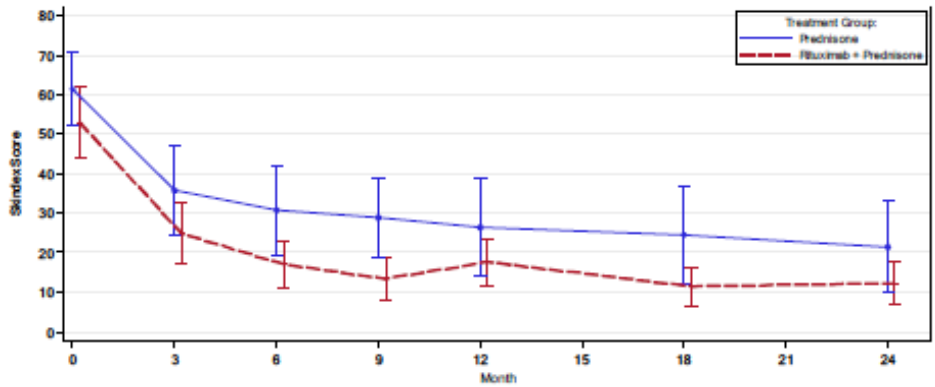
Table 15

Completion rates for PRO questionnaires

	Skindex		DLQI	
	Rituximab + Prednisone n=38	Prednisone n=36	Rituximab + Prednisone n=38	Prednisone n=36
Baseline (Day1)	32 (84%)	28 (78%)	38 (100%)	33 (92%)
M3	33 (87%)	27 (75%)	36 (95%)	28 (78%)
M6	32 (84%)	26 (72%)	35 (92%)	28 (78%)
M9	32 (84%)	26 (72%)	35 (92%)	28 (78%)
M12	33 (87%)	23 (64%)	34 (89%)	27 (75%)
M18	28 (74%)	22 (61%)	35 (92%)	26 (72%)
M24	29 (76%)	21 (58%)	36 (95%)	26 (72%)

PRO = patient-reported outcomes
Source: tqs001it, tqs002it

Figure 3 Mean (95% CI) Skindex-France Score by Visit (ITT-PV)



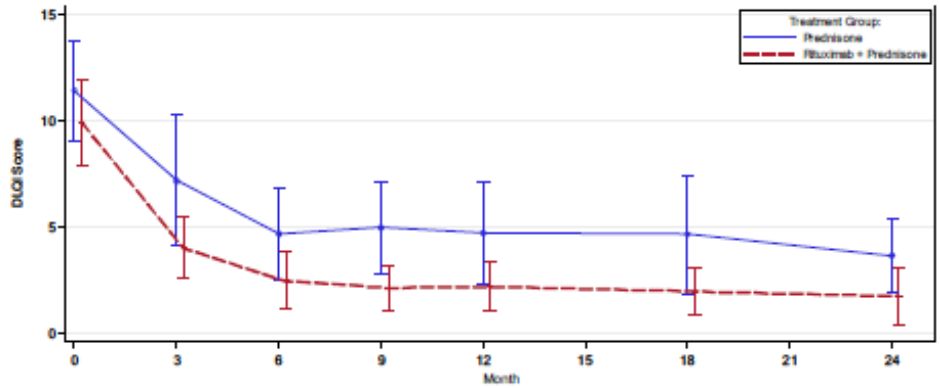
CI=confidence level
Modified from fqs003it

The mean Skindex-France score at baseline (Day 1) was lower in the rituximab + prednisone arm than in the prednisone arm (52.9 vs. 61.3). The mean change from baseline (SD) at M3 was -28.6 (24.47) in the rituximab + prednisone arm and -28.3 (22.92) in the prednisone arm. At M24, the mean Skindex-France score was 12.3 in the rituximab + prednisone arm compared to 21.5 in the prednisone arm. Mean change from baseline (SD) at M24 was -40.5 (22.84) in the rituximab + prednisone arm and -37.5 (23.22) in the prednisone arm. Similar results were obtained when Skindex-France scores were analyzed by mixed model repeated measures (MMRM). At the M24 visit, estimated mean change from baseline (SD) was -39.6 (4.39) in the rituximab + prednisone arm and -35.6 (5.03) in the prednisone arm.

Dermatology life quality index

A total DLQI score is calculated on a scale of 0 to 30 where higher scores mean greater impairment of the patient's health-related QoL. A change in DLQI scores is considered clinically meaningful when a patient's DLQI score changed by at least 4 points from the previous score. Completion rates for the DLQI questionnaire were >85% in the rituximab + prednisone arm and >70% in the prednisone arm (Table 22). Mean score improvements were clinically meaningful at M3 for both arms and the improvement was maintained in both arms until M24 (Figure 4).

Figure 4 Mean (95% CI) DLQI Score by Visit (ITT-PV)



CI=confidence interval; DLQI=Dermatology Quality of Life Index
Source: fqs004it

Exploratory endpoint: Number of patients who relapsed at month 36

Table 16

Number of Relapses from Month 24 to Month 36 in Patients who Achieved CRoff prednisone at Month 24 (ITT-PV Population)

	Rituximab + Prednisone (N = 20)	Prednisone (N = 20)
Achieved Primary Outcome (CR off Treatment at Month 24)	34	10
Severe/Moderate Relapses per Patient From Month 24 to 36		
0	32 (94.1%)	6 (60.0%)
1	2 (5.9%)	4 (40.0%)
2	0 (0.0%)	0 (0.0%)
3	0 (0.0%)	0 (0.0%)
>3	0 (0.0%)	0 (0.0%)

Summary of main study

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

Table 1. Summary of Efficacy for trial ML22196

Title: Comparison of treatment with anti-CD20 monoclonal antibody rituximab (Mabthera) in combination with short-term systemic corticosteroid therapy compared to long-term systemic corticosteroid therapy in patients with Pemphigus.		
Study identifier	ML22196	
Design	This was a Phase III, randomized, active-controlled, open-label, multi-center, investigator-sponsored study. Patients with newly diagnosed pemphigus (vulgaris or foliaceus) were randomised 1:1 to receive rituximab in combination with short-term, low dose systemic corticosteroids (oral prednisone) or standard dose systemic corticosteroid therapy, for 24 months. Randomisation was stratified for disease severity. A follow-up visit was performed at month 36. Main analyses were performed in the majority subgroup of patients with pemphigus vulgaris.	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	24 months Not applicable 12 months
Hypothesis	Superiority	

Treatments groups	Rituximab and corticosteroids		N=38. Rituximab 1000 mg iv was given at baseline and after 2 weeks, and as 500 mg iv at month 12 and month 18 as maintenance treatment. Corticosteroids were started at 1.0 mg/kg/day (severe disease) or 0.5 mg/kg/day (moderate disease) and tapered during 6 to 3 months, respectively.
	Standard corticosteroids		N=36. Corticosteroids were started at 1.5 mg/kg/day (severe disease) or 1.0 mg/kg/day (moderate disease) and tapered during 18 to 12 months, respectively.
Endpoints and definitions	Primary endpoint	CRoff 2 months at 24 months	Complete remission (complete epithelialization and absence of new and/or established lesions) at Month 24 without corticosteroid therapy for at least 2 months.
	Secondary endpoints	Number of relapses	Proportions of patients with >1 severe/ moderate relapse (specified criteria) from baseline to months 24.
		CR minimal CS	Complete remission at Month 24 with minimal CS treatment (≤10 mg/day).
		Duration of remission	The mean duration of complete remission (healing of the mucocutaneous lesions) without general corticosteroid therapy at month 24.
		Cumulative prednisone dose	Cumulative dose of prednisone from baseline up to month 24.
		CRoff at 36 months	Maintained complete remission of month 24 to month 36.
Database lock	Last patient out: 22th March 2016 Data transfer from sponsor to applicant: December 2016		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	ITT analysis in the Pemphigus Vulgaris subpopulation from baseline to 24 months.		
Descriptive statistics and estimate variability	Treatment group	Rituximab + corticosteroids	Corticosteroids-only
	Number of subjects	n=38	n=36
	CRoff 2 months	90% (34/38)	28% (10/36)
	Variability statistic	Not provided	Not provided
Effect estimate per comparison	Primary endpoint	Comparison groups	Rituximab *versus* corticosteroids-only
		Fisher's Exact test	--
		Variability statistic	--
		P-value	<0.0001
Notes	See flow chart (Figure 2) for size of total (PV + PF) population.		

Analysis description	**Secondary analysis**		
Analysis population and time point description	ITT analysis in the Pemphigus Vulgaris subpopulation from baseline to 36 months.		
	Treatment group	Rituximab + corticosteroids	Corticosteroids-only

	Number of subjects	n=38	n=36
	Patients with relapses	24% (9/38)	50% (18/36)
	Variability	Not provided	Not provided
	CR minimal CS	90% (34/38)	33% (12/36)
	Variability	Not provided	Not provided
	Median duration of remission*	490 days	125 days
	(P25-P75)	(91-609)	(56-680)
	Median cumulative prednisone dose	5800 mg	20.520 mg
	(P25-P75) (Min-Max)	(5030-7074) (2304-29.303)	(16.263-28.282) (2409-60.565)
	CRoff maintained at 36 months	94% (32/34)	60% (6/10)
	Variability	Not provided	Not provided
Effect estimate per comparison	Secondary endpoint	Comparison groups	Rituximab *versus* corticosteroids-only
	Patients with relapses	Fisher's Exact test	
		Variability statistic	--
		P-value	0.0163
	CR minimal CS	Fisher's Exact test	
		Variability statistic	--
		P-value	<0.0001
	Median duration of remission*	Mann-Whitney U-test	
		Variability statistic	--
		P-value	0.0030
	Median cumulative prednisone dose	Mann-Whitney U-test	
		Variability statistic	--
		P-value	<0.0001
	CRoff maintained at 36 months	Test statistic	Not provided
		Variability statistic	--
		P-value	--

2.4.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The MAH has provided the results of the study MM22196, an open-label, phase III, multicentre, and randomised study in patients with newly diagnosed moderate to severe pemphigus. The study was run by academia (Rouen University Hospital, France). The MAH had no role in study design, conduct, data collection or publication of results. The database was transferred from the Sponsor to the MAH in December 2016 after database lock.

The open-label nature of the study may have led to bias, e.g. by overestimation of the beneficial effects of rituximab and/or overestimation of adverse events in the corticosteroid-only treated group. It is considered that also well designed and well conducted trials are prone to bias if open label, instead of double blinded. Especially, the primary outcome (clinical remission off corticosteroids for at least 2 months) is vulnerable for bias, since it relies completely on physician's judgement regarding the examination of lesions as well as the decisions regarding tapering. The primary outcome is thus not completely objective. The degree of experience/training of the investigators and standardisation of outcome assessment may contribute to reduction of bias due to the open-label design, although they cannot completely prevent it. Therefore, the CHMP requested sensitivity analyses, which are critical in assuring that a substantial part of the observed effects could not be explained by bias, and that accounting for the size of probable bias will not reduce the size of the treatment effects beyond clinical meaningfulness.

The main objective of the study was to investigate the possibility to control disease with rituximab in combination with low-dose and short-term use of CS. One primary endpoint, several secondary and exploratory endpoints are defined. The primary endpoint is fully acceptable from a clinical point of view. The secondary endpoints are clinically meaningful and relevant endpoints that all supplement the primary endpoint.

Primary endpoint

The primary outcome as originally proposed by the sponsor-investigator, CRoff for 3 months, was changed post-hoc by the Applicant to CRoff for 2 months, in reference to the outcome guideline [Harman 2008]. The original outcome (CRoff for 3 months) is also presented, which is understood as sensitivity analysis rather than as secondary outcome or co-primary outcome; correction for multiplicity is therefore unnecessary.

According to the protocol and CRF, photographs were taken at all time points. However, according to the Applicant, photographs were not taken systematically and standardized methods for photographic assessment were not implemented in this study. Unfortunately, blinded assessment of photographs is no option to at least partly circumvent the unblinded nature of the study.

Patient global assessment (PGA), Pemphigus Disease Area Index (PDAI) and the Autoimmune Bullous Skin Disorder Intensity Score (ABSIS) questionnaires were included in the CRF just before the questions on clinical status, apparently for a validation study. PDAI and ABSIS are regarded as established instruments for pemphigus [Harman 2017]. The Applicant was asked to discuss the validity and reliability of including PGA, PDAI and ABSIS as outcomes and include them in the results if justifiable. It is understood that results on PDAI and ABSIS will be separately reported, as validation study but not in the context of the current study. This is accepted; PDAI and ABSIS will not necessarily add to the interpretation of the treatment effects.

The primary and secondary outcomes concentrate on month 24 and month 36. However, it is considered clinically relevant to also assess the disease course between baseline and month 24. Therefore, the Applicant was asked to perform between-group analyses of appropriate outcomes, for example: proportion of patients 'in control' (start of tapering), time-to-clinical remission, time-to-first-relapse, proportions of patients in CRoff for all time points, patients in CR for all time points, patients with minimal corticosteroids

at all time points, PGA, PDAI and ABSIS over time. The outcomes (1-7) of intermediate time points between baseline and month 24 support the efficacy of rituximab+prednisone versus high dose prednisone. Some of the results, e.g. time to CRoff for 2 months and prednisone use ≤10 mg/day might be considered for the EPAR. Also for that purpose, survival curves would have been preferred over analysis of medians for the 'time-to-event' data. Despite baseline differences in PDAI of median (P25-P75) 55 (27-63) in the prednisone arm versus 26 (14-41) in the rituximab+prednisone arm, in both arms PDAI reduced to a median of 0 in 6 months.

Baseline demographics showed an imbalance with regard to gender, but this is not expected to have any major impact on the interpretation of results. Overall, the baseline disease characteristics are well-balanced.

Maintenance treatment /choice of dose

The studied initial dose of rituximab 2x1000 mg iv 2 weeks apart was chosen because of its known B-cell depleting effects, which is acceptable as rationale for choice in this confirmatory 'phase 3' trial. B-cell depleting effects were also seen in a small (n=21) cohort of patients with pemphigus treated with rituximab in a regimen as for ANCA-positive Vasculitis, which is supportive. Premedication was given before infusion with rituximab, in agreement with the SmPC for rheumatoid arthritis.

The studied maintenance dose of rituximab was 500 mg iv at months 12 and 18, which had been applied in ANCA-positive vasculitis. The rationale was to prevent the common relapses in pemphigus, which is accepted as rationale for its choice in the phase 3 study.

The maintenance treatment wording as proposed in the SmPC was discussed with the applicant during the assessment and agreed as follows :

"A maintenance infusion of 500 mg IV should be administered at months 12 and 18, and then every 6 months thereafter if needed, based on clinical evaluation."

Treatment of relapses

For pemphigus vulgaris, retreatment to prevent relapses or to treat residual disease activity other than flares is currently unjustified.

For treatment of relapses it is proposed in the SmPC to administer rituximab 1 x 1000 mg, not sooner than 16 weeks after a previous infusion with rituximab. Corticosteroid treatment may be resumed. This is similar as performed in the study and could therefore be agreed. The period of 16 weeks comes from the experience in RA, which is accepted. According to the MAH, findings in RA patients demonstrated peripheral B-cell recovery between 6 to 9 months after treatment, and as early as 16 weeks. It can be assumed that the B-cell depleting effects of rituximab are similar for RA patients and PV patients.

It is agreed that corticosteroid is used concomitant to rituximab, to 'bridge' the period that rituximab will begin to become effective. This is in line with treatment guidelines for pemphigus for start of immune suppressive treatment [Harman 2017]. There are no firm guidelines for starting dose, tapering and treatment of flares using corticosteroids in pemphigus, but the implemented corticosteroid schemes are in line with treatment guidelines [Murrell 2008; Harman 2017]. This includes that it is waited for 3-4 weeks or longer till disease activity is 'in control' before tapering is started, as was performed in the study.

The criteria for disease activity being 'in control' and for 'flares' were in agreement with established consensus definitions [Murrell 2008].

Efficacy data and additional analyses

The study met its primary endpoint showing a statistically significant and clinically relevant difference between the treatment arms in favour of rituximab. In total 89.5% (34/38) of the patients in the

rituximab+prednisone arm had CR off prednisone therapy for at least 2 months at month 24. In comparison only 27.8% (10/36) of the patients in the prednisone arm experienced CR off prednisone for at least 2 months at month 24. Looking at CRoff prednisone for at least 3 months at month 24 (the original primary endpoint) similar results are observed. No single centre was dominating the inclusion, which is supportive for robustness of the results.

Differences in baseline variables between treatment groups were overall relatively small, except for gender and PDAI for which sensitivity analyses for the primary outcome were performed. Importantly, disease severity and pattern of lesions were similar at baseline.

In the primary outcome, clinical remission off corticosteroids for at least 2 months (at month 24), there was a numerically large and statistically highly significant ($p<0.0001$) treatment effect between the rituximab group (90%) and the corticosteroid-only group (28%). The size of this treatment effect would be regarded as clinically relevant. The results are supported by the results of the sensitivity analyses (CRoff for 3 months, CRoff in total PF+PV sample, correction for gender and for baseline PDAI). There was no evidence for confounding, or effect modification, by gender.

According to the sensitivity analyses: a) if patients in the prednisone arm who withdrew from treatment or did not complete the month 24 visit were assumed to be responders, the effect in CRoff for rituximab+prednisone versus high dose prednisone was: 90% versus 62%, and it can be calculated that the 95%-CI for the difference is above 6.8%; b) if patients in the prednisone arm who withdrew from treatment or did not complete the month 24 visit were removed from analysis, the effect in CRoff was 90% versus 42%; c) a conservative CRoff in the rituximab+prednisone arm just lower that the lower limit of the 95%CI for the rituximab+prednisone arm of 74% supported the robustness of the treatment effects in the sense that the difference would still at least be 20% (according to the 95%-CI for the difference). This argument can be taken a few steps further: if the rituximab+prednisone arm would have a response rate of 68.4% (26/38), 63.2% (24/38), 57.9% (22/38), 52.6% (20/38) then the difference would still at least be 15%, 10%, 5%, 0% respectively.

The explanation of the MAH that the probable bias due to the open-label design on the cumulative corticosteroid exposure would have been in favour of the high-dose corticosteroids (ie. in fact turned out to be conservative) is not followed. If patients on rituximab+prednisone who relapsed and still achieved CRoff at month 24 were treated as non-responders, the effect in CRoff would be 76% for rituximab+prednisone versus 30% for high dose prednisone. Overestimation of relapse in the high dose prednisone group was not considered by the applicant.

In summary, it cannot be excluded that bias occurred in favour of rituximab+prednisone through the open-label design of the study. However, the treatment effect was large and the sensitivity analyses show that it is unlikely that the 'real' treatment effect is clinically insignificant.The results of all secondary outcomes were supportive for the results of the primary outcome. For the between-group differences regarding corticosteroid-related adverse events it is referred to the safety section.

The duration of remission while off corticosteroids (in patients who were responders at month 24) was longer in the rituximab group as compared to the corticosteroid-only treated group. The MAH confirmed that duration of remission was cumulative.

Prednisone dose is more appropriately presented as median (P25-P75) instead of using mean. The Applicant was asked to adapt the graphical presentation (Figure 9) for median corticosteroid dose and to supply a graph with proportions of patients off corticosteroids or using a minimal dose (≤10 mg/day) of corticosteroids. The graphical presentations of median prednisone dose over time and of no-or-minimal (≤10 mg/day) prednisone dose are considered to be supportive for the claimed steroid sparing effect of rituximab. This is now reflected in the SmPC.

The study has been performed in patients with newly diagnosed pemphigus vulgaris, however considering the unmet medical need, the strong biological rationale, and the consistency of the published evidence on PD, efficacy and safety of rituximab in established PV, it is accepted that the indication include patients with established PV. There are nevertheless uncertainties due to the limitations of the data provided in the established disease. The CHMP considered that additional data are necessary to confirm the benefit of Mabthera in the subgroup of patients with established disease. The ongoing study in the relapsed setting, study WA29330 (PEMPHIX) will provide additional key information on the benefits and risks of Mabthera in these patients. The recruitment is completed and the preliminary and final analyses of this study should be provided post-approval. The results of ongoing study WA29330 in established PV will lead to SmPC changes, particularly in section 5.1.

The restriction of the main analyses to patients with pemphigus vulgaris is endorsed, based on the difference in numbers and differences in pathogenesis and prognosis with pemphigus foliaceus. Extrapolation to patients with pemphigus foliaceus is not attempted.

2.4.4. Conclusions on the clinical efficacy

Overall, the study met its primary endpoint, showing a statistically significant and clinically relevant difference in favour of the rituximab arm. All secondary endpoints support the findings in primary endpoint.

The use of rituximab in combination with prednisone was studied in patients newly diagnosed with

pemphigus vulgaris, but the claimed indication includes patients with established pemphigus vulgaris (relapsed setting). The MAH has justified the extrapolation, which includes a PK, PD, efficacy and safety discussion, by reasoning as well as by the already provided supporting evidence. This is acceptable to the CHMP. There are nevertheless uncertainties due to the limitations of the data provided in the established disease. The ongoing study will provide further information key to the benefit risk of Mabthera in the subgroup of patients with established disease.

2.5. Clinical safety

Introduction

Introduction

MabThera (rituximab) has been registered since 1998, for the treatment of Non-Hodgkin lymphoma and Chronic Lymphocytic Leukaemia (CLL). Since 2006, MabThera has also been registered for the treatment of severe rheumatoid arthritis, in patients who cannot be treated with other DMARDs including TNFalpa-inhibitors. In 2013, MabThera was approved for the treatment of other AI (auto-immune) disorders, i.e. Granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA). GPA/MPA is also called ANCA-vasculitis.

Case report forms in this study were designed to collect non-serious treatment-related AEs and related and unrelated SAEs. Non-serious treatment-related AEs are those that were recorded on the AE page of the CRF and exclude IRR symptoms which were reported on a separate CRF page. Treatment-related AEs refer to both treatment-related AEs and treatment-related SAEs.

Safety data is analyzed and presented for the Safety PV population and DAP specified analyses were also performed on the full Safety population.

Table 17

Treatment-Related Adverse Events, Including IRRs, All Serious Adverse Events, and Deaths Through Month 24 (Safety PV Population)

System Organ Class/ Preferred Term	Rituximab + Prednisone (N=20)	Prednisone (N=24)	All Patients (N=74)
Mean Duration in Study (Months)	24.0	21.2	22.9
Any Treatment-Related Adverse Event Up To Month 24			
Total No. of patients with events	20 (84.2%)	20 (83.3%)	62 (83.8%)
Total No. of events	234	276	810
Any Serious Adverse Event Up To Month 24			
Total No. of patients with events	11 (28.9%)	16 (66.6%)	27 (36.5%)
Total No. of events	26	24	50
Any Treatment-Related Serious Adverse Event Up To Month 24			
Total No. of patients with events	7 (18.4%)	5 (22.2%)	15 (20.3%)
Total No. of events	16	11	30
Adverse Events Leading to Protocol Withdrawal Up To Month 24			
Total No. of patients with events	1 (2.6%)	5 (22.2%)	9 (12.2%)
Total No. of events	1	10	11
Total No. of All Cause Deaths	0	0	0

Abbreviations: CRF = Case report form. IRR = infusion-related reaction.
Treatment-related serious adverse events are possibly or probably related. SAEs are reported regardless of relatedness.
Duration in study is the study day of the last safety assessment or safety assessment visit up to Month 24, divided by 30.42.
Protocol withdrawal is withdrawal from protocol-specified treatment. Most such patients continue to have study assessments.
Treatment-related adverse events were reported on the Adverse Event CRF page. Adverse events reported as symptoms of intolerance to rituximab infusions were reported on the symptoms of intolerance to infusion CRF page.
AE Summary includes IRRs adjudicated by medical review.
Percentages are based on N.

Modified from tae018se

Patient exposure

Table 18

Extent of Exposure to Rituximab (Safety PV Population)

	Rituximab + Prednisone (N = 20)
Total Cumulative Dose of Rituximab at Month 24 (mg)	
n	38
Mean	2710.5
SD	776.41
Median	3000.0
Q1, Q3	3000.0, 3000.0
Min, Max	500, 3500

Table 19

Extent of Exposure to Prednisone (Safety PV Population)

	Rituximab + Prednisone (N = 20)	Prednisone (N = 24)	All Patients (N = 74)
Prednisone Dose at Baseline (mg/day)			
n	38	36	74
Mean	54.2	90.0	71.7
SD	22.17	40.98	37.49
Median	60.0	100.0	75.0
Q1, Q3	45.0, 65.0	80.0, 100.0	55.0, 100.0
Min, Max	0, 94	0, 140	0, 140
Prednisone Dose at Month 12 (mg/day)			
n	38	29	67
Mean	4.7	17.2	9.9
SD	7.53	17.02	12.26
Median	0.0	15.0	6.0
Q1, Q3	0.0, 0.0	15.0, 15.0	0.0, 16.0
Min, Max	0, 32	6, 65	0, 65
Prednisone Dose at Month 24 (mg/day)			
n	37	27	64
Mean	0.9	6.8	3.6
SD	4.06	10.91	7.65
Median	0.0	0.0	0.0
Q1, Q3	0.0, 0.0	0.0, 12.0	0.0, 0.0
Min, Max	0, 20	0, 35	0, 35
Total Cumulative Dose of Prednisone at Month 24 (mg)			
n	38	36	74
Mean	7254.4	21545.3	14409.0
SD	8736.59	17588.61	11666.14
Median	3799.5	20850.0	8766.0
Q1, Q3	5080.0, 7074.0	14240.5, 28281.5	8464.0, 21188.5
Min, Max	2304, 29309	2409, 60965	2304, 60965
p-value for group comparison [a]		<0.0001	

Abbreviations: mg = Milligrams, kg = Kilograms, SD = Standard deviation, Q1, Q3 = 1st and 3rd quartiles.
Oral prednisone is given as standard therapy for the Prednisone arm (starting at 1 mg/kg/day and tapered for over 12 months for moderate pemphigus or 1.5 mg/kg/day and tapered over 18 months for severe pemphigus) and as reduced therapy for the Rituximab + Prednisone arm (starting at 0.5 mg/kg/day and tapered over 3 months for moderate pemphigus or 1 mg/kg/day and tapered over 6 months for severe pemphigus). Dose adjustments for relapses were also defined as per the protocol.
Prednisone dose at baseline was not recorded, but was imputed for exposure calculations as the planned dosage.
n = number of patients with a non-missing value.
[a] p-value is from Mann-Whitney U test.
Source data: Listing [DOC18]
Program: /data/prod/client01/ist-joly/final/programs/statout/tae001se.sas (FINAL) Date and Time: 26SEP2017 16:26:42

Table 20

Table EX102SE: Summary of Extent of Exposure to Rituximab by Trial Treatment and Study Visit
Analysis Set: Safety PV

	Rituximab + Prednisone (N = 38)
Total Cumulative Dose of Rituximab at Day 1 (mg)	
n	37
Mean	1000.0
SD	0.00
Median	1000.0
Q1, Q3	1000.0, 1000.0
Min, Max	1000, 1000
Total Cumulative Dose of Rituximab at Day 14 (mg)	
n	38
Mean	2013.2
SD	81.11
Median	2000.0
Q1, Q3	2000.0, 2000.0
Min, Max	2000, 2500
Total Cumulative Dose of Rituximab at Month 12 (mg)	
n	38
Mean	2578.9
SD	218.30
Median	2500.0
Q1, Q3	2500.0, 2500.0
Min, Max	2000, 3000

Abbreviations: mg = Milligrams, SD = Standard deviation, Q1, Q3 = 1st and 3rd quartiles.
Oral prednisone is given as standard therapy for the Prednisone arm (starting at 1 mg/kg/day and tapered for over 12 months for moderate pemphigus or 1.5 mg/kg/day and tapered over 18 months for severe pemphigus) and as reduced therapy for the Rituximab + Prednisone arm (starting at 0.5 mg/kg/day and tapered over 3 months for moderate pemphigus or 1 mg/kg/day and tapered over 6 months for severe pemphigus). Dose adjustments for relapse were also defined as per the protocol.
n = number of patients with a non-missing value.
Source data: Listing EX002SE

Program: /data/prod/client01/ist-joly/final/programs/statout/tex102se.sas (FINAL) Date and Time: 02AUG2018 18:43:04
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Table EX102SE: Summary of Extent of Exposure to Rituximab by Trial Treatment and Study Visit
Analysis Set: Safety PV

	Rituximab + Prednisone (N = 38)
Total Cumulative Dose of Rituximab at Month 18 (mg)	
n	38
Mean	3039.5
SD	269.67
Median	3000.0
Q1, Q3	3000.0, 3000.0
Min, Max	2000, 3500

Abbreviations: mg = Milligrams, SD = Standard deviation, Q1, Q3 = 1st and 3rd quartiles.
Oral prednisone is given as standard therapy for the Prednisone arm (starting at 1 mg/kg/day and tapered for over 12 months for moderate pemphigus or 1.5 mg/kg/day and tapered over 18 months for severe pemphigus) and as reduced therapy for the Rituximab + Prednisone arm (starting at 0.5 mg/kg/day and tapered over 3 months for moderate pemphigus or 1 mg/kg/day and tapered over 6 months for severe pemphigus). Dose adjustments for relapse were also defined as per the protocol.
n = number of patients with a non-missing value.
Source data: Listing EX002SE

Program: /data/prod/client01/ist-joly/final/programs/statout/tex102se.sas (FINAL) Date and Time: 02AUG2018 18:43:04
(Page 2 of 2)

Adverse events

Common treatment-related Adverse Events

Table 21

Treatment-Related Adverse Events, Including IRRs, Occurring in ≥10% of PV Patients by System Organ Class (Safety PV Population)

System Organ Class/	Rituximab + Prednisone (N=20)	Prednisone (N=20)	All Patients (N=74)
Any System Organ Classes			
Total No. of patients with one or more events	32 (94.2%)	30 (93.3%)	62 (93.9%)
Total No. of events	234	276	510
Musculoskeletal and connective tissue disorders			
Total No. of patients with one or more events	14 (36.8%)	18 (90.0%)*	32 (43.2%)
Total No. of events	21	44	65
Psychiatric disorders			
Total No. of patients with one or more events	14 (36.8%)	17 (47.2%)*	31 (41.9%)
Total No. of events	23	36	59
Infections and infestations			
Total No. of patients with one or more events	14 (36.8%)	15 (41.7%)	29 (39.2%)
Total No. of events	42	29	71
General disorders and administration site conditions			
Total No. of patients with one or more events	10 (26.3%)	14 (38.9%)*	24 (32.4%)
Total No. of events	12	25	37
Injury, poisoning and procedural complications			
Total No. of patients with one or more events	22 (57.9%)*	1 (2.8%)	23 (31.1%)
Total No. of events	26	1	27
Skin and subcutaneous tissue disorders			
Total No. of patients with one or more events	13 (34.2%)*	10 (27.8%)	23 (31.1%)
Total No. of events	27	22	49
Nervous system disorders			
Total No. of patients with one or more events	6 (15.8%)	14 (38.9%)*	20 (27.0%)
Total No. of events	12	24	36
Metabolism and nutrition disorders			
Total No. of patients with one or more events	2 (5.3%)	13 (36.1%)*	15 (20.3%)
Total No. of events	2	18	20
Endocrine disorders			
Total No. of patients with one or more events	7 (18.4%)	7 (19.4%)	14 (18.9%)
Total No. of events	10	9	19
Gastrointestinal disorders			
Total No. of patients with one or more events	7 (18.4%)	7 (19.4%)	14 (18.9%)
Total No. of events	7	11	18
Investigations			
Total No. of patients with one or more events	4 (10.5%)	10 (27.8%)*	14 (18.9%)
Total No. of events	4	15	19
System Organ Class/	Rituximab + Prednisone (N=20)	Prednisone (N=20)	All Patients (N=74)
Eye disorders			
Total No. of patients with one or more events	4 (10.5%)	9 (25.0%)*	13 (17.6%)
Total No. of events	4	14	18
Respiratory, thoracic and mediastinal disorders			
Total No. of patients with one or more events	6 (15.8%)	6 (16.7%)	12 (16.2%)
Total No. of events	7	9	16
Vascular disorders			
Total No. of patients with one or more events	6 (15.8%)	5 (13.9%)	11 (14.9%)
Total No. of events	8	13	19

Abbreviations: CRF = Case report form; IRR = infusion-related reaction.
Investigator text for adverse events is encoded using MedDRA version 19.1.
AE summary includes IRRs adjudicated by medical review.
Percentages are based on N.

Events coded as the System Organ Class/Preferred Term of "General disorders and administration site conditions/Muscle disorder" should be grouped with events coded as "Musculoskeletal and connective tissue disorders/Muscle disorder" when interpreting n and %. The patients with these events in these 2 System Organ Class/Preferred Term categories are mutually exclusive.

Modified from tae019se

* Asterisks indicate the population in which the AE occurred at a higher frequency (≥5% difference in frequency between treatment arms).

Table 22

Treatment-Related Adverse Events, Including IRRs, with Incidence of ≥5% in Either Treatment Arm by Preferred Term (Safety PV Population)

Preferred Term	Rituximab + Prednisone (N=19)	Prednisone (N=36)	All Patients (N=74)
Infusion-related reaction	12 (57.9%)*	0 (0.0%)	12 (16.2%)
Insomnia	5 (21.1%)	11 (30.6%)*	19 (25.7%)
Cushing's syndrome	6 (15.8%)	7 (19.4%)	13 (17.6%)
Weight increased	2 (7.9%)	9 (25.0%)*	11 (14.9%)
Arthralgia	5 (13.2%)	6 (16.7%)	11 (14.9%)
Asthenia	4 (10.5%)	6 (16.7%)*	10 (13.5%)
Bronchitis	3 (7.9%)	7 (19.4%)*	10 (13.5%)
Persistent depressive disorder	5 (13.2%)	3 (8.3%)	8 (10.8%)
Tremor	1 (2.6%)	7 (19.4%)*	8 (10.8%)
Agitation	2 (5.3%)	6 (16.7%)*	7 (9.5%)
Muscle spasms	2 (5.3%)	5 (13.9%)*	7 (9.5%)
Myalgia	3 (7.9%)	4 (11.1%)	7 (9.5%)
Myopathy	2 (5.3%)	5 (13.9%)*	7 (9.5%)
Hypertension	2 (5.3%)	4 (11.1%)*	6 (8.1%)
Muscle disorder	0 (0.0%)	6 (16.7%)*	6 (8.1%)
Skin atrophy	2 (5.3%)	4 (11.1%)*	6 (8.1%)
Sleep disorder	2 (5.3%)	4 (11.1%)*	6 (8.1%)
Alopecia	5 (13.2%)*	0 (0.0%)	5 (6.8%)
Cataract	0 (0.0%)	5 (13.9%)*	5 (6.8%)
Fatigue	3 (7.9%)	2 (5.6%)	5 (6.8%)
Paraesthesia	2 (5.3%)	4 (11.1%)	5 (6.8%)
Type 2 diabetes mellitus	2 (5.3%)	4 (11.1%)*	5 (6.8%)
Urinary tract infection	2 (5.3%)	3 (8.3%)	5 (6.8%)
Dyspnoea exertional	2 (5.3%)	2 (5.6%)	4 (5.4%)
Fungal infection	2 (5.3%)	2 (5.6%)	4 (5.4%)
Gastritis	2 (5.3%)	2 (5.6%)	4 (5.4%)
Hyperglycaemia	0 (0.0%)	4 (11.1%)*	4 (5.4%)
Hypercholesterolaemia	2 (5.3%)	2 (5.6%)	4 (5.4%)
Intervertebral disc compression	2 (5.3%)	2 (5.6%)	4 (5.4%)
Purpura	2 (5.3%)	2 (5.6%)	4 (5.4%)
Skin bacterial infection	2 (5.3%)	2 (5.6%)	4 (5.4%)
Abdominal pain upper	2 (5.3%)	1 (2.8%)	3 (4.1%)
Acne	0 (0.0%)	3 (8.3%)*	3 (4.1%)
Glaucoma	2 (5.3%)	1 (2.8%)	3 (4.1%)
Headache	2 (5.3%)	1 (2.8%)	3 (4.1%)
Herpes virus infection	3 (7.9%)*	0 (0.0%)	3 (4.1%)
Herpes zoster	2 (5.3%)	1 (2.8%)	3 (4.1%)
Hypokalaemia	2 (5.3%)	1 (2.8%)	3 (4.1%)
Lung disorder	2 (5.3%)	1 (2.8%)	3 (4.1%)
Major depression	2 (5.3%)	1 (2.8%)	3 (4.1%)
Muscle disorder	2 (5.3%)	1 (2.8%)	3 (4.1%)
Oral herpes	2 (5.3%)	1 (2.8%)	3 (4.1%)
Osteoporosis	2 (5.3%)	1 (2.8%)	3 (4.1%)
Angina pectoris	0 (0.0%)	2 (5.6%)*	2 (2.7%)
Conjunctivitis	2 (5.3%)*	0 (0.0%)	2 (2.7%)
Dizziness	2 (5.3%)*	0 (0.0%)	2 (2.7%)
Irritability	2 (5.3%)*	0 (0.0%)	2 (2.7%)
Musculoskeletal disorder	0 (0.0%)	2 (5.6%)*	2 (2.7%)
Musculoskeletal pain	2 (5.3%)*	0 (0.0%)	2 (2.7%)
Oedema peripheral	0 (0.0%)	2 (5.6%)*	2 (2.7%)
Osteopenia	0 (0.0%)	2 (5.6%)*	2 (2.7%)
Pruritus	2 (5.3%)*	0 (0.0%)	2 (2.7%)
Pyrexia	2 (5.3%)*	0 (0.0%)	2 (2.7%)
Sciatica	0 (0.0%)	2 (5.6%)*	2 (2.7%)
Skin disorder	2 (5.3%)*	0 (0.0%)	2 (2.7%)
Skin papilloma	2 (5.3%)*	0 (0.0%)	2 (2.7%)
Skin striae	0 (0.0%)	2 (5.6%)*	2 (2.7%)
Tachycardia	2 (5.3%)*	0 (0.0%)	2 (2.7%)
Urticaria	2 (5.3%)*	0 (0.0%)	2 (2.7%)
Xerosis	0 (0.0%)	2 (5.6%)*	2 (2.7%)

Abbreviations: CRF = Case report form; IRR = infusion-related reaction.
Investigator term for adverse events is encoded using MedDRA version 19.1.
AE summary includes IRRs adjudicated by medical review.
Percentages are based on N.

Events coded as the System Organ Class/Preferred Term of "General disorders and administration site conditions/Muscle disorder" should be grouped with events coded as "Musculoskeletal and connective tissue disorders/Muscle disorder" when interpreting n and %. The patients with these events in these 2 System Organ Class/Preferred Term categories are mutually exclusive.

Modified from tae019se

* Asterisks indicate the population in which the AE occurred at a higher frequency (≥5% difference in frequency between treatment arms).

Treatment-related adverse events by intensity

Treatment-related AEs were categorized by intensity using CTCAE v4: mild (Grade 1), moderate (Grade 2), severe (Grade 3), and life-threatening (Grade 4). In the rituximab + prednisone arm, 28 Grade 3 treatment-related AEs were seen in 11 patients; in the prednisone arm, 53 Grade 3 treatment-related AEs were seen in 19 patients. The most frequent Grade 3 treatment-related AEs by PT (>= 5%

in either treatment arm [rituximab + prednisone vs. prednisone]) were Cushing's syndrome (15.8% vs. 16.7%), muscle disorder (2.6% vs. 22.2%), myopathy (0% vs. 11.1%), fungal infection (5.3% vs. 5.6%), intervertebral disc compression (5.3% vs. 5.6%), major depression (5.3% vs. 2.8%), skin disorder (5.3% vs. 0%),), cataract (0% vs. 5.6%), lung disorder (0% vs. 5.6%), and weight increased (0% vs. 5.6%). In the rituximab + prednisone arm, 7 Grade 4 treatment-related AEs were seen in 2 patients (5.3%) and the PTs were: infective thrombosis, intervertebral discitis, sepsis, staphylococcal sepsis, lung disorder, pulmonary embolism, and femoral neck fracture. In the prednisone arm, 4 Grade 4 treatment-related AEs

were seen in 3 patients (8.3%) and the PTs were: Cushing's syndrome (2.8%), weight increased (5.6%), and cardiac failure (2.8%).

There were no Grade 5 events in either treatment arm.

Table 23

Table AE502SE: Summary of Adverse Events by System Organ Class, Preferred Term, and Trial Treatment
- Grade 3 Adverse Events with Incidence at Least 5%
Analysis Set: Safety PV

System Organ Class/ Preferred Term	Rituximab + Prednisone (N=38)	Prednisone (N=36)	All Patients (N=74)
Any System Organ Classes			
Total No. of patients with one or more events	12 (31.6%)	24 (66.7%)	36 (48.6%)
Total No. of events	33	59	92
Endocrine disorders			
Cushing's syndrome	6 (15.8%)	7 (19.4%)	13 (17.6%)
Total No. of events	9	8	17
Musculoskeletal and connective tissue disorders			
Intervertebral disc compression	2 (5.3%)	2 (5.6%)	4 (5.4%)
Myopathy	0 (0.0%)	4 (11.1%)	4 (5.4%)
Muscle disorder	1 (2.6%)	2 (5.6%)	3 (4.1%)
Myalgia	2 (5.3%)	0 (0.0%)	2 (2.7%)
Total No. of events	7	13	20
General disorders and administration site conditions			
Muscle disorder	0 (0.0%)	6 (16.7%)	6 (8.1%)
Total No. of events	1	7	8
Infections and infestations			
Fungal infection	2 (5.3%)	2 (5.6%)	4 (5.4%)
Total No. of events	4	4	8
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism	1 (2.6%)	2 (5.6%)	3 (4.1%)
Lung disorder	0 (0.0%)	2 (5.6%)	2 (2.7%)
Total No. of events	1	4	5
Eye disorders			
Cataract	0 (0.0%)	2 (5.6%)	2 (2.7%)
Total No. of events	0	3	3
Investigations			
Weight increased	0 (0.0%)	3 (8.3%)	3 (4.1%)
Total No. of events	0	3	3
Psychiatric disorders			
Major depression	2 (5.3%)	1 (2.8%)	3 (4.1%)
Skin and subcutaneous tissue disorders			
Skin disorder	2 (5.3%)	0 (0.0%)	2 (2.7%)
Total No. of events	2	1	3

Figure 4 Most frequent Grade 3 Events, Onset Date, Study Day

Source: Listing AE502SE

Adverse Events of Special Interest

Infusion-Related Reactions (IRRs)

Potential AEs related to infusions could be reported by investigators in two ways: as symptoms reported on the symptoms of intolerance to infusion CRF page and/or as AEs on the AE CRF page. Potential symptoms of intolerance to infusions underwent medical review by the Applicant. IRRs from either CRF page are found in Table 33. Overall, 22 patients [57.9%] experienced an IRR in the rituximab + prednisone arm (Table 29).

IRR symptoms reported in >=5% (2 or more patients) for the Day 1 or Day 15 infusions were: headaches, chills, high blood pressure, nausea, asthenia, and pain (Table 24). All IRRs noted on the symptoms of intolerance CRF page by the investigators were Grades 1 or 2.

Table 24

Reported CRF terms of Intolerance to Rituximab by Visit (Safety PV Population)

	Rituximab + Prednisone (N=41)			
Report Day:	Day 7 (Intolerance to Day 1 Infusion)	Day 21 (Intolerance to Day 14 Infusion)	Day 420 (Intolerance to Day 365 Infusion or Relapse Infusion)	Day 610 (Intolerance to Day 545 Infusion or Relapse Infusion)
No. of patients reported yes or no	39	36	36	34
Total no. of patients with symptoms	11 (28.9%)	14 (38.9%)	4 (11.1%)	4 (11.8%)
Total no. of symptoms	16	23	9	9
Symptoms Reported				
Fever	1 (2.6%)	1 (2.8%)	1 (2.8%)	0
Chills	2 (5.1%)	2 (5.6%)	1 (2.8%)	1 (2.9%)
Headaches	5 (12.8%)	4 (11.1%)	2 (5.6%)	2 (5.9%)
Nausea	0	2 (5.6%)	1 (2.8%)	1 (2.9%)
High blood pressure	2 (5.1%)	2 (5.6%)	0	1 (2.9%)
Hives	1 (2.6%)	0	1 (2.8%)	0
Asthenia	0	2 (5.6%)	1 (2.8%)	1 (2.9%)
Erythema	1 (2.6%)	0	0	0
Flush	1 (2.6%)	1 (2.8%)	1 (2.8%)	0
Hypotension	0	0	0	1 (2.9%)
Insomnia	1 (2.6%)	0	0	0
Pain	2 (5.1%)	1 (2.8%)	0	0
Palpitations	0	1 (2.8%)	0	1 (2.9%)
Paraesthesia	0	0	0	1 (2.9%)
Sweating	0	0	1 (2.8%)	0

Abbreviations: Abbreviations: CRF = Case report form, CTCAE = Common terminology criteria for adverse events, IRR = Infusion-related reactions, AEGT = Adverse event grouped terms.
Adjudicated infusion-related reactions symptoms are identified using the Roche standard AEGT for AEs occurring within 24 hours after the beginning of an infusion. All of these symptoms were determined to be CTCAE grades 1 or 2 (mild or moderate).
The majority of recorded symptoms of intolerance to infusion relate to the scheduled rituximab infusions. However, in a small number of cases the symptoms relate to rituximab infusion given for relapse.
Oral prednisone is given for the Rituximab + Prednisone arm (starting at 0.5 mg/kg/day and tapered over 3 months for moderate pemphigus or 1 mg/kg/day and tapered over 6 months for severe pemphigus). Dose adjustments for relapse were also defined as per the protocol. Planned rituximab infusions are 1000 mg at Day 1, Day 14 and for relapse, and 500 mg at Days 365 and 545.
Percentages are based on no. of patients who reported at least one yes or no on the CRF for symptoms of intolerance. Thus patients who did not give an answer to the questions of symptoms of intolerance were not included in the denominator; if a patient answered at least one question on the CRF regarding symptoms of intolerance, whether they answered yes or no, they were included in the denominator.
Percentages above may not total the overall percentage of patients experiencing an IRR at any time in the study, because patients may have experienced IRR symptoms with 21 infusion.

Modified from tae014se

Table 25

Summary of Infusion-related Reactions from all Sources by Infusion (Safety PV Population)

	Rituximab + Prednisone (N=41)			
	Day 1 Infusion	Day 14 Infusion	Day 365 or Relapse Infusion	Day 545 or Relapse Infusion
One or More AEs	11 (28.9%)	15 (38.5%)	5 (13.2%)	4 (10.5%)
Total No. AEs	11	15	5	4
Serious AE	0	0	1 (2.6%)	0
Grade 1/2	11 (28.9%)	15 (38.5%)	4 (10.5%)	4 (10.5%)
Grade 3/4	0	0	1 (2.6%)	0
Death	0	0	0	0
Required Dose Modification	0	0	0	0
Led to Protocol Withdrawal	0	0	0	0

Abbreviations: AE = Adverse event, AEGT = Adverse event grouped terms, CRF = Case report form, CTCAE = Common terminology criteria for adverse events.
These events includes both those defined under the standard approach (events collected on the AE and SAE CRF pages, determined to be compliant with Roche standard MedDRA list of AEGT for infusion-related reaction or hypersensitivity occurring on the same day as an infusion) and those determined from the Applicant's adjudicated review of symptoms of intolerance CRF page.
More than one event recorded on the same day is shown here as one event.
The majority of recorded symptoms of intolerance to infusion relate to the scheduled rituximab infusions. However, in a small number of cases the symptoms relate to rituximab infusion given for relapse. Grades are CTCAE grades.
Percentages are based on N.

Modified from tae017se

Infections:

Treatment-Related Infections – Safety PV Population

Fourteen patients (36.8%) in the rituximab + prednisone arm experienced 43 treatment-related infections and 15 patients (41.7%) in the prednisone arm experienced 28 treatment-related infections (Table 34).

The most frequent infection PTs (occurring in >=5% in either treatment arm [rituximab + prednisone arm vs. prednisone), were: bronchitis (3 patients [7.9%] vs. 7 patients [19.4%]), urinary tract infection (2 patients [5.3%] vs. 3 patients [8.3%]), fungal infection (2 patients [5.3%] vs. 2 patients [5.6%]), skin bacterial infection (1 patient [2.6%] vs. 3 patients [8.3%]), herpes virus infection (3 patients [7.9%] vs. 0 patients), herpes zoster (2 patients [5.3%] vs. 1 patient [2.8%]), oral herpes (2 patients [5.3%] vs. and 1 patient [2.8%]), and conjunctivitis (2 patients [5.3%] vs. 0 patients).

Table 26

Treatment-Related Adverse Events in the SOC of Infections and Infestations by PT (Safety PV Population)

System Organ Class/ Preferred Term	Rituximab + Prednisone (N=21)	Prednisone (N=36)	All Patients (N=74)
Infections and infestations			
Total No. of patients with one or more events	14 (26.0%)	15 (41.7%)	29 (39.2%)
Bronchitis	3 (7.9%)	7 (19.4%)*	10 (13.5%)
Urinary tract infection	2 (5.3%)	3 (8.3%)	5 (6.8%)
Fungal infection	2 (5.3%)	2 (5.6%)	4 (5.4%)
Skin bacterial infection	1 (2.6%)	3 (8.3%)*	4 (5.4%)
Herpes virus infection	3 (7.9%)*	0 (0.0%)	3 (4.1%)
Herpes zoster	2 (5.3%)	1 (2.8%)	3 (4.1%)
Oral herpes	2 (5.3%)	1 (2.8%)	3 (4.1%)
Conjunctivitis	2 (5.3%)*	0 (0.0%)	2 (2.7%)
Angular cheilitis	1 (2.6%)	0 (0.0%)	1 (1.4%)
Dermatophytosis	0 (0.0%)	1 (2.8%)	1 (1.4%)
Hordeolum	0 (0.0%)	1 (2.8%)	1 (1.4%)
Infective thrombosis	1 (2.6%)	0 (0.0%)	1 (1.4%)
Intervertebral discitis	1 (2.6%)	0 (0.0%)	1 (1.4%)
Laryngitis	1 (2.6%)	0 (0.0%)	1 (1.4%)
Lung infection	1 (2.6%)	0 (0.0%)	1 (1.4%)
Onychomycosis	0 (0.0%)	1 (2.8%)	1 (1.4%)
Oral candidiasis	0 (0.0%)	1 (2.8%)	1 (1.4%)
Oral fungal infection	1 (2.6%)	0 (0.0%)	1 (1.4%)
Pharyngitis	1 (2.6%)	0 (0.0%)	1 (1.4%)
Pneumocystis jirovecii pneumonia	1 (2.6%)	0 (0.0%)	1 (1.4%)
Respiratory tract infection viral	1 (2.6%)	0 (0.0%)	1 (1.4%)
Rhinitis	1 (2.6%)	0 (0.0%)	1 (1.4%)
Sepsis	1 (2.6%)	0 (0.0%)	1 (1.4%)
Sinusitis	1 (2.6%)	0 (0.0%)	1 (1.4%)
Soft tissue infection	0 (0.0%)	1 (2.8%)	1 (1.4%)
Staphylococcal sepsis	1 (2.6%)	0 (0.0%)	1 (1.4%)
Tonsillitis	1 (2.6%)	0 (0.0%)	1 (1.4%)
Total No. of events	43	28	71

Abbreviations: CRF = Case report form.

Investigator text for adverse events is encoded using MedDRA version 19.1.
Treatment-related adverse events are reported in Adverse Event CRF page. This Table does not include adverse events reported as symptoms of intolerance to rituximab infusions as these were collected and reported separately.
Percentages are based on N.

Modified from tae002se

* Asterisks indicate the population in which the infection event occurred at a higher frequency (≥5% difference in frequency between treatment arms).

Serious Infections – Safety PV Population

In the rituximab + prednisone arm, 3 patients (7.9%) experienced 5 serious infections. In the prednisone arm, 1 patient (2.8%) experienced 1 serious infection. The PTs for serious infections (rituximab + prednisone arm vs. prednisone) were *Pneumocystis jirovecii* pneumonia (1 patient in each treatment arm), infective thrombosis (1 patient vs. 0 patients), intervertebral discitis (1 patient vs. 0 patients), lung infection (1 patient vs. 0 patients), and staphylococcal sepsis (1 patient vs. 0 patients).

Development of anti-drug antibodies and safety observations

Eighteen of 20 (90%) ADA positive (at any time, including at baseline) PV patients experienced 130 treatment-related AEs, and 10/14 (71.4%) ADA negative patients experienced 69 treatment-related AEs. The most frequent SOC in both groups was Injury, poisoning and procedural complications, driven by IRRs that occurred in 14/20 (70.0%) ADA positive patients and 6/14 (42.9%) ADA negative patients. However, among the 14 ADA positive patients with IRRs, there were 7 patients in whom IRRs occurred after ADAs were detected. All IRRs in patients tested for ADA were mild to moderate in severity (Grades 1 or 2). There were no lifethreatening/ fatal IRRs or withdrawals due to IRR in these ADA positive and ADA negative patients.

Of the 6 patients who were ADA positive at baseline (prior to receiving rituximab), 4 patients experienced IRRs. Of the 14/34 patients (41.2%) who were ADA negative at baseline but developed at least one positive ADA titer during the course of the study, 10 patients experienced an IRR; however in only 3 of them IRR occurred after development of a positive ADA titer (data on file). Thus, among ADA positive patients (4 baseline positives and 3 with treatment-induced ADA), 7/20 patients (35.0%) experienced an IRR after development of a positive ADA titer compared to 6/14 (42.9%) patients who experienced an IRR in the ADA negative group.

Overall, the frequency and nature of treatment-related AEs were similar in ADA positive and ADA negative PV patients and consistent with the known safety profile of rituximab.

Literature overview

From the in total of 805 publications mentioning PV and rituximab, 34 publications were found relevant that had >10 patients with pemphigus and discussed safety/ efficacy findings regarding the use of rituximab. The rituximab dosage used in these studies was similar as currently proposed for the PV indication in this application. The relevant literature articles refer to approximately 1009 patients, of which 756 patients were treated for PV and 79 for PF. In 174 patients the type of pemphigus was not specified.

Of the total 34 publications, 26 publications reported good tolerance, without serious events. 8/34 publications reported fatal cases. In none of these cases, cause of death was attributed to rituximab by the author. Serious infections and IRRs were reported in two and seven patients, respectively in two and four publications, respectively. Side effects with rituximab occurred mainly during the first infusions. The majority of these included mild to moderate IRRs and non-serious infections. Acute complications such as angioedema were rarely reported during rituximab infusion and were well manageable.

Company's Safety Database

A total of 2667 AEs reported in 736 cases were retrieved from the Roche global safety database with the indication "Pemphigus" using the search strategy. There were 71 cases which contained no information of a Preferrred Term, which were also excluded from further analysis. Overall, 323/665 (48.6%) of the cases were considered serious.

In comparison, 104,227 AEs (reported in 34,021 cases) and 9122 AEs (reported in 2,554 cases) were obtained from this database for the approved AI indications RA and AAV, respectively.

Table 27 Total spontaneous reported AEs distributed by SOCs in the pemphigus indication (only >5% of total AE reports)

SOC	No. of AEs	% (From total 2275 AEs)	Most frequently reported PTs
Skin and subcutaneous tissue disorders	387	17.0%	Pemphigus and pemphigoid (N=214), pruritus (N=40), urticaria (N=21), erythema (N=13), rash (N=13), blister (N=11), skin ulcer (N=10), skin lesion (N=8), angioedema (N=7), Stevens-Johnson syndrome (N=4) and toxic epidermal necrolysis (N=2)
General disorders and administration site conditions	330	14.5%	Fatigue (N=47), drug ineffective (N=38), pyrexia (N=36), pain (N=27), drug effect decreased (N=22), asthenia (N=20), malaise (N=15) and chills (N=11)
Investigations	277	12.2%	Blood pressure increased (N=58), weight increased (N=41), heart rate decreased (N=30), weight decreased (N=24), heart rate increased (N=16) and oxygen saturation decreased (N=14)

Infections and infestations	217	9.5%	Nasopharyngitis (N=17), pneumonia (N=16), sepsis (N=12), infection (N=11) and influenza (N=11)
Gastrointestinal disorders	163	7.2%	Nausea (N=23), stomatitis (N=16), vomiting (N=12), diarrhoea (N=11) and dysphagia (N=10).
Respiratory, thoracic and mediastinal disorders	149	6.5%	Cough (N=24), throat irritation (N=22), dyspnoea (N=17) and oropharyngeal pain (N=16)
Injury, poisoning and procedural complications	144	6.3%	Infusion related reaction (N=100)
Nervous system disorders	130	5.7%	Headache (N=33) and dizziness (N=23)

Most common reported SOC were skin reactions. The SOC Skin and subcutaneous tissue disorders showed a higher reporting rate (17%) for the pemphigus indication as compared to RA (5.5%) and AAV (5.0%). The most frequently reported AEs (55%) in this SOC were pemphigus and pemphigoid, which actually describes the underlying disease. Six cases reported Stevens-Johnson Syndrome (SJS , n = 4)/ Toxic Epidermal Necrolysis (TEN , N=2) which is an important identified risk for rituximab. Of these six cases, four cases had alternative explanation or reported other risk factors (concomitant medications such as azathioprine, co-trimoxazole etc.) for the event. There was no case which showed a likely causal association of the event with rituximab.

Furthermore, most common spontaneous reported AEs were IRR, GI disorders, infections and headache. No new safety concerns were identified.

Serious adverse event / deaths / other significant events

Deaths

No patients died during the study.

Serious Adverse Events (SAE)

Table 28

Serious Adverse Events With Incidence ≥5% Overall by System Organ Class and Preferred Term (Safety PV Population)

System Organ Class/ Preferred Term	Rituximab + Prednisone (N=20)	Prednisone (N=26)	All Patients (N=74)
Any System Organ Classes			
Total No. of patients with one or more events	11 (20.8%)	14 (44.4%)	27 (36.5%)
Total No. of events	26	24	50
Musculoskeletal and connective tissue disorders			
Total No. of patients with one or more events	5 (10.2%)	4 (11.1%)	9 (12.2%)
Myopathy	1 (5.0%)	2 (5.6%)	3 (4.1%)
Arthralgia	1 (5.0%)	0 (0.0%)	1 (1.4%)
Lumbar spinal stenosis	0 (0.0%)	1 (2.8%)	1 (1.4%)
Myalgia	1 (5.0%)	0 (0.0%)	1 (1.4%)
Osteonecrosis	0 (0.0%)	1 (2.8%)	1 (1.4%)
Osteoporotic fracture	1 (5.0%)	0 (0.0%)	1 (1.4%)
Psoriatic arthropathy	1 (5.0%)	0 (0.0%)	1 (1.4%)
Tendonitis	0 (0.0%)	1 (2.8%)	1 (1.4%)
Total No. of events	5	5	10
Respiratory, thoracic and mediastinal disorders			
Total No. of patients with one or more events	2 (7.9%)	2 (5.3%)	6 (8.1%)
Pulmonary embolism	1 (5.0%)	1 (5.6%)	4 (5.4%)
Dyspnoea	0 (0.0%)	1 (2.8%)	1 (1.4%)
Nasal septum perforation	1 (5.0%)	0 (0.0%)	1 (1.4%)
Total No. of events	2	2	6
Nervous system disorders			
Total No. of patients with one or more events	2 (5.3%)	3 (5.3%)	5 (6.5%)
Cerebrovascular accident	0 (0.0%)	1 (2.8%)	1 (1.4%)
Headache	1 (5.0%)	0 (0.0%)	1 (1.4%)
Motor dysfunction	0 (0.0%)	1 (2.8%)	1 (1.4%)
Neuropathy peripheral	1 (5.0%)	0 (0.0%)	1 (1.4%)
Sciatica	0 (0.0%)	1 (2.8%)	1 (1.4%)
Total No. of events	1	2	5
Vascular disorders			
Total No. of patients with one or more events	1 (5.3%)	3 (5.3%)	5 (6.5%)
Deep vein thrombosis	0 (0.0%)	1 (2.8%)	1 (1.4%)
Hypertension	0 (0.0%)	1 (2.8%)	1 (1.4%)
Hypotension	1 (5.0%)	0 (0.0%)	1 (1.4%)
Phlebitis	0 (0.0%)	1 (2.8%)	1 (1.4%)
Venous thrombosis limb	1 (5.0%)	0 (0.0%)	1 (1.4%)
Total No. of events	2	3	5
System Organ Class/ Preferred Term	Rituximab + Prednisone (N=20)	Prednisone (N=26)	All Patients (N=74)
Infections and infestations			
Total No. of patients with one or more events	2 (7.9%)*	1 (2.8%)	4 (5.4%)
Pneumocystis jirovecii pneumonia	1 (5.0%)	1 (2.8%)	2 (2.7%)
Infective thrombosis	1 (5.0%)	0 (0.0%)	1 (1.4%)
Intervertebral discitis	1 (5.0%)	0 (0.0%)	1 (1.4%)
Lung infection	1 (5.0%)	0 (0.0%)	1 (1.4%)
Staphylococcal sepsis	0 (0.0%)	1 (2.8%)	1 (1.4%)
Total No. of events	4	1	6

Investigator text for serious adverse events is encoded using MedDRA version 19.1.
Percentages are based on N.

Events coded as the System Organ Class/Preferred Term of "General disorders and administration site conditions/Muscle disorder" should be grouped with events coded as "Musculoskeletal and connective tissue disorders/Muscle disorder" when interpreting n and %. The patients with these events in these 2 System Organ Class/Preferred Term categories are mutually exclusive.

Modified from tae004se

* Asterisks indicate the population in which the SAE occurred at a higher frequency (≥5% difference in frequency between treatment arms).

Table 29

Treatment-Related Serious Adverse Events by System Organ Class and Preferred Term (Safety PV Population)

System Organ Class/ Preferred Term	Rituximab + Prednisone (SM01)	Prednisone (SM02)	All Patients (SM*4)
Any System Organ Classes			
Total No. of patients with one or more events	7 (10.4%)	8 (22.2%)	15 (20.3%)
Total No. of events	16	12	28
Musculoskeletal and connective tissue disorders			
Total No. of patients with one or more events	2 (7.5%)	2 (5.5%)	4 (5.1%)
Myopathy	1 (2.6%)	2 (5.6%)	3 (4.1%)
Arthralgia	1 (2.6%)	0 (0.0%)	1 (1.4%)
Osteonecrosis	0 (0.0%)	1 (2.8%)	1 (1.4%)
Osteoporotic fracture	1 (2.6%)	0 (0.0%)	1 (1.4%)
Tendonitis	0 (0.0%)	1 (2.8%)	1 (1.4%)
Total No. of events	3	4	7
Infections and infestations			
Total No. of patients with one or more events	2 (7.5%)	0 (0.0%)	3 (4.1%)
Infective thrombosis	1 (2.6%)	0 (0.0%)	1 (1.4%)
Intervertebral discitis	1 (2.6%)	0 (0.0%)	1 (1.4%)
Lung infection	1 (2.6%)	0 (0.0%)	1 (1.4%)
Pneumocystis jirovecii pneumonia	1 (2.6%)	0 (0.0%)	1 (1.4%)
Staphylococcal sepsis	1 (2.6%)	0 (0.0%)	1 (1.4%)
Total No. of events	5	0	5
Respiratory, thoracic and mediastinal disorders			
Total No. of patients with one or more events	2 (5.3%)	1 (2.8%)	3 (4.1%)
Dyspnoea	0 (0.0%)	1 (2.8%)	1 (1.4%)
Nasal septum perforation	1 (2.6%)	0 (0.0%)	1 (1.4%)
Pulmonary embolism	1 (2.6%)	0 (0.0%)	1 (1.4%)
Total No. of events	2	1	3
General disorders and administration site conditions			
Total No. of patients with one or more events	1 (2.6%)	1 (2.8%)	2 (2.7%)
Malaise	1 (2.6%)	0 (0.0%)	1 (1.4%)
Oedema peripheral	0 (0.0%)	1 (2.8%)	1 (1.4%)
Total No. of events	1	1	2
Investigations			
Total No. of patients with one or more events	0 (0.0%)	2 (5.6%)	2 (2.7%)
Weight increased	0 (0.0%)	2 (5.6%)	2 (2.7%)
Total No. of events	0	2	2
Vascular disorders			
Total No. of patients with one or more events	1 (2.6%)	1 (2.8%)	2 (2.7%)
Hypertension	0 (0.0%)	1 (2.8%)	1 (1.4%)
Hypotension	1 (2.6%)	0 (0.0%)	1 (1.4%)
Total No. of events	1	1	2

System Organ Class/ Preferred Term	Rituximab + Prednisone (SM01)	Prednisone (SM02)	All Patients (SM*4)
Endocrine disorders			
Total No. of patients with one or more events	0 (0.0%)	1 (2.8%)	1 (1.4%)
Cushing's syndrome	0 (0.0%)	1 (2.8%)	1 (1.4%)
Total No. of events	0	1	1
Gastrointestinal disorders			
Total No. of patients with one or more events	0 (0.0%)	1 (2.8%)	1 (1.4%)
Oesophagitis	0 (0.0%)	1 (2.8%)	1 (1.4%)
Total No. of events	0	1	1
Hepatobiliary disorders			
Total No. of patients with one or more events	1 (2.6%)	0 (0.0%)	1 (1.4%)
Hepatocellular injury	1 (2.6%)	0 (0.0%)	1 (1.4%)
Total No. of events	1	0	1
Injury, poisoning and procedural complications			
Total No. of patients with one or more events	1 (2.6%)	0 (0.0%)	1 (1.4%)
Femoral neck fracture	1 (2.6%)	0 (0.0%)	1 (1.4%)
Total No. of events	1	0	1
Nervous system disorders			
Total No. of patients with one or more events	1 (2.6%)	0 (0.0%)	1 (1.4%)
Neuropathy peripheral	1 (2.6%)	0 (0.0%)	1 (1.4%)
Total No. of events	1	0	1
Psychiatric disorders			
Total No. of patients with one or more events	0 (0.0%)	1 (2.8%)	1 (1.4%)
Psychiatric decompensation	0 (0.0%)	1 (2.8%)	1 (1.4%)
Total No. of events	0	1	1
Skin and subcutaneous tissue disorders			
Total No. of patients with one or more events	1 (2.6%)	0 (0.0%)	1 (1.4%)
Urticaria	1 (2.6%)	0 (0.0%)	1 (1.4%)
Total No. of events	1	0	1

Investigator term for serious adverse events is encoded using MedDRA version 19.1.
Treatment-related serious adverse events are possibly or probably related.
Percentages are based on N.

Events coded as the System Organ Class/Preferred Term of "General disorders and administration site conditions/Muscle disorder" should be grouped with events coded as "Musculoskeletal and connective tissue disorders/Muscle disorder" when interpreting n and %. The patients with these events in these 2 System Organ Class/Preferred Term categories are mutually exclusive.

Modified from tae005se

Serious Adverse Events by Intensity – PV Population

SAEs were categorized by intensity using CTCAE v4: mild (Grade 1), moderate (Grade 2), severe (Grade 3), and life-threatening (Grade 4). Two patients (5.3%) experienced 6 Grade 3 SAEs in the rituximab + prednisone arm and 6 patients (16.7%) experienced 10 Grade 3 SAEs in the prednisone arm. In the rituximab + prednisone arm, Grade 3 events occurred in 1 patient each in the following PTs: arthralgia, myalgia, headache, malaise, nausea, and vertigo. In the prednisone arm, Grade 3 SAEs occurred in 1 patient each in the following PTs: myopathy, lumbar spinal stenosis, osteonecrosis, tendonitis, pulmonary embolism, sciatica, hypertension, phlebitis, pemphigus, and chorioretinopathy. In the rituximab + prednisone arm, 7 Grade 4 SAEs were observed in 2 patients in the following PTs: pulmonary embolism (5.3%), venous thrombosis limb (2.6%), infective thrombosis (2.6%), intervertebral discitis (2.6%), staphylococcal sepsis (2.6%), and femoral neck fracture (2.6%). In the prednisone arm, 4 Grade 4 SAEs were seen in 3 patients in the following PTs: *Pneumocystis jirovecii* pneumonia (2.8%), weight increased (5.6%), and Cushing's syndrome (2.8%). There were no Grade 5 SAEs.

Table 30

Grade 3 and 4 SAEs in the Rituximab+Prednisone Arm, PV Safety

Patient No.	Event PT	Grade	Investigator's causality assessment to rituximab	Investigator's causality assessment to prednisone	Onset, Study Day	Outcome, Study Day
#26-045	Pulmonary embolism	4	Doubtfully related	-	D80	Resolved
	Venous thrombosis limb	4	Doubtfully related	-	D88	Resolved
#26-050	Femoral neck fracture	4	Possibly related	-	D264	Resolved on D268
	Pulmonary embolism	4	Possibly related	-	-	-
	Staphylococcal sepsis	4	Possibly related	-	-	-
	Infective thrombosis	4	Possibly related	-	-	-
	Intervertebral discitis	4	Possibly related	-	-	-
#29-068	Arthralgia*	3	Possibly related	-	D359	Resolved on D372
#33-075	Vertigo	3	-	-	-	Resolved
	Nausea	3	-	-	-	Resolved
	Myalgia	3	-	-	-	Resolved
	Headache	3	-	-	-	Resolved
	Malaise	3	-	-	D165	Resolved on D170

*This event is a rituximab infusion-related reaction identified by the MAH

Source: ML22196 CSR Listing AE002SE

Table 31

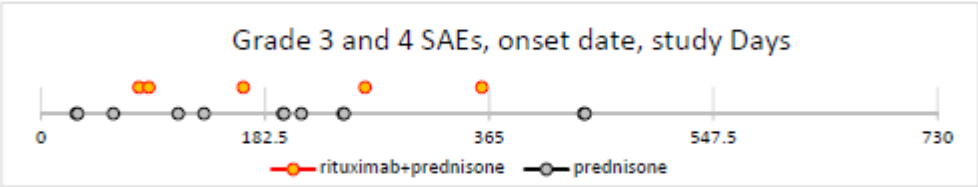
Grade 3 and 4 SAEs in the Prednisone Arm, PV Safety

Patient No.	Event PT	Grade	Investigator's causality assessment to prednisone	Onset, Study Day	Outcome, Study Day
#06-009	Tendonitis	3	Likely related	-	Resolved on D282
	Hypertension	3	Likely related	-	Resolved on D282
	Osteonecrosis	3	Likely related	D212	Unresolved
#08-067	Myopathy	3	Likely related	D59	Unresolved
#09-008	Weight increased	4	Likely related	-	Unresolved
#13-007	*Pneumocystis jirovecii* pneumonia	4	Unrelated	D112	Resolved on D120
#20-046	Cushing's syndrome	4	Likely related	D442	Resolved in ~2 months
	Weight increased	4	Likely related	D442	Unresolved
#21-065	Psychiatric decompensation	3	Likely related	D133	Unresolved
#29-002	Lumbar spinal stenosis	3	Not reported	D246	Resolved on D288
	Sciatica	3	Unrelated	D246	Resolved on D288
#29-076	Pemphigus	3	Unrelated	D29	Resolved
#30-078	Chorioretinopathy	3	Related*	D30	Resolved on D39
#44-072	Pulmonary embolism	3	Related*	D197	Resolved on D202
	Phlebitis	3	Related	D197	Resolved on D202

*Reported as related in AE form and unrelated in SAE form

Source: ML22196 CSR Listing AE002SE

Figure 5 Grade 3 and 4 SAEs, Onset Date, Study Days



Source: ML22196 CSR Listing AE002SE

Laboratory findings

Testing of clinical chemistry and haematology parameters was performed locally and was not reported in the study database -though abnormalities could be reported as AEs in the CRF-. Only cases reported were blood sodium abnormal (1 case of each study group), one case of anemia (rituximab group) and one case of lymphopenia (prednisone group). None of them were reported as serious.

Anti-drug antibodies

The main PV study did not have a prospective plan for immunogenicity assessment as part of the study

protocol. Immunogenicity data of Human Anti-Chimeric Antibody [HACA] was analysed as a post-hoc evaluation by the Applicant from available stored serum samples. In total, 20/34 (58.8%) patients had at least one positive HACA titre at any time during the study. To be noted, 5 subjects had already HACAs at baseline, which increased after rituximab treatment.

The incidence of HACA is higher than reported for other indications in earlier studies. For comparison, a total of 392/3095 (12.7%) patients with rheumatoid arthritis tested positive for HACA in clinical studies following therapy with MabThera. However, it is noted that comparisons between studies is challenging, given differences in assay specificity/sensitivity. HACA was not associated with an increased risk of IRR or loss of efficacy in the main study. Therefore, no further questions are raised.

Haematology and clinical chemistry data were not systematically reported. Neutropenia is known to be common for rituximab in the treatment of other auto-immune disorders, however, this was not reported in the PV study.

Safety in special populations

No analyses were made with regards to intrinsic or extrinsic factors.

Safety related to drug-drug interactions and other interactions

No additional information on potential drug-drug interactions was obtained from Study ML22196.

Therapeutic antibodies such as rituximab are not metabolized via cytochrome P450 and accordingly, the rituximab label (Rituxan USPI/EU SmPC) states that formal drug interaction studies have not been performed with rituximab. In clinical trials of patients with RA, concomitant administration of MTX or cyclophosphamide did not alter the pharmacokinetics of rituximab.

In patients with chronic lymphoid leukemia, rituximab did not alter systemic exposure to fludarabine or cyclophosphamide. In patients with non-Hodgkin lymphoma, renal toxicity has been seen in patients treated with cisplatin; therefore the combination of cisplatin and rituximab is not an approved treatment regimen.

A population pharmacokinetic analysis of RA patients suggested that co-administration with cyclophosphamide, MTX, or glucocorticoids has no effect on the pharmacokinetics of rituximab. Furthermore, as the elimination of rituximab is mediated by both the specific CD20 – receptor-mediated pathway and the non-specific immunoglobulin G clearance pathway, rituximab is not expected to interact with other drugs through protein binding, effects on cytochrome P450 activity, renal excretion, and/or competition for common drug transporter proteins.

Use in Pregnancy and Lactation

There was 1 pregnancy in a patient in the rituximab+prednisone arm during the ML22196 study; the patient delivered a healthy baby with no subsequent AEs reported. Eight pregnancy-related events in patients with pemphigus in the rituximab+prednisone arm were reported in the applicant's global safety database, of which 1 was pregnancy of partner. No adverse pregnancy outcomes were observed in patients treated with rituximab except in the case of pregnancy of partner, where the baby was preterm and had low birth weight. However, this case contained no perinatal details or details about the patient's partner, which would allow a meaningful assessment.

There are no adequate and well-controlled studies of rituximab in pregnant women. Post marketing data indicate that B-cell lymphocytopenia generally lasting less than 6 months can occur in infants exposed to rituximab in-utero. Rituximab was detected postnatally in the serum of infants exposed in-utero.

Reproduction studies in cynomolgus monkeys at maternal exposures similar to human therapeutic exposures showed no evidence of teratogenic effects as described in the labeling for rituximab (Rituxan USPI/MabThera SmPC). However, B-cell lymphoid tissue was reduced in the offspring of treated dams. The B-cell counts returned to normal levels, and immunologic function was restored within 6 months of birth (Rituximab PBRER [Report no. 1073199]).

PV is a serious life-threatening condition that requires treatment. Rituximab should be used during pregnancy only if the potential benefit to the mother justifies the potential risk to the fetus.

Discontinuation due to adverse events

Adverse Events That Led to Withdrawal of Study Treatment – Safety PV Population

AEs leading to protocol withdrawal were collected on the End of Study (EoS) CRF page, and if an SAE, also on the SAE form. All AEs leading to protocol withdrawal in this study were SAEs. In the rituximab + prednisone arm, 1 patient out of 38 patients (2.6%) withdrew from study treatment due to the AE of pregnancy, which was reported as an SAE by the Investigator.

The Applicant identified an instance where there was a discrepancy in the data collected on the EoS page and the SAE form for a PV prednisone patient (19-059) resulting in showing this patient's reason for protocol withdrawal as 'ineffectiveness of treatment' and 7 PV patients in the prednisone arm whose reason for withdrawal was an AE; whereas in tae018se, this patient is counted among the 8 patients in the prednisone arm who had an AE leading to protocol withdrawal. Therefore, in the prednisone arm, 8 patients out of 36 patients (22.2%) withdrew from study treatment due to 10 AEs of which all 10 were SAEs (Table 25). AEs leading to withdrawal in the prednisone arm were largely related to corticosteroid use and included necrosis of the femoral heads, corticosteroid-induced myopathy, Cushing's syndrome, psychiatric decompensation, and chorioretinitis. The listing of any AE leading to protocol withdrawal is lae009se. Narratives for all patients who experienced SAEs are provided.

Adverse events that led to dose modification

One PV patient in the rituximab + prednisone treatment group had the second rituximab infusion delayed due to bronchitis.

Dose modifications of prednisone were not collected in the study. Prednisone doses could have been escalated with relapse or failure to respond. Other than in these situations, doses given that deviated from the protocol can be seen in the listing of protocol deviations (lds004ap).

Post marketing experience

Rituximab is not marketed in any country for the indication of PV. No new safety signals were identified in the ML22196 study compared with the overall rituximab safety data in approved AI indications as presented in the PBRER (Report 1073199).

The proven and observed benefit of rituximab in clinical trials and clinical practice far outweighs the known and generally manageable identified risks associated with rituximab treatment.

Since the international birth data (26 November 1997) until 30 September 2016, approximately 5,378,160 patient-market exposures have been estimated for rituximab:

- Hematological malignancies: approximately 4,431,334
- AI indications: Approximately 946,826 (approximately 554,080 unique patients)
  - RA: approximately 717,362 (approximately 386,682 unique patients)
  - Other AI indications: approximately 229,464 (approximately 157,398 unique patients)

2.5.1. Discussion on clinical safety

Overall, the majority of patients in both treatment arms experienced treatment-related AEs, however, there are significant differences in favour of the rituximab arm with regards to SAEs, treatment-related SAEs and withdrawal of study treatment. Looking at AEs occurring >= 10% of patients it is seen that in most SOCs the rituximab+prednisone arm fares better, which is most likely explained by the fact that exposure to prednisone was considerable lower in this arm. However, in two SOCs ("injury, poisoning and procedural complications" and "skin and subcutaneous tissue disorders") rituximab+prednisone arm fares worse than the prednisone arm. This is related to IRR. Following AEs occurred frequently in the rituximab-prednisone arm: IRR, insomnia, Cushing's syndrome, arthralgia, asthenia, persistent depressive order and alopecia. These are all well-known AEs related to rituximab and clearly reflected in the SmPC, except for Cushing's syndrome, which is related to prednisone.

The use of rituximab in combination with prednisone did not lead to an increase in infections. This is reassuring. However, the numbers are small and no clear pattern can be observed.

There were no deaths in this study, and overall there were more patients in the prednisone arm who experienced an SAE, however, looking at the number of SAEs there is no difference between the two treatment arms. Looking at SAEs with an incidence of >=5%, most SAEs are related to musculoskeletal system. Some of these SAEs, e.g. osteoporotic fracture, are related to prednisone, while other, e.g. arthralgia, are related to rituximab. The majority of events occurred in only one patient.

2.5.2. Conclusions on clinical safety

Overall, the use of rituximab in combination with low-dose prednisone was well-tolerated. No new safety finding were observed during the study, and the observed AEs/SAEs are in line with the well-known and well-characterised safety profile of rituximab. However an update of section 4.8 of the SmPC was introduced in order to reflect the safety profile observed in patients with PV.

2.5.3. PSUR cycle

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

2.6. Risk management plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 19.1 is acceptable. This RMP version 19.1 also includes approved RMP version 17.1 (based on version 16.1 and including relevant updates from version 17.0, EMEA/H/C/000165/II/0149). In addition changes arising from versions 17.0 (current procedure EMEA/H/C/000165/II/0150), 18.0 (EMEA/H/C/000165/II/0152) and 19.0 (EMEA/H/C/000165/II/0157 and EMEA/H/C/000165/II/0158) have been merged resulting in new version 19.1.

The PRAC endorsed PRAC Rapporteur assessment report is attached.

The CHMP endorsed this advice without changes.

The CHMP endorsed the Risk Management Plan version 19.1 with the following content:

Safety concerns

Summary of safety concerns	
Important identified risks	• Infusion related reactions • Infections including serious infections • Progressive multifocal leukoencephalopathy • Hepatitis B reactivation • Hypogammaglobulinemia (non-oncology indications)
Important potential risks	• Malignant events (non-oncology indications) • Impact on cardiovascular disease (non-oncology indications) • Relapses (GPA/MPA only) • Off label use in paediatric patients • Off label use of the subcutaneous formulation (NHL/CLL subcutaneous formulations) • Administration route error (NHL/CLL subcutaneous formulations)
Missing information	• Long term use in GPA/MPA patients (GPA/MPA only) • Use in pregnancy and lactation

The following safety concerns have been removed from the RMP with reference to GVP module V guideline (rev 2):

Important identified risks (approved via EMEA/000165/II/0144):

- Impaired immunisation response

- Neutropenia (including prolonged neutropenia)

- Stevens-Johnson syndrome / toxic epidermal necrolysis

- Tumour lysis syndrome (NHL/CLL)

- Gastrointestinal perforation (NHL/CLL)

- Local cutaneous reactions (NHL/CLL subcutaneous formulations)

Important potential risks:

- Prolonged B-cell depletion (EMEA/000165/II/0157, EMEA/000165/II/158)

- Second malignancies (EMEA/000165/II/0144)

- Posterior reversible encephalopathy syndrome (EMEA/000165/II/0144)

- Acute myeloid leukaemia and myelodysplastic syndrome (NHL/CLL) (EMEA/000165/II/0144)

- Increased risk of grade 3-4 and serious blood and lymphatic system adverse events in older patients (>70 years of age) (EMEA/000165/II/0144)

-Off label use in autoimmune disease (RA & GPA/MPA) (EMEA/000165/II/0152)

Missing information

- Immunogenicity associated with the subcutaneous formulation (NHL/CLL subcutaneous formulations) (EMEA/000165/II/0157, EMEA/000165/II/158)

Pharmacovigilance plan

Study **Status**	**Summary of objectives**	**Safety concerns addressed**	**Milestones**	**Due dates**
Category 3 - Required additional pharmacovigilance activities				
WA25615/PePRS Phase IIa, international, multicenter, open-label, single-arm study in pediatric GPA/MPA patients Ongoing	Evaluate the safety and tolerability of rituximab in pediatric patients with severe GPA/MPA	Off-label use in pediatric patients	FPFV	23 May 2013
			LPLV	May 2018
			Study end	The common closeout date will occur 18 months after the enrollment of the last patient
Plasma exchange and glucocorticoid dosing in the treatment of ANCA-associated vasculitis (PEXIVAS) Ongoing	Capture long-term safety data in order to further evaluate dose regimen of rituximab in relation to infection's frequency, seriousness and severity	Infections including serious infections	Final CSR	Expected in April 2019
Intergroup B-NHL-2010 Open-label, randomized, controlled, parallel-group, multicenter trial to evaluate the pharmacokinetics, pharmacodynamics, safety and efficacy or rituximab add-on to standard chemotherapy in children from 6 months to less than 18 years of age with advanced stage B-cell lymphoma (excluding primary mediastinal B-cell lymphoma), Burkitt and Burkitt-like lymphoma/Leukemi	Evaluate the safety and tolerability of rituximab in pediatric patients with advanced stage B-cell lymphoma (excluding primary mediastinal B-cell lymphoma), Burkitt and Burkitt-like lymphoma/Leukemia	Off-label use in pediatric patients	Study Start	November 2011
			Study end	June 2019

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
a conducted in accordance with the approved PIP Ongoing				
An international, open label, randomized controlled trial comparing rituximab with azathioprine as maintenance therapy in relapsing ANCAassociated vasculitis (RITAZAREM)-Pha se III, interventional, randomized, openlabel, comparative trial Ongoing	Time to relapse / the primary endpoint is the time to disease relapse (either minor or major relapse) from randomization. Proportion of patients who maintain remission at 24 and 48 months	Relapses	Estimated study completion date	January 2021
BE29950 (RIVAS): Prospective, single center, secondary data use, long-term surveillance, noninterventionalP ASS. Ongoing	Registry to collect serious adverse event data over 5 years to determine the long-term safety of rituximab for the treatment of GPA/MPA.	Long term use in GPA/MPA patients	Study start	Q4 2016
			Interim analyses	Annual reporting of cumulative data in PBRER
			Interim report	3 year after study start
			Final report	5 year after study start
Category 4: Stated additional pharmacovigilance activities				
WA27893/RaAVeR: A multi-centre (US-based), prospective, observational study designed to follow 100 rituximab treated patients with granulomatosis with polyangiitis (GPA) or microscopic polyangiitis (MPA) for a maximum of 4 years. Completed NI-PASS	*Primary objective* of this study is to characterize the long-term safety of rituximab in the treatment of *GPA* or MPA. *Secondary objective* of this study is to collect data on the safety of re-treatment with rituximab in patients with *GPA* or MPA.	Infusion-related reactions (All Indications) Infections, including serious infections (All Indications) Hepatitis B reactivation (All Indications) Malignant events (RA and GPA/MPA) Impact on cardiovascular disease (RA and GPA/MPA) Relapses (GPA/MPA) Use in pregnancy and lactation (All Indications)	First patient in Last patient in Last Patient Last Visit Interim Clinical Study Report Final Report expected	20 Jun 2012 19 May 2013 19 May 2017 April 2016 April 2018
Anti Rheumatic Therapy in Sweden	To initiate a nationwide post-marketing inception	Infections, including serious infections (All	First patient in	Q2 2007

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
(ARTIS)- Nation-wide safety monitoring of MabThera treatment in patients with rheumatic Diseases in Sweden Ongoing NI-PASS	cohort of patients treated with rituximab (MabThera), including all patients with rheumatoid arthritis (RA)	Indications) Malignant events (RA and GPA/MPA) Impact on cardiovascular disease (RA and GPA/MPA) Use in pregnancy and lactation (All Indications)	3-year report 5-year report Final report expected	Dec 2011 Dec 2013 Annual updates in PBRERs
British Society of Rheumatology Biologics Registry (BSRBR) Ongoing NI-PASS	Evaluate the safety profile of rituximab in Rheumatoid arthritis patients in comparison to RA patients treated with anti- tumor necrosis factor (TNF)α agents and standard disease-modifying anti rheumatic drugs (DMARD) medicines	Infections, including serious infections (All Indications) Malignant events (RA and GPA/MPA) Impact on cardiovascular disease (RA and GPA/MPA) Use in pregnancy and lactation (All Indications)	First patient in 3-year report 5-year report Final report expected	Q2 2008 August 2013 Q1 2015 Q3 2019 Annual updates in PBRERs
RABBIT(Rheumatoid arthritis observation of biologic therapy) Ongoing NI-PASS	Evaluate long term effectiveness of treatment with biological agents with regard to treatment continuation and clinical outcomes, and to study the long term safety of treatment with biologic therapy in RA.	Infections, including serious infections (All Indications) Malignant events (RA and GPA/MPA) Impact on cardiovascular disease (RA and GPA/MPA) Use in pregnancy and lactation (All Indications)	First Patient In Planned submission of final data	Q2 2007 Q4 2022 Annual updates in PBRERs

Risk minimisation measures

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Infusion related reactions	SmPC section 4.4 & 4.8 Other risk minimisation measures: Medicinal product subject to restricted medical prescription Additional risk minimisation measures:	Routine pharmacovigilance activities Additional pharmacovigilance activities: RAVeR (WA27893)

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	Educational outreaches (RA and GPA/MPA only)	
Infections including serious infections	SmPC sections 4.4 & 4.8 Other risk minimisation measures: Medicinal product subject to restricted medical prescription Additional risk minimisation measures: Patient alert card (non-oncology indications only) Educational material for HCPs and patients (non-oncology indications only)	Routine pharmacovigilance activities Additional pharmacovigilance activities: Evaluate results from PEXIVAS study in GPA/MPA Study RAVeR (WA27893) Anti-rheumatic Therapy in Sweden (ARTIS) British Society of Rheumatology Biologics Registry (BSRBR) RABBIT (Rheumatoid arthritis observation of biology therapy)
Progressive multifocal leukoencephalopathy	SmPC sections 4.4 Other risk minimisation measures: Medicinal product subject to restricted medical prescription Additional risk minimisation measures: Patients alert card (non-oncology indications only) Educational material for HCPs and patients (non-oncology indications only)	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Guided questionnaires
Hepatitis B reactivation	SmPC section 4.4 Other risk minimisation measures: Medicinal product subject to restricted medical prescription	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Guided questionnaires Additional pharmacovigilance activities: Study RAVeR (WA27893)

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Hypogammaglubulinemia (non-oncology indications)	SmPC sections 4.4 & 4.8 Other risk minimisation measures: Medicinal product subject to restricted medical prescription	Routine pharmacovigilance activities
Malignant events (non-oncology indications)	SmPC section 4.4 Other risk minimisation measures: Medicinal product subject to restricted medical prescription	Routine pharmacovigilance activities Additional pharmacovigilance activities: Study RaVeR (WA27893) Anti-rheumatic Therapy in Sweden (ARTIS) British Society of Rheumatology Biologics Registry (BSRBR) RABBIT (Rheumatoid arthritis observation of biologic therapy)
Impact on cardiovascular disease (non-oncology indications)	SmPC section 4.4 Other risk minimisation measures: Medicinal product subject to restricted medical prescription	Routine pharmacovigilance activities Additional pharmacovigilance activities: Study RaVeR (WA27893) Anti-rheumatic Therapy in Sweden (ARTIS) British Society of Rheumatology Biologics Registry (BSRBR) RABBIT (Rheumatoid arthritis observation of biologic therapy)
Relapses (GPA/MPA only)	SmPC section 5.1 Other risk minimisation measures: Medicinal product subject to restricted medical prescription	Routine pharmacovigilance activities Additional pharmacovigilance activities: Observation and evaluation of data from ongoing studies on maintenance therapy (MAINRITSAN II and RITAZAREM). Study RaVeR (WA27893)

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Off label use in paediatric patients	SmPC sections 4.1 & 4.2 Other risk minimisation measures: Medicinal product subject to restricted medical prescription	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Guided questionnaires Additional pharmacovigilance activities: Study WA25615 (an interventional PASS) Intergroup trial (Inter-BNHL 2010) for children or adolescents with B-cell NHL or B-AL in accordance with the approved Paediatric Investigation Plan
Off label use of the subcutaneous formulation (NHL/CLL subcutaneous formulations)	SmPC sections 4.1, 4.2 & 4.4 Other risk minimisation measures: Medicinal product subject to restricted medical prescription Additional risk minimization measures: Educational material for HCPs	Routine pharmacovigilance activities
Administration route error (NHL/CLL subcutaneous formulations	SmPC section 4.2 Other risk minimisation measures: Medicinal product subject to restricted medical prescription Additional risk minimization measures: Educational material for HCPs	Routine pharmacovigilance activities
Use in pregnancy and lactation	SmPC section 4.6 Other risk minimisation measures: Medicinal product subject to restricted	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Standard pregnancy report form for follow-up.

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	medical prescription	Additional pharmacovigilance activities: Study RaVeR (WA27893) Anti-rheumatic Therapy in Sweden (ARTIS) British Society of Rheumatology Biologics Registry (BSRBR) RABBIT (Rheumatoid arthritis observation of biologic therapy)
Long term use in GPA/MPA patients (GPA/MPA)	Other risk minimisation measures: Medicinal product subject to restricted medical prescription	Routine pharmacovigilance activities Additional pharmacovigilance activities: WA27893 (RaVeR) RIVAS (BE29950) registry

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.3, 4.4, 4.5, 4.8 and 5.1 of the SmPC have been updated.The Package Leaflet has been updated accordingly.

2.7.1. User consultation

No justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH. However, the changes to the package leaflet are minimal and do not require user consultation with target patient groups.

3. Benefit-Risk Balance

3.1. Therapeutic Context

The MAH seeks regulatory approval for rituximab in the following indication:

Rituximab is indicated for the treatment of adult patients with moderate to severe pemphigus vulgaris.

3.1.1. Disease or condition

Pemphigus vulgaris (PV) is a rare, serious and life-threatening autoimmune blistering disease affecting the mucosa and skin, and there is a high unmet medical need for safer and more effective treatment options. Due to the rarity of pemphigus, few prospective clinical trials are available and these are limited by the low numbers of patients studied and treatment arms that do not demonstrate statistically significant differences.

3.1.2. Available therapies and unmet medical need

Corticosteroids and, in some European countries, azathioprine are the only EU-approved treatments for patients with PV. Systemic corticosteroids have been the mainstay of treatment for pemphigus patients since the 1950s based on limited and uncontrolled clinical data. Similarly, the use of adjuvant immunosuppressant therapy, such as azathioprine, which has been approved alone and in combination with systemic corticosteroids, for the treatment of PV in the European Union for over 15 years, has been established in treatment guidelines in Europe despite the scarcity of well-designed randomized controlled studies, and evidence that adjuvant therapies have only a minimal steroid-sparing effect.

Based on the literature, chronic and/or high dose corticosteroid therapy alone results in an estimated remission rate of <30%. Remission may be short lived. Serious and sometimes fatal AEs, resulting from immunosuppression due to long-term use of steroids, may occur. Despite widespread use, there is no consensus on whether unapproved steroid-sparing agents are beneficial due to the scarcity of well-designed randomized controlled studies. PV remains a serious life-threatening disease and given the unsatisfactory safety and efficacy profile of the existing approved therapies (corticosteroids and azathioprine), a major unmet medical need exists for safer and more effective novel, targeted mechanism-based treatment options for moderately to severely active PV.

3.1.3. Main clinical studies

The MAH has provided study MM22196, an open-label, phase III, multicentre, and randomised study in patients with newly diagnosed moderate to severe pemphigus. The study was run by academia (Rouen University Hospital, France). The MAH had no role in study design, conduct, data collection or publication of results. The database was transferred from the Sponsor to the MAH in December 2016 after database lock.

3.2. Favourable effects

The study met its primary endpoint showing a statistically significant and clinically relevant difference between the treatment arms in favour of rituximab. In total 89.5% (34/38) of the patients in the rituximab+prednisone arm had CR off prednisone therapy for at least 2 months at month 24. In comparison only 27.8% (10/36) of the patients in the prednisone arm experienced CR off prednisone for at least 2 months at month 24. Looking at CR off prednisone for at least 3 months at month 24 (the original primary endpoint) similar results are observed. This is reassuring.

With regard to the secondary endpoints it was shown that the number of patients who had at least one severe/moderate relapse at month 24 was considerable lower in the rituximab arm (23.7% vs. 50.0%). Number of patients with CR at month 24 on minimal prednisone treatment was significantly higher in the rituximab arm. Total cumulative dose prednisone at month 24 was significantly lower in the rituximab arm. Finally, the duration of CRoff prednisone at month 24 in responders was considerable longer in the rituximab arm. Overall, all secondary endpoints support the findings in relation to the primary endpoint.

Considering the QoL results, the sponsor had used Skindex-France and DLQI. No relevant differences are observed, however, considering the open-label nature of the study, no major emphasis is put on this results.

3.3. Uncertainties and limitations about favourable effects

The use of rituximab in combination with prednisone was studied in patients newly diagnosed with pemphigus vulgaris, but the claimed indication includes patients with established pemphigus vulgaris (relapsed setting). The MAH has justified the extrapolation, which includes a PK, PD, efficacy and safety discussion, by reasoning as well as by the already provided supporting evidence. There are nevertheless uncertainties due to the limitations of the data provided in the established disease.

3.4. Unfavourable effects

Overall, the majority of patients in both treatment arms experienced treatment-related AEs, however, there are significant differences in favour of the rituximab arm with regards to SAEs, treatment-related SAEs and withdrawal of study treatment. Looking at AEs occurring >= 10% of patients it is seen that in most SOCs the rituximab+prednisone arm fares better, which is most likely explained by the fact that exposure to prednisone was considerable lower in this arm. However, in two SOCs ("injury, poisoning and procedural complications" and "skin and subcutaneous tissue disorders") rituximab+prednisone arm fares worse than the prednisone arm. This is related to IRR. Following AEs occurred frequently in the rituximab-prednisone arm: Infusion Related Reactions (IRR), insomnia, Cushing's syndrome, arthralgia, asthenia, persistent depressive order and alopecia. These are all well-known AEs related to rituximab and clearly reflected in the SmPC, except for Cushing's syndrome, which is related to prednisone. The use of rituximab in combination with prednisone did not lead to an increase in infections. This is reassuring. The numbers are small and no clear pattern can be observed.

3.5. Uncertainties and limitations about unfavourable effects

There are no uncertainties or limitations about the unfavourable effects.

3.6. Effects Table

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects						
CRoff at Month 24	Clinical remission off-CS therapy for 2 months	%	90	28	Probable bias by open-label design (CI not reported)	[1]
Relapses	Patients with relapses	%	24	50	idem	[1]
CR min.	Clinical remission on minimal CS therapy	%	90	33	idem	[1]
Remission duration	Median duration of remission in patients CRoff	days	490	125	idem	[1]
Prednisone	Median cumulative CS dose	mg	5800	20.520	idem	[1]
CRoff maintained	CRoff maintained at month 36	%	94	60	Influenced by differential drop-out	[1]
Unfavourable Effects						
AEs	Number of subjects with one or more AEs	%	32/38 (84.2)	30/36 (83.3)	For non-serious AEs, only treatment-related AEs were reported: risk of underreporting	[1]
SAE	Number of subjects with one or more SAEs	n/N, %	11/38 (28.9)	16/36 (44.4)	Potential bias open-label design over-estimation for CS treatment	[1]
Withdrawal due to AEs	Number of subjects withdrawn because of	n/N, %	1/38 (2.6)	8/36 (22.2)	Potential bias open-label design, over-estimation for CS treatment	[1]

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
	SAE					
IRR	Infusion related reactions (during any course)	n/N, %	22/38 (57.9)	NA	IRR were only scored for rituximab (IV), since prednisone was given orally	1
Infections		n/N, %	14/38 (36.8)	15/36 (41.7)		1
Serious infections		n/N, %	3/38 (7.9)	1/36 (2.8)		1
Myopathy/ muscle disorder		n/N, %	1/38 [2.6]	8/36 (22.2)		1
Weight increased		n/N, %	3/38 (7.9)	9/36 (25)		1
Hyperglycaemia		n/N, %	0	4/36 (11.1)		1
Type II diabetes		n/N, %	1/38 (2.6)	4/36 (11.1)		1
Insomnia			8/38 (21.1)	11/36 (30.6)		1
Agitation		n/N, %	1/38 (2.6)	6/36 (16.7)		1
Cataract		n/N, %	0	5/36 (13.8)		1

3.7. Discussion on the benefit-risk assessment

3.7.1. Importance of favourable and unfavourable effects

High-dose CS is effective in controlling the disease, but long-term use is associated with severe and serious adverse events. Thus, CS sparing treatment options are highly needed. The addition of rituximab to prednisone leads to clinically meaningful decrease in prednisone use. This is highly valued from both a patient and clinicians perspective. The safety profile of this combination is acceptable, with only IRRs standing out. However, IRRs are well-known in relation to the use of rituximab. Clinicians are familiar with this AE and it is manageable in the clinical setting.

3.7.2. Balance of benefits and risks

The benefit-risk balance is positive in newly diagnosed patients and patient with established disease. However there are limitations in the data provided for the patients with established disease.

The CHMP considered that additional data are necessary to confirm the benefit of Mabthera in the subgroup of patients with established disease. The ongoing study in the relapsed setting, study WA29330 (PEMPHIX) will provide additional key information on the benefits and risks of Mabthera in these patients. The recruitment is completed and the preliminary and final analyses of this study should be provided post-approval.

3.8. Conclusions

The overall B/R is positive.

The CHMP considers the following measures to address issues related to efficacy and safety:

The ongoing study in the relapsed setting, study WA29330 (PEMPHIX) will provide additional key information on the benefits and risks of Mabthera in patients with established disease. The recruitment is completed and the preliminary and final analyses of this study should be provided post-approval.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include the treatment of patients with moderate to severe pemphigus vulgaris (PV) for MabThera; as a consequence, sections 4.1, 4.2, 4.3, 4.4, 4.8 and 5.1 of the SmPC are updated. The MAH provided data from a phase III, randomized, controlled, multicenter, open-label study (Study ML22196) evaluating rituximab treatment plus short-term, low dose prednisone treatment compared to long-term, standard dose prednisone treatment as first-line treatment in patients with moderate to severe pemphigus. The Package leaflet is updated accordingly. Minor corrections are also proposed for the sake of accuracy and clarity. An updated RMP (v19.1) was agreed. The annex II is updated to include submission of results of the ongoing PEMPHIX clinical study.

The variation leads to amendments to the Summary of Product Characteristics and Package Leaflet, the annex II and to the Risk Management Plan (RMP).

Conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list)) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

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

Obligation to conduct post-authorisation measures

The MAH shall complete, within the stated timeframe, the below measures:

Description	Due date
Post-authorisation efficacy study (PAES): In order to further investigate the efficacy of Mabthera in the subgroup of patients with established PV as well as to further characterise its long term efficacy and safety on disease progression, the MAH should submit the preliminary study and the final study report of the ongoing randomised phase 3 study (PEMPHIX WA29330).	by Q4 2019 (preliminary CSR) by Q4 2020 (final CSR)

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Extension of indication to include the treatment of patients with moderate to severe pemphigus vulgaris (PV) for MabThera; as a consequence, sections 4.1, 4.2, 4.3, 4.4, 4.8 and 5.1 of the SmPC are updated. The MAH provided data from a phase III, randomized, controlled, multicenter, open-label study (Study ML22196) evaluating rituximab treatment plus short-term, low dose prednisone treatment compared to long-term, standard dose prednisone treatment as first-line treatment in patients with moderate to severe pemphigus. The Package leaflet is updated accordingly. Minor corrections are also proposed for the sake of accuracy and clarity. An updated RMP (v19.1) was agreed. The annex II is updated to include submission of results of the ongoing PEMPHIX clinical study.

Summary

Please refer to Scientific Discussion MabThera-H-C-165-II-150.