Ublituximab (multiple sclerosis 1)

Addendum to Project A24-13 (dossier assessment)[1]

ADDENDUM

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List of abbreviations

Abbreviation	Meaning
9-HPT	9-Hole Peg Test
AWMF	Association of the Scientific Medical Societies in Germany
CD20	cluster of differentiation 20
CTCAE	Common Terminology Criteria for Adverse Events
EDSS	Expanded Disability Status Scale
FIS	Fatigue Impact Scale
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
GD	gadolinium
IPD	individual patient data
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
MHCS	Mental Health Composite Score
MRI	magnetic resonance imaging
MSFC	Multiple Sclerosis Functional Composite
MSQoL-54	Multiple Sclerosis Quality of Life-54
PASAT-3	Paced Auditory Serial Addition Test-3
PHCS	Physical Health Composite Score
RMS	relapsing multiple sclerosis
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SOC	System Organ Class
T25-FW	Timed 25-Foot Walk
TEAE	treatment emergent adverse event

1 Background

On 11 June 2024, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Project A24-13 (Ublituximab – Benefit assessment according to § 35a Social Code Book V) [1].

The commission comprises the assessment of the analyses on the studies ULTIMATE I and ULTIMATE II submitted by the pharmaceutical company (hereinafter referred to as the "company") for the relevant subpopulation in the commenting procedure [2] as well as in the follow-up to the oral hearing [3], taking into account the information provided in the dossier [4].

The responsibility for the present assessment and the assessment result lies exclusively with IQWiG. The assessment is sent to the G-BA. The G-BA decides on the added benefit.

2 Assessment

As explained in detail in dossier assessment A24-13 [1], the analyses on the total population of the studies ULTIMATE I and ULTIMATE II were not used for the benefit assessment of ublituximab, as less than 80% of the total population corresponded to the relevant population for research question 1 (treatment-naive patients without indication of a severe course of disease) of the benefit assessment. No data were available for research question 2 (treatment-naive patients with indication of a severe course of disease and pretreated patients with an active course of disease). With the comments and following the oral hearing, the company subsequently submitted analyses on a relevant subpopulation for research question 1. The analyses based on the subpopulation presented by the company are used for the present benefit assessment. There are still no data available for research question 2.

The benefit assessment in the context of the present addendum is based on the studies ULTIMATE I und ULTIMATE II (see Table 1). For the relevant subpopulation, the company presents analyses of the individual studies as well as meta-analyses based on individual patient data (IPD) of the studies ULTIMATE I and ULTIMATE II.

Table 1: Study pool – RCT, direct comparison: ublituximab vs. teriflunomide

Study	**Study category**			**Available sources**		
	Study for the approval of the drug to be assessed (yes/no)	**Sponsored study[a] (yes/no)**	**Third-party study (yes/no)**	**CSR (yes/no [citation])**	**Registry entries[b] (yes/no [citation])**	**Publication (yes/no [citation])**
RMS301 (ULTIMATE I)[c]	Yes	Yes	Yes	Yes [5]	Yes [6,7]	Yes [8]
RMS302 (ULTIMATE II)[c]	Yes	Yes	Yes	Yes [9]	Yes [10,11]	Yes [8]

a. Study sponsored by the company.
b. Citation of the trial registry entries and, if available, of the reports on study design and/or results listed in the trial registries.
c. In the tables below, the study will be referred to using this acronym.

G-BA: Federal Joint Committee; RCT: randomized controlled trial; RMS: relapsing multiple sclerosis;

2.1 Study characteristics

A detailed characterization of the studies ULTIMATE I and ULTIMATE II can be found in dossier assessment A24-13 [1] and its Appendix B.

Operationalization of the subpopulation of treatment-naive patients without indication of a severe course of disease

The population relevant for research question 1 of the present benefit assessment comprises treatment-naive patients with no indication of a severe course of disease. With the comments, the company subsequently submitted analyses on a subpopulation of ULTIMATE I and ULTIMATE II, which were to represent the relevant population for research question 1. For the operationalization of a treatment-naive population that shows no indication of a severe course of disease, the company follows Statement A27 of the current guideline of the Association of the Scientific Medical Societies in Germany (AWMF) on the diagnosis and treatment of multiple sclerosis [12]. Accordingly, it can be assumed that treatment-naive patients are likely to have a highly active course if 1 or more of the following criteria are met:

- a relapse has led to a severe deficit relevant to everyday life after exhaustion of relapse therapy and/or
- poor recovery from the first two relapses and/or
- high relapse frequency (≥ 3 in the first 2 [approx.] years or ≥ 2 in the 1st [approx.] year after the onset of the disease) and/or
- a value of the Expanded Disability Status Scale [EDSS] ≥ 3.0 in the 1st (approx.) year of illness and/or
- pyramidal tract involvement in the 1st year of illness and/or
- at the time of diagnosis there are ≥ 2 contrast medium-absorbing lesions and a high T2 lesion load with special weighting of spinal or infratentorial lesions in the magnetic resonance imaging (MRI) findings.

Of these criteria, the company used the criteria on relapse frequency and number of MRI lesions and in this respect formed a counter-set to Statement A27 of the AWMF guideline. According to the company's definition, treatment-naive patients show no indications of a severe/highly active course of disease if

- there are < 3 relapses in the 2 years before screening AND < 2 relapses in the year before screening
- and if
- there are < 2 gadolinium (Gd)-enhancing lesions at baseline OR < 9 T2 lesions at baseline.

For the criteria on the relapse frequency or number of MRI lesions, the company refers to the respective periods before screening or to the time at the start of the study, and not, as described in the AWMF guideline, to the respective years after disease onset or at the time of

diagnosis, as corresponding data were often lacking for the patients of ULTIMATE I and ULTIMATE II, because the onset of the disease or the diagnosis of multiple sclerosis dated back a long time. The fact that in some cases the disease started long before the start of the study also justified the fact that the EDSS value at baseline was not suitable as a criterion for assessing a non-severe/non-highly active course of the disease, as the baseline EDSS value could not provide any information about its development and thus the progression of the disability over time up to the time of the start of the study. In addition to the criteria relating to relapse frequency, the company defined, among other things, the number of T2 lesions falling below 9 as a sign that there are no indications of a severe/highly active course of disease. Deviating from this, statement A27 of the AWMF guideline does not provide any information on the number of T2 lesions as a possible criterion for assessing a severe/highly active course of disease in treatment-naive patients. This is not commented on further, as this criterion is not used in the formation of the relevant subpopulation (see section on the characteristics of the relevant subpopulation).

Overall, the company's operationalization regarding a non-severe/non-highly active course of disease based on the relapse frequency in the period before screening and the number of MRI lesions at the time of study start is considered adequate. Nevertheless, there is uncertainty regarding the pretreatment of the patients in the subpopulation presented by the company. Information on patient characteristics (see Table 2) shows that around 17.5% of patients in the subpopulation of the pooled ULTIMATE studies had been treated with multiple sclerosis therapy before the start of the study, the majority of whom had received treatment with laquinimod (18 out of 26 patients in the ublituximab arm and 26 out of 36 patients in the teriflunomide arm, see Table 2). These patients were treated with laquinimod as study medication in clinical trials for an average duration of 1156 days in the ublituximab arm and 1003 days in the teriflunomide arm (data from the pooled ULTIMATE studies). The company stated that on average, treatment with laquinimod was completed 563 days (ublituximab arm) or 521 days (teriflunomide arm) before randomization into the ULTIMATE studies. However, laquinimod was not approved for the treatment of patients with multiple sclerosis due to safety and efficacy concerns. The company therefore argues that this pretreatment of the patients in the subpopulation cannot be regarded as adequate pretreatment with a disease-modifying therapy in the sense of the definition of the population of research question 1 (treatment-naive patients without indications of a severe course of disease).

Since the proportion of pretreated patients is less than 20%, the subpopulation presented by the company can be used for the present benefit assessment for adults with relapsing multiple sclerosis (RMS) who have not yet received any disease-modifying therapy and show no signs of a severe course of disease. The relevant subpopulation comprises approx. 34% of all ULTIMATE I patients and approx. 31% of all ULTIMATE II patients. All information stated below is based on this relevant subpopulation.

Characteristics of the relevant subpopulation

Table 2 shows the characteristics of the patients of the relevant subpopulation in the studies ULTIMATE I and ULTIMATE II.

Table 2: Characteristics of the study populations as well as study/treatment discontinuation – RCT, direct comparison: ublituximab vs. teriflunomide (multipage table)

Study characteristic category	ULTIMATE I		ULTIMATE II	
	ublituximab	teriflunomide	ublituximab	teriflunomide
	N[a] = 97	N[a] = 90	N[a] = 75	N[a] = 93
Age [years], mean (SD)	38 (9)	39 (10)	36 (9)	37 (9)
Sex [F/M], %	57/43	61/39	57/43	61/39
Family origin, n (%)				
White	97 (100)	88 (98)	74 (99)	91 (98)
Black or African American	0 (0)	0 (0)	1 (1)	1 (1)
Other	0 (0)	2 (2)	0 (0)	1 (1)
Region, n (%)				
Eastern Europe	93 (96)	82 (91)	71 (95)	85 (91)
USA and Western Europe	4 (4)	8 (9)	4 (5)	8 (9)
Duration of disease from onset of symptoms [years], median [min; max]	5 [0; 28]	5 [0; 28]	6 [0; 30]	7 [0; 33]
Duration of disease since first diagnosis [years], median [min; max]	2.6 [0.1; 27.5]	2.6 [0.1; 25.7]	2.0 [0.1; 28.3]	2.8 [0.1; 30.1]
Number of relapses in the last year, n (%)				
0	3 (3)	3 (3)	4 (5)	7 (8)
1	94 (97)	87 (97)	71 (95)	86 (92)
Number of relapses in the past 2 years, n (%)				
0	0 (0)	0 (0)	0 (0)	3 (3)
1	56 (58)	60 (67)	52 (69)	52 (56)
2	41 (42)	30 (33)	23 (31)	38 (41)
EDSS, median [min; max]	3.0 [0.0; 5.5]	2.5 [1.0; 5.5]	2.5 [0.0; 5.5]	3.0 [0.0; 5.5]
EDSS, n (%)				
≤ 3.5	70 (72)	71 (79)	60 (80)	72 (77)
> 3.5	27 (28)	19 (21)	15 (20)	21 (23)
Number of Gd-enhancing lesions, n (%)				
0	74 (76)	65 (72)	54 (72)	70 (75)
1	23 (24)	25 (28)	21 (28)	23 (25)

Table 2: Characteristics of the study populations as well as study/treatment discontinuation – RCT, direct comparison: ublituximab vs. teriflunomide (multipage table)

Study characteristic category	ULTIMATE I		ULTIMATE II	
	ublituximab	teriflunomide	ublituximab	teriflunomide
	N[a] = 97	N[a] = 90	N[a] = 75	N[a] = 93
Number of T2 lesions, median [min; max]	48 [8; 146]	58 [15; 172]	45 [9; 186]	43 [9; 162]
MS therapies before study start, n (%)[b]				
Yes (≥ 1 month)	12 (12)	19 (21)	14 (19)	17 (18)
Interferon beta	2 (2)[c]	0 (0)	2 (3)	1 (1)
Glatiramer acetate	2 (2)	2 (2)	1 (1)	1 (1)
Laquinimod	9 (9)	13 (14)	9 (12)	13 (14)
Daclizumab	0 (0)	2 (2)	2 (3)	3 (3)
Ozanimod	0 (0)	2 (2)	0 (0)	0 (0)
Secukinumab	0 (0)	0 (0)	0 (0)	1 (1)
Treatment discontinuation[d, e], n (%)	10 (10)	8 (9)	3 (4)	11 (12)
Study discontinuation, n (%)	ND	ND	ND	ND

a. Number of randomized patients in the relevant subpopulation. Values that are based on other patient numbers are marked in the corresponding line if the deviation is relevant.
b. Treatment was carried out in the context of clinical studies as study medication.
c. Institute's calculation, pretreatment with "interferon beta" or "interferon beta 1a" added.
d. According to the company: Patients who discontinued treatment also had to end the core part of the study and complete the visit for early treatment discontinuation. This visit was planned for all premature discontinuations (study and therapy discontinuations).
e. The most common reason for treatment discontinuation in ULTIMATE I (4 vs. 6 patients) and ULTIMATE II (2 vs. 10 patients) was the withdrawal of consent.

EDSS: Expanded Disability Status Scale; f: female; m: male; max: maximum; MD: mean difference; min: minimum; MS: multiple sclerosis; n: number of patients in the category; N: number of randomized patients; ND: no data; RCT: randomized controlled trial; SD: standard deviation

In both studies, the demographic and clinical characteristics of the patients are largely comparable between the treatment groups. Also between the studies, the patient characteristics were balanced. The average age of the patients in ULTIMATE I was 38 to 39 years at the start of the study, while the patients in ULTIMATE II were slightly younger with an average age of 36 to 37 years. In both studies, around 59% were female and a majority of > 98% were of White family origin. The majority of patients (> 90%) in both studies came from Eastern Europe (Belarus, Croatia, Georgia, Poland, Russia, Serbia, Ukraine), while the remaining patients (< 10 %) came from the USA or Western Europe (Spain, United Kingdom).

All patients in the subpopulation of both studies (172 vs. 183) had < 2 relapses in the last year and < 3 relapses in the last 2 years before screening and < 2 Gd-enhancing lesion at baseline. These criteria were used by the company to form the relevant subpopulation of treatment-naive patients with no signs of a severe course of disease (see also the text section on the

operationalization of the subpopulation in the current Section 2.1). The majority of this population (97% in ULTIMATE I and 94% in ULTIMATE II) had 1 relapse in the last year before screening. Within 2 years before screening, slightly less than 2 thirds of the population in both studies had 1 relapse and slightly more than 1 third had 2 relapses. Around 74%, i.e. the majority of patients, had no Gd-enhancing lesion at the start of the study. In the operationalization of the relevant subpopulation, the company defined, among other things, the number of T2 lesions falling below 9 as a sign that there are no indications of a severe/highly active course of disease in addition to the criteria relating to relapse frequency. The number of T2 lesions at baseline was clearly above this threshold, with a median of 48 and 58 in ULTIMATE I and 45 and 43 in ULTIMATE II, in the ublituximab arm and teriflunomide arm, respectively. Data on the minimum number of T2 lesions show that all ULTIMATE II patients had at least 9 T2 lesions. In ULTIMATE I, at least 1 patient had a number of 8 T2 lesions at baseline. Nevertheless, all patients in the subpopulation presented by the company fulfilled the criterion regarding the number of Gd-enhancing lesions at the start of the study (< 2), so that the criterion regarding the number of T2 lesions (< 9) did not apply when forming the relevant subpopulation.

Around 75% of patients in ULTIMATE I and 79% of patients in ULTIMATE II had a baseline EDSS score of ≤ 3.5. The median time of the occurrence of first symptoms of the disease was 5 years ago in ULTIMATE I, but 6 years ago in the intervention arm of ULTIMATE II and 7 years ago in its comparator arm. The median duration of disease since diagnosis was 2.6 years in ULTIMATE I, 2.0 years in the intervention arm of ULTIMATE II and 2.8 years in its comparator arm. Before the start of the study, approx. 17% of patients in ULTIMATE I and approx. 18% patients in ULTIMATE II had received multiple sclerosis therapy. The majority had been treated with the drug laquinimod.

In ULTIMATE I, treatment discontinuation occurred in about 10% in the ublituximab arm and about 9 % in the teriflunomide arm. In ULTIMATE II, the proportion of patients who discontinued treatment was higher in the teriflunomide arm (around 12%) than in the ublituximab arm (4%). The most common reason for treatment discontinuation in both studies was withdrawal of consent. No data are available on study discontinuation.

Risk of bias across outcomes (study level)

Table 3 shows the risk of bias across outcomes (risk of bias at study level).

Table 3: Risk of bias across outcomes (study level) – RCT, direct comparison: ublituximab vs. teriflunomide

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of the results	No additional aspects	Risk of bias at study level
			Patients	Treating staff			
ULTIMATE I	Yes	Yes	Yes	Yes	Yes	Yes	Low
ULTIMATE II	Yes	Yes	Yes	Yes	Yes	Yes	Low
RCT: randomized controlled trial							

The risk of bias across outcomes was rated as low for both studies.

Transferability of the study results to the German health care context

In the company's opinion, the results of the studies ULTIMATE I and ULTIMATE II are transferable to the German health care context. It justifies the assessment by stating that the majority of the patients included were of Caucasian origin and that outcomes relevant to the German health care context were recorded. According to the company, there were also no effect modifications relevant to the conclusion by the subgroup characteristic "region" (USA/Western Europe vs. Eastern Europe).

The company did not provide any further information on the transferability of the study results to the German health care context.

2.2 Meta-analyses of the ULTIMATE I and ULTIMATE II studies presented by the company

Results from IPD meta-analyses based on the relevant subpopulations of the ULTIMATE I and ULTIMATE II studies are available for the benefit assessment in the context of this addendum. Both studies are identical in terms of design and methods, as they are based on identical protocols. In addition, the demographic and clinical characteristics of the patients in the subpopulations presented are sufficiently similar between the studies (see Section 2.1). A meta-analytical summary of both studies is therefore considered appropriate and used for the benefit assessment.

2.3 Results on added benefit

2.3.1 Outcomes included

The following patient-relevant outcomes were to be included in the assessment:

- Mortality

- All-cause mortality

- Morbidity
  - Confirmed relapses (operationalized through the annualized relapse rate)
  - Confirmed disability progression (EDSS-based, confirmed over a 24-month period)
  - Disability severity (recorded using the Multiple Sclerosis Functional Composite [MSFC] score)
  - Fatigue measured using the Fatigue Impact Scale (FIS)
- Health-related quality of life
  - Measured using the Multiple Sclerosis Quality of Life-54 (MSQoL-54 questionnaire)
- Side effects
  - Serious adverse events (SAEs)
  - Severe adverse events (AEs) (Common Terminology Criteria for Adverse Events [CTCAE] grade ≥ 3)
  - Discontinuation due to AEs
  - Infusion-related reactions (AEs)
  - Infections and infestations (System Organ Class [SOC], SAE)
  - Other specific AEs, if any

The choice of patient-relevant outcomes deviates from that made by the company, which used further outcomes in the dossier.

Table 4 shows the outcomes for which data were available from the studies ULTIMATE I and ULTIMATE II.

Table 4: Matrix of outcomes – RCT, direct comparison: ublituximab vs. teriflunomide

Study	Outcomes											
	All-cause mortality[a]	Confirmed relapses[b]	Confirmed disability progression (based on EDSS)[c]	Disability severity (MSFC)d	Fatigue (FIS)	Health-related quality of life (MSQoL-54)	SAEs	Severe AEs[e]	Discontinuation due to AEs	Infusion-related reactions (AEs)[f]	Infections and infestations (SOC, SAE)	Further specific AEs[g]
ULTIMATE I	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
ULTIMATE II	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

a. The results on all-cause mortality are based on the information on fatal AEs.
b. Operationalized through the annual relapse rate; a relapse was defined as new or worsening neurological symptoms lasting ≥ 24 hours without fever, injury, infection or drug side effects. The symptoms had to be due to the disease and had to be preceded by a period of neurological stability or neurological improvement of ≥ 30 days. The symptoms had to be accompanied by an increase in the EDSS score by ≥ 0.5 points or an increase by ≥ 2 points in one of the relevant EDSS functional systems or an increase by 1 point in ≥ 2 of the relevant EDSS functional systems. Each relapse had to be confirmed by an independent committee (IRAP) on the basis of the documented neurological examinations.
c. Defined as an increase in EDSS score by ≥ 1 point from baseline in patients with an EDSS score of 0 to 5.5 at baseline or by ≥ 0.5 points from baseline in patients with an EDSS score of > 5.5 points at baseline. Disability progression was considered confirmed if the increase in EDSS score had been confirmed over a period of at least 24 weeks after the initial documentation of neurological deterioration.
d. The validated version of the instrument comprises T25-FW (walking ability), 9-HPT (coordination), and PASAT-3 (cognition).
e. Severe AEs are operationalized as CTCAE grade ≥ 3.
f. Operationalized via a PT list compiled by the company.
g. The following events (MedDRA coding) are considered: “alopecia (PT, AEs)”, "lymphocyte count decreased (PT, severe AEs[e])".

9-HPT: 9-Hole Peg Test; AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EDSS: Expanded Disability Status Scale; FIS: Fatigue Impact Scale; IRAP: Independent Relapse Adjudication Panel; MedDRA: Medical Dictionary for Regulatory Activities; MSFC: Multiple Sclerosis Functional Composite; MSQoL-54: Multiple Sclerosis Quality of Life-54; PASAT-3: Paced Auditory Serial Addition Test-3; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; T25-FW: Timed 25-Foot Walk

Notes on outcomes

Confirmed disability progression (EDSS-based)

In addition to analyses on confirmed disability progression, the company also presented analyses on confirmed improvement in disability (also EDSS-based), each operationalized as time to disability progression or to improvement in disability confirmed over a period of 24

weeks. The analyses on confirmed improvement in disability were not used for the present benefit assessment. The majority of patients in the relevant subpopulation of the ULTIMATE studies had a baseline EDSS score of ≤ 3.5 (75% in ULTIMATE I and 79% in ULTIMATE II, see Table 2). The EDSS scale ranges from 0 to 10 points and increases in 0.5-point increments from an EDSS value of 1.0. An increasing score means an increase in disability in various functional systems such as motor function. An EDSS value of ≤ 3.5 is therefore at the lower end of the scale and includes patients with no, minimal or at most moderate disability in a functional system. A deterioration of disability therefore represents the more relevant operationalization for the patients in the relevant subpopulation of the ULTIMATE studies and is used for the present benefit assessment. Irrespective of this, no statistically significant differences between treatment groups were found for confirmed improvement of disability.

Disability severity (recorded using the MSFC/SDMT)

The MSFC is a multidimensional instrument for mapping the severity of disability caused by multiple sclerosis. Thereby, a standardized total score (MSFC z score) is calculated from the results of the Timed 25-Foot Walk (T25-FW) test for walking ability, the 9-Hole Peg Test (9-HPT) for coordination, and the Paced Auditory Serial Addition Test-3 (PASAT-3) for cognition [13]. In addition to the MSFC, the company also presented results of the SDMT. The SDMT is a test for measuring attention and cognitive processing speed in patients; it is occasionally used to replace PASAT-3 as part of the MSFC. The ULTIMATE studies surveyed both SDMT and PASAT-3, with PASAT-3 also being included as a component in the MSFC analyses. The present benefit assessment uses these MSFC analyses to depict disability severity. As cognitive impairment is therefore already considered in the present benefit assessment via the PASAT-3 as a component of the MSFC, the results for the SDMT are not presented.

With the documents subsequently submitted in the commenting procedure, the company presented responder analyses on the proportion of patients with improvement or deterioration by at least 15% of the scale range (PASAT-3) or by at least 15% in relation to the individual value at baseline (MSFC-z, T25-FW and 9-HPT) for the outcome "severity of disability recorded using the MSFC". The company also presents continuous analyses of the change since the start of the study as supplementary information in the appendix. The MSFC-z score and its components T25-FW and 9-HPT do not have a fixed scale range. The scales of the T25-FW and 9-HPT (walking time and time for completing the coordination test) are open-ended. The MSFC-z score also has no fixed limits, as it can deviate both upwards and downwards from the value of a reference population. Therefore, the use of responder analyses with a defined response criterion is not suitable. The company's approach of using the improvement or deterioration by 15% of the individual baseline value instead leads to different threshold values per patient. It is unclear whether a change in MSFC-z, T25-FW and 9-HPT with a response threshold of 15% in relation to the individual baseline value represents a patient-relevant change in each case. The responder analyses on the MSFC presented by the company

were therefore not used for the present benefit assessment. Instead, the continuous analyses on the change from the start of the study at Week 96 are used for the outcome “severity of disability recorded using MSFC”.

Fatigue (recorded using the FIS)

The FIS is a questionnaire that depicts fatigue-related symptoms and their impact on the daily lives of patients with multiple sclerosis in 3 dimensions (cognitive, physical, social). The questionnaire comprises a total of 40 items, which patients rate on a scale of 0 to 4, with a low score indicating a low impact of fatigue. The scores for the cognitive dimension and the physical dimension, each with a scale of 0 to 40, and the social dimension with a scale of 0 to 80 are used to calculate a total score, which can range from 0 to 160.

With the documents subsequently submitted in the commenting procedure, the company presented responder analyses on the proportion of patients with improvement or deterioration by at least 15% of the scale range at Week 96 for the individual dimensions and for the total score. The results on the follow-up values of the FIS additionally presented by the company in the appendix show that the patients in the relevant subpopulation were in the lower range of the scale with a score of around 49 in the total score in the ublituximab arm and around 45 in the teriflunomide arm at the start of the study, meaning that fatigue at the start of the study had a rather low impact on everyday life in the cognitive, physical and social dimensions. Nevertheless, both an improvement and a worsening of fatigue are possible and relevant for patients in this therapeutic indication. In the pooled ULTIMATE studies, almost the same number of patients in the subpopulation also showed an improvement or deterioration in the FIS total score over the course of the study. For this reason, both improvement and deterioration are considered suitable operationalizations for the outcome of fatigue, recorded using the FIS. The results are interpreted for the overall assessment of the added benefit.

Health-related quality of life (recorded using the MSQoL-54/SF-36)

The MSQoL-54 is a questionnaire for recording health-related quality of life on the basis of general and indication-specific questions. It was specifically developed for patients with multiple sclerosis based on Version 1 of the SF-36. The MSQoL-54 comprises 12 subscales (physical health, physical role restrictions, emotional role restrictions, pain, emotional well-being, energy, health perception, social functioning, cognitive functioning, health burden, general quality of life and sexual functioning) and 2 individual items (satisfaction with sexual functioning and change in health status). The two composite scores Physical Health Composite Score (PHCS) and Mental Health Composite Score (MHCS), which summarize physical health and mental health respectively, can be formed from the values of the subscales. The 2 individual items are not included in the PHCS and MHCS composite scores. Values from 0 to

100 can be achieved in the individual subscales as well as in the composite scores and individual items, with higher scores meaning a higher quality of life.

With the documents subsequently submitted in the commenting procedure, the company presented responder analyses for the outcome health-related quality of life recorded using the MSQoL-54 on the proportion of patients with improvement or deterioration at Week 96 for the PHCS and MHCS sum scores and for the individual subscales and for the two individual items. In each case, the company used a value of at least 15% of the scale range as a response criterion. The analyses presented by the company were used for the benefit assessment. The results on the follow-up values of the MSQoL-54 additionally presented by the company in the appendix show that the patients in the relevant subpopulation of the ULTIMATE studies were in the middle range of the scale at baseline with a score of 62 in the PHCS and 64 in the MHCS (ublituximab arm) and 65 in the PHCS and 67 in the MHCS (teriflunomide arm). As both an improvement and a deterioration in health-related quality of life recorded using the MSQoL-54 are therefore possible for patients in this therapeutic indication, both the improvement and the deterioration are considered suitable operationalizations in the benefit assessment. The results are interpreted for the overall assessment of the added benefit.

The results on the SF-36 (responder analyses on the proportion of patients with improvement or deterioration in the SF-36 at Week 96 with a response criterion of 15% of the scale range) additionally presented by the company are not used for the present assessment, as the information is already included in the MSQoL-54.

Side effects

SAEs and severe AEs

With the documents subsequently submitted in the commenting procedure, the company presented additional analyses on treatment emergent adverse events (TEAEs) for the outcomes of SAEs and severe AEs, in which disease-related events were excluded. According to the company, the events defined as disease-related were compiled independently by two medical experts in Module 4 A of the original dossier and comprise an extensive list consisting of 135 different Preferred Terms (PTs) according to Medical Dictionary for Regulatory Activities (MedDRA). This list contains a large proportion of unspecific AE events that can also occur as a result of a disease other than multiple sclerosis, such as the PT events “fall”, “bronchitis” and “obesity”. In addition, PTs that are clearly associated with multiple sclerosis or its progression, such as multiple sclerosis relapse, are not included in this list. This approach is not appropriate. Therefore, the analyses of the TEAEs excluding disease-related events are not used for the present benefit assessment. The analyses on the overall rates of SAEs and severe AEs, in each case without exclusion of disease-related events, are nevertheless suitable in the present situation, as the lists of events that occurred according to PT/SOC show that no events were included in the analyses that clearly represent a progression of the underlying

disease (such as multiple sclerosis relapse). The overall rates of SAEs and severe AEs without exclusion of disease-related events were therefore used for the benefit assessment.

Infusion-related reactions (AEs)

With the documents subsequently submitted in the commenting procedure, the company presented analyses on the outcome "infusion-related reactions" based on the events of a PT list that, according to the company, was pre-specified in Module 4 A of the original dossier. However, as already described in dossier assessment A24-13, this is still not clear from the study documents and the documents subsequently submitted by the company. Among other things, the PT list includes symptoms that refer to the skin (e.g. pruritus, urticaria), the respiratory tract (e.g. dyspnoea, bronchospasm), the circulation (e.g. hypotension) and the gastrointestinal tract (e.g. nausea, vomiting), as well as occasional clinical diagnoses of an infusion reaction resulting from the symptoms (e.g. the PTs “infusion reaction”, “hypersensitivity”). According to the information in the study protocol, events that occurred during the infusion or up to 24 hours after the end of the infusion were documented as infusion-related reactions. This operationalization is regarded as a suitable representation of infusion-related reactions and is used for the benefit assessment in the present data constellation. The analyses at AE level presented by the company were used for the outcome "infusion-related reactions", irrespective of the severity.

As already described in dossier assessment A24-13, it was not clear from the original dossier whether the events underlying the outcome of infusion-related reactions were also included in the general AE analysis of the TEAEs. With the comments, the company clarifies that the general AE analysis of the TEAEs covers all AEs that occurred during the study. This means that the interpretability of the common PTs/SOCs is not restricted.

2.3.2 Risk of bias

Table 5 describes the risk of bias for the results of the relevant outcomes.

Table 5: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: ublituximab vs. teriflunomide

Study	Study level	Outcomes											
		All-cause mortality[a]	Confirmed relapses[b]	Confirmed disability progression (based on EDSS)[c]	Disability severity (MSFC)[d]	Fatigue (FIS)	Health-related quality of life (MSQoL-54)	SAEs	Severe AEs[e]	Discontinuation due to AEs	Infusion-related reactions (AEs)[f]	Infections and infestations (SOC, SAE)	Further specific AEs[g]
ULTIMATE I	L	L	L	L	L	L	L	L	L	L	L	L	L
ULTIMATE II	L	L	L	L	L	L	L	L	L	L	L	L	L

a. The results on all-cause mortality are based on the information on fatal AEs.
b. Operationalized through the annual relapse rate; a relapse was defined as new or worsening neurological symptoms lasting ≥ 24 hours without fever, injury, infection or drug side effects. The symptoms had to be due to the disease and had to be preceded by a period of neurological stability or neurological improvement of ≥ 30 days. The symptoms had to be accompanied by an increase in the EDSS score by ≥ 0.5 points or an increase by ≥ 2 points in one of the relevant EDSS functional systems or an increase by 1 point in ≥ 2 of the relevant EDSS functional systems. Each relapse had to be confirmed by an independent committee (IRAP) on the basis of the documented neurological examinations.
c. Defined as an increase in EDSS score by ≥ 1 point from baseline in patients with an EDSS score of 0 to 5.5 at baseline or by ≥ 0.5 points from baseline in patients with an EDSS score of > 5.5 points at baseline. Disability progression was considered confirmed if the increase in EDSS score had been confirmed over a period of at least 24 weeks after the initial documentation of neurological deterioration.
d. The validated version of the instrument comprises T25-FW (walking ability), 9-HPT (coordination), and PASAT-3 (cognition).
e. Severe AEs are operationalized as CTCAE grade ≥ 3.
f. Operationalized via a PT list compiled by the company.
g. The following events (MedDRA coding) are considered: “alopecia (PT, AEs)”, "lymphocyte count decreased (PT, severe AEs[e])".

9-HPT: 9-Hole Peg Test; AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EDSS: Expanded Disability Status Scale; FIS: Fatigue Impact Scale; H: high; IRAP: Independent Relapse Adjudication Panel; L: low; MedDRA: Medical Dictionary for Regulatory Activities; MSFC: Multiple Sclerosis Functional Composite; MSQoL-54: Multiple Sclerosis Quality of Life-54; PASAT-3: Paced Auditory Serial Addition Test-3; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; T25-FW: Timed 25-Foot Walk

The risk of bias of the results for all outcomes is rated as low.

2.3.3 Results

Table 6, Table 7, Table 8 and Table 9 summarize the results of the comparison of ublituximab with teriflunomide in treatment-naive patients with RMS without indications of a severe

course of disease. Where necessary, data subsequently submitted by the company in the commenting procedure and after the oral hearing are supplemented by the Institute's calculations.

Kaplan-Meier curves on the presented time-to-event analyses can be found in Appendix A of the full dossier assessment. Forest plots for the Institute's calculation are shown in Appendix B. The results on common AEs, SAEs, severe AEs and discontinuations due to AEs are presented in Appendix C.

Table 6: Results (mortality, morbidity, [dichotomous], health-related quality of life, side effects) – RCT, direct comparison: ublituximab vs. teriflunomide (multipage table)

Outcome category outcome study	Ublituximab N	Ublituximab patients with event n (%)	Teriflunomide N	Teriflunomide patients with event n (%)	Ublituximab vs. teriflunomide RR [95% CI]; p-value
Mortality					
All-cause mortality[a]					
ULTIMATE I	99	1 (1.0)	91	0 (0.0)	–[b]
ULTIMATE II	75	0 (0.0)	94	0 (0.0)	–[b]
Total					–[b]
Morbidity					
Fatigue (FIS - improvement/worsening at Week 96[c])					
Total score					
Improvement					
ULTIMATE I	97	17 (17.5)	90	9 (10.0)	1.75 [0.82; 3.73]; 0.144[d]
ULTIMATE II	75	15 (20.0)	93	12 (12.9)	1.55 [0.77; 3.11]; 0.229[d]
Total[e]					1.64 [0.99; 2.74]; 0.057
Deterioration					
ULTIMATE I	97	12 (12.4)	90	10 (11.1)	1.11 [0.51; 2.45]; 0.808[d]
ULTIMATE II	75	6 (8.0)	93	9 (9.7)	0.83 [0.31; 2.22]; 0.734[d]
Total[e]					0.99 [0.53; 1.83]; 0.970
Cognitive domain					
Improvement					
ULTIMATE I	97	21 (21.6)	90	14 (15.6)	1.39 [0.75; 2.57][d]
ULTIMATE II	75	17 (22.7)	93	19 (20.4)	1.11 [0.62; 1.98][d]
Total[e]					1.24 [0.81; 1.89]
Deterioration					
ULTIMATE I	97	16 (16.5)	90	16 (17.8)	0.93 [0.49; 1.74][d]
ULTIMATE II	75	7 (9.3)	93	10 (10.8)	0.87 [0.35; 2.17][d]
Total[e]					0.91 [0.54; 1.53]
Physical domain					
Improvement					
ULTIMATE I	97	23 (23.7)	90	14 (15.6)	1.52 [0.84; 2.78][d]
ULTIMATE II	75	18 (24.0)	93	17 (18.3)	1.31 [0.73; 2.37][d]
Total[e]					1.42 [0.93; 2.16]

Table 6: Results (mortality, morbidity, [dichotomous], health-related quality of life, side effects) – RCT, direct comparison: ublituximab vs. teriflunomide (multipage table)

Outcome category outcome study	Ublituximab N	Ublituximab patients with event n (%)	Teriflunomide N	Teriflunomide patients with event n (%)	Ublituximab vs. teriflunomide RR [95% CI]; p-value
Deterioration					
ULTIMATE I	97	19 (19.6)	90	16 (17.8)	1.10 [0.60; 2.01][d]
ULTIMATE II	75	7 (9.3)	93	14 (15.1)	0.62 [0.26; 1.46][d]
Total[e]					0.89 [0.55; 1.46]
Social dimension					
Improvement					
ULTIMATE I	97	15 (15.5)	90	10 (11.1)	1.39 [0.66; 2.94][d]
ULTIMATE II	75	12 (16.0)	93	13 (14.0)	1.14 [0.56; 2.36][d]
Total[e]					1.26 [0.75; 2.12]
Deterioration					
ULTIMATE I	97	15 (15.5)	90	10 (11.1)	1.39 [0.66; 2.94][d]
ULTIMATE II	75	6 (8.0)	93	12 (12.9)	0.62 [0.24; 1.57][d]
Total[e]					1.00 [0.56; 1.77]
Health-related quality of life					
MSQoL-54 – improvement/deterioration at Week 96[f]					
PHCS sum score					
Improvement					
ULTIMATE I	97	24 (24.7)	90	12 (13.3)	1.86 [0.99; 3.49]; 0.049[d]
ULTIMATE II	75	11 (14.7)	93	10 (10.8)	1.36 [0.61; 3.04]; 0.592[d]
Total[e]					1.65 [1.01; 2.70]; 0.047
Deterioration					
ULTIMATE I	97	5 (5.2)	90	7 (7.8)	0.66 [0.22; 2.01]; 0.532[d]
ULTIMATE II	75	1 (1.3)	93	10 (10.8)	0.12 [0.02; 0.95]; 0.014[d]
Total[e]					0.37 [0.14; 0.93]; 0.035
MHCS sum score					
Improvement					
ULTIMATE I	97	20 (20.6)	90	15 (16.7)	1.24 [0.68; 2.27]; 0.532[d]
ULTIMATE II	75	19 (25.3)	93	17 (18.3)	1.39 [0.78; 2.47]; 0.354[d]
Total[e]					1.31 [0.86; 1.99]; 0.205
Deterioration					
ULTIMATE I	97	7 (7.2)	90	7 (7.8)	0.93 [0.34; 2.54]; 0.911[d]
ULTIMATE II	75	5 (6.7)	93	16 (17.2)	0.39 [0.15; 1.01]; 0.046[d]
Total[e]					0.57 [0.29; 1.12]; 0.104

Table 6: Results (mortality, morbidity, [dichotomous], health-related quality of life, side effects) – RCT, direct comparison: ublituximab vs. teriflunomide (multipage table)

Outcome category outcome study	Ublituximab		Teriflunomide		Ublituximab vs. teriflunomide
	N	patients with event n (%)	N	patients with event n (%)	RR [95% CI]; p-value
Physical health					
Improvement					
ULTIMATE I	97	26 (26.8)	90	11 (12.2)	2.19 [1.15; 4.18][d]
ULTIMATE II	75	11 (14.7)	93	13 (14.0)	1.05 [0.50; 2.21][d]
Total[e]					1.62 [1.00; 2.61]
Deterioration					
ULTIMATE I	97	17 (17.5)	90	12 (13.3)	1.31 [0.67; 2.60][d]
ULTIMATE II	75	6 (8.0)	93	15 (16.1)	0.50 [0.20; 1.22][d]
Total[e]					0.89 [0.52; 1.51]
Health perception					
Improvement					
ULTIMATE I	97	19 (19.6)	90	17 (18.9)	1.04 [0.58; 1.87][d]
ULTIMATE II	75	16 (21.3)	93	22 (23.7)	0.90 [0.51; 1.59][d]
Total[e]					0.97 [0.64; 1.45]
Deterioration					
ULTIMATE I	97	9 (9.3)	90	14 (15.6)	0.60 [0.27; 1.31][d]
ULTIMATE II	75	11 (14.7)	93	22 (23.7)	0.62 [0.32; 1.20][d]
Total[e]					0.61 [0.37; 1.01]
Energy					
Improvement					
ULTIMATE I	97	30 (30.9)	90	20 (22.2)	1.39 [0.85; 2.27][d]
ULTIMATE II	75	27 (36.0)	93	23 (24.7)	1.46 [0.91; 2.32][d]
Total[e]					1.42 [1.02; 1.99]
Deterioration					
ULTIMATE I	97	8 (8.2)	90	5 (5.6)	1.48 [0.50; 4.37][d]
ULTIMATE II	75	5 (6.7)	93	15 (16.1)	0.41 [0.16; 1.09][d]
Total[e]					0.71 [0.36; 1.41]
Physical role restrictions					
Improvement					
ULTIMATE I	97	35 (36.1)	90	21 (23.3)	1.55 [0.98; 2.45][d]
ULTIMATE II	75	26 (34.7)	93	24 (25.8)	1.34 [0.84; 2.14][d]
Total[e]					1.45 [1.04; 2.00]

Table 6: Results (mortality, morbidity, [dichotomous], health-related quality of life, side effects) – RCT, direct comparison: ublituximab vs. teriflunomide (multipage table)

Outcome category outcome study	Ublituximab		Teriflunomide		Ublituximab vs. teriflunomide
	N	patients with event n (%)	N	patients with event n (%)	RR [95% CI]; p-value
Deterioration					
ULTIMATE I	97	16 (16.5)	90	16 (17.8)	0.93 [0.49; 1.74][d]
ULTIMATE II	75	12 (16.0)	93	24 (25.8)	0.62 [0.33; 1.16][d]
Total[e]					0.75 [0.49; 1.17]
Social functioning					
Improvement					
ULTIMATE I	97	22 (22.7)	90	22 (24.4)	0.93 [0.55; 1.56][d]
ULTIMATE II	75	19 (25.3)	93	18 (19.4)	1.31 [0.74; 2.31][d]
Total[e]					1.09 [0.74; 1.59]
Deterioration					
ULTIMATE I	97	17 (17.5)	90	14 (15.6)	1.13 [0.59; 2.15][d]
ULTIMATE II	75	11 (14.7)	93	24 (25.8)	0.57 [0.30; 1.08][d]
Total[e]					0.79 [0.51; 1.25]
Pain					
Improvement					
ULTIMATE I	97	23 (23.7)	90	20 (22.2)	1.07 [0.63; 1.81][d]
ULTIMATE II	75	25 (33.3)	93	15 (16.1)	2.07 [1.18; 3.63][d]
Total[e]					1.46 [1.00; 2.13]
Deterioration					
ULTIMATE I	97	14 (14.4)	90	18 (20.0)	0.72 [0.38; 1.36][d]
ULTIMATE II	75	9 (12.0)	93	18 (19.4)	0.62 [0.30; 1.30][d]
Total[e]					0.67 [0.42; 1.09]
Emotional wellbeing					
Improvement					
ULTIMATE I	97	17 (17.5)	90	12 (13.3)	1.31 [0.67; 2.60][d]
ULTIMATE II	75	24 (32.0)	93	18 (19.4)	1.65 [0.97; 2.81][d]
Total[e]					1.51 [0.99; 2.29]
Deterioration					
ULTIMATE I	97	10 (10.3)	90	10 (11.1)	0.93 [0.41; 2.12][d]
ULTIMATE II	75	8 (10.7)	93	21 (22.6)	0.47 [0.22; 1.01][d]
Total[e]					0.63 [0.37; 1.10]

Table 6: Results (mortality, morbidity, [dichotomous], health-related quality of life, side effects) – RCT, direct comparison: ublituximab vs. teriflunomide (multipage table)

Outcome category outcome study	Ublituximab N	Ublituximab patients with event n (%)	Teriflunomide N	Teriflunomide patients with event n (%)	Ublituximab vs. teriflunomide RR [95% CI]; p-value
Emotional role restrictions					
Improvement					
ULTIMATE I	97	26 (26.8)	90	23 (25.6)	1.05 [0.65; 1.70][d]
ULTIMATE II	75	20 (26.7)	93	20 (21.5)	1.24 [0.72; 2.13][d]
Total[e]					1.13 [0.79; 1.62]
Deterioration					
ULTIMATE I	97	14 (14.4)	90	11 (12.2)	1.18 [0.57; 2.46][d]
ULTIMATE II	75	9 (12.0)	93	21 (22.6)	0.53 [0.26; 1.09][d]
Total[e]					0.78 [0.47; 1.29]
Cognitive functioning					
Improvement					
ULTIMATE I	97	20 (20.6)	90	13 (14.4)	1.43 [0.76; 2.70][d]
ULTIMATE II	75	24 (32.0)	93	18 (19.4)	1.65 [0.97; 2.81][d]
Total[e]					1.55 [1.03; 2.33]
Deterioration					
ULTIMATE I	97	16 (16.5)	90	6 (6.7)	2.47 [1.01; 6.05][d]
ULTIMATE II	75	5 (6.7)	93	15 (16.1)	0.41 [0.16; 1.09][d]
Total[e]					1.07 [0.59; 1.94]
Sexual functioning					
Improvement					
ULTIMATE I	97	16 (16.5)	90	15 (16.7)	0.99 [0.52; 1.88][d]
ULTIMATE II	75	7 (9.3)	93	11 (11.8)	0.79 [0.32; 1.94][d]
Total[e]					0.91 [0.54; 1.54]
Deterioration					
ULTIMATE I	97	17 (17.5)	90	16 (17.8)	0.99 [0.53; 1.83][d]
ULTIMATE II	75	15 (20.0)	93	20 (21.5)	0.93 [0.51; 1.69][d]
Total[e]					0.96 [0.62; 1.47]
Health burden					
Improvement					
ULTIMATE I	97	37 (38.1)	90	29 (32.2)	1.18 [0.80; 1.75][d]
ULTIMATE II	75	29 (38.7)	93	24 (25.8)	1.50 [0.96; 2.34][d]
Total[e]					1.31 [0.98; 1.76]

Table 6: Results (mortality, morbidity, [dichotomous], health-related quality of life, side effects) – RCT, direct comparison: ublituximab vs. teriflunomide (multipage table)

Outcome category outcome study	Ublituximab N	Ublituximab patients with event n (%)	Teriflunomide N	Teriflunomide patients with event n (%)	Ublituximab vs. teriflunomide RR [95% CI]; p-value
Deterioration					
ULTIMATE I	97	12 (12.4)	90	16 (17.8)	0.70 [0.35; 1.39][d]
ULTIMATE II	75	10 (13.3)	93	17 (18.3)	0.73 [0.36; 1.50][d]
Total[e]					0.71 [0.43; 1.17]
General quality of life					
Improvement					
ULTIMATE I	97	11 (11.3)	90	9 (10.0)	1.13 [0.49; 2.61][d]
ULTIMATE II	75	10 (13.3)	93	11 (11.8)	1.13 [0.51; 2.51][d]
Total[e]					1.13 [0.63; 2.01]
Deterioration					
ULTIMATE I	97	7 (7.2)	90	7 (7.8)	0.93 [0.34; 2.54][d]
ULTIMATE II	75	6 (8.0)	93	8 (8.6)	0.93 [0.34; 2.56][d]
Total[e]					0.93 [0.45; 1.90]
Change in health status (presented as supplementary information)[g]					
Improvement					
ULTIMATE I	*97*	*38 (39.2)*	*90*	*42 (46.7)*	*0.84 [0.60; 1.17][d]*
ULTIMATE II	*75*	*44 (58.7)*	*93*	*35 (37.6)*	*1.56 [1.13; 2.15][d]*
Total[e]					*1.14 [0.91; 1.43]*
Deterioration					
ULTIMATE I	*97*	*13 (13.4)*	*90*	*9 (10.0)*	*1.34 [0.60; 2.98][d]*
ULTIMATE II	*75*	*8 (10.7)*	*93*	*19 (20.4)*	*0.52 [0.24; 1.13][d]*
Total[e]					*0.81 [0.47; 1.39]*
Satisfaction with sexual functioning (supplementary information)[g]					
Improvement					
ULTIMATE I	*97*	*21 (21.6)*	*90*	*19 (21.1)*	*1.03 [0.59; 1.78][d]*
ULTIMATE II	*75*	*15 (20.0)*	*93*	*29 (31.2)*	*0.64 [0.37; 1.11][d]*
Total[e]					*0.81 [0.55; 1.19]*
Deterioration					
ULTIMATE I	*97*	*23 (23.7)*	*90*	*24 (26.7)*	*0.89 [0.54; 1.46][d]*
ULTIMATE II	*75*	*14 (18.7)*	*93*	*20 (21.5)*	*0.87 [0.47; 1.60][d]*
Total[e]					*0.88 [0.60; 1.29]*

Table 6: Results (mortality, morbidity, [dichotomous], health-related quality of life, side effects) – RCT, direct comparison: ublituximab vs. teriflunomide (multipage table)

Outcome category outcome study	Ublituximab		Teriflunomide		Ublituximab vs. teriflunomide
	N	patients with event n (%)	N	patients with event n (%)	RR [95% CI]; p-value
Side effects					
AEs (supplementary information)					
ULTIMATE I	99	81 (81.8)	91	76 (83.5)	–
ULTIMATE II	75	63 (84.0)	94	85 (90.4)	–
SAEs					
ULTIMATE I	99	5 (5.1)	91	7 (7.7)	0.66 [0.22; 2.00]; 0.531[d]
ULTIMATE II	75	10 (13.3)	94	5 (5.3)	2.51 [0.90; 7.02]; 0.071[d]
Total[e]					1.36 [0.66; 2.77]; 0.404
Severe AEs[h]					
ULTIMATE I	99	17 (17.2)	91	13 (14.3)	1.20 [0.62; 2.33]; 0.623[d]
ULTIMATE II	75	12 (16.0)	94	4 (4.3)	3.76 [1.26; 11.18]; 0.010[d]
Total[e]					1.73 [0.9996; 3.01]; 0.0502
Discontinuation due to AEs					
ULTIMATE I	99	6 (6.1)	91	0 (0)	11.96 [0.68; 209.36]; 0.018[d]
ULTIMATE II	75	1 (1.3)	94	0 (0)	3.75 [0.15; 90.75]; 0.343[d]
Total[e]					8.18 [0.99; 67.83]; 0.051
Infusion-related reactions (AEs)[i]					
ULTIMATE I	99	44 (44.4)	91	10 (11.0)	4.04 [2.17; 7.55]; < 0.001[d]
ULTIMATE II	75	30 (40.0)	94	11 (11.7)	3.42 [1.84; 6.36]; < 0.001[d]
Total[e]					3.74 [2.41; 5.82]; < 0.001
Infections and infestations (SOC, SAEs)					
ULTIMATE I	99	4 (4.0)	91	2 (2.2)	1.84 [0.34; 9.80]; 0.533[d]
ULTIMATE II	75	2 (2.7)	94	3 (3.2)	0.84 [0.14; 4.87]; 0.910[d]
Total[e]					1.28 [0.39; 4.20]; 0.688
Lymphocyte count decreased (PT, severe AEs)					
ULTIMATE I	99	6 (6.1)	91	0 (0)	11.96 [0.68; 209.36]; 0.018[d]
ULTIMATE II	75	5 (6.7)	94	0 (0)	13.75 [0.77; 244.78]; 0.011[d]
Total[e]					12.78 [1.68; 97.37]; 0.014
Alopecia (PT, AEs)					
ULTIMATE I	99	1 (1.0)	91	10 (11.0)	0.09 [0.01; 0.70]; 0.003[d]
ULTIMATE II	75	4 (5.3)	94	17 (18.1)	0.29 [0.10; 0.84]; 0.013[d]
Total[e]					0.21 [0.09; 0.53]; < 0.001

Table 6: Results (mortality, morbidity, [dichotomous], health-related quality of life, side effects) – RCT, direct comparison: ublituximab vs. teriflunomide (multipage table)

Outcome category outcome study	Ublituximab N	Ublituximab patients with event n (%)	Teriflunomide N	Teriflunomide patients with event n (%)	Ublituximab vs. teriflunomide RR [95% CI]; p-value
a. The results on all-cause mortality are based on the information on fatal AEs. b. An effect estimate (including confidence interval and p-value) was not performed due to the low number of events. c. An increase/decrease by ≥ 15% of the score range compared to baseline is considered a clinically relevant deterioration/improvement (score range for the cognitive dimension and for the physical dimension 0 to 40, for the social dimension 0 to 80 and for the total score 0 to 160). d. Institute's calculation of RR, CI (asymptotic), and p-value (unconditional exact test, CSZ method according to [14]). In case of 0 events in one study arm, the correction factor 0.5 was used for the calculation of effect and CI in both study arms. Discrepancy between p-value (exact) and CI (asymptotic) is possible due to different calculation methods. e. Institute's calculation of RR, CI (asymptotic) and p-value (meta-analysis according to Mantel and Haenszel). f. An increase/decrease by ≥ 15 points from baseline is defined as a clinically relevant improvement/deterioration (score range 0 to 100). g. The item is not taken into account in any of the sum scores. h. Operationalized as CTCAE grade ≥ 3. i. Including: flu-like illness (PT, AEs), fever (PT, AEs). AE: adverse event; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; FIS: Fatigue Impact Scale; MHCS: mental health composite score; MSQoL-54: Multiple Sclerosis Quality of Life-54; n: number of patients with (at least 1) event; N: number of analysed patients; PHCS: physical health composite score; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; SOC: System Organ Class					

Table 7: Results (morbidity, confirmed relapses) – RCT, direct comparison: ublituximab vs. teriflunomide

Outcome category outcome study	Ublituximab			Teriflunomide			Ublituximab vs. teriflunomide
	N	n_E	annualized relapse rate [95% CI][a]	N	n_E	annualized relapse rate [95% CI][a]	rate ratio [95% CI]; p-value[a]
Morbidity							
Confirmed relapses (EDSS-based)							
Annualized relapse rate							
ULTIMATE I	97	13	ND[b]	90	19	ND[b]	0.62 [0.13; 1.11]; 0.231
ULTIMATE II	75	5	0.04 [0.01; 0.15]	93	24	0.14 [0.05; 0.41]	0.27 [-0.01; 0.55]; 0.014
Total[c]							0.42 [0.15; 0.68]; 0.007

a. Annualized relapse rate and CI (per treatment arm) as well as rate ratio with CI and p-value (group comparison): negative binomial model, adjusted for prespecified stratification factors (EDSS strata and region) and logarithm of treatment duration as offset variable.
b. According to the company: As the regression models did not converge, effect estimates could not be reported.
c. Calculated from meta-analysis.

CI: confidence interval; EDSS: Expanded Disability Status Scale; N: number of analysed patients; n: number of events (several events per patient possible); ND: no data; RCT: randomized controlled trial

Table 8: Results (morbidity, time to event) – RCT, direct comparison: ublituximab vs. teriflunomide

Outcome category outcome study	Ublituximab		Teriflunomide		Ublituximab vs. teriflunomide
	N	median time to event in months [95% CI] patients with event n (%)	N	median time to event in months [95% CI] patients with event n (%)	HR [95% CI]; p-value[a]
Morbidity					
Confirmed disability progression (EDSS-based)[b]					
ULTIMATE I	97	NA 1 (1.0)	90	NA 2 (2.2)	0.46 [0.04; 5.10]; 0.518
ULTIMATE II	75	NA 3 (4.0)	93	NA 6 (6.5)	0.59 [0.15; 2.38]; 0.457
Total[c]					0.52 [0.16; 1.72]; 0.276

a. Effect, CI and p-value: stratified Cox proportional hazards model, unclear which factors were used for adjustment and/or stratification; p-value: score test
b. Defined as an increase in the EDSS score by ≥ 1 point from baseline in patients with a baseline EDSS score of 0 to 5.5, or by ≥ 0.5 points from baseline in patients with a baseline EDSS score of > 5.5 points; confirmed over a 24-month period.
c. Calculated from meta-analysis.

CI: confidence interval; EDSS: Expanded Disability Status Scale; HR: hazard ratio; N: number of analysed patients; n: number of patients with event; NA: not achieved; RCT: randomized controlled trial

Table 9: Results (morbidity, continuous) – RCT, direct comparison: ublituximab vs. teriflunomide (multipage table)

Outcome category outcome study	Ublituximab N[a]	values at baseline mean (SD)	change at Week 96 mean [95 % CI]	Teriflunomide N[a]	values at baseline mean (SD)	change at Week 96 mean [95 % CI]	Ublituximab vs. teriflunomide MD [95% CI]; p-value[b]
Morbidity							
Disability severity (MSFC)							
z -score[c]							
ULTIMATE I	97	0.03 (1.94)	0.64 [0.39; 0.89]	90	0.09 (1.74)	0.39 [0.14; 0.64]	0.25 [-0.01; 0.52]; 0.062
ULTIMATE II	75	-0.18 (2.58)	0.66 [0.36; 0.97]	93	0.01 (1.85)	0.54 [0.27; 0.82]	0.12 [-0.19; 0.43]; 0.455
Total[d]							0.19 [-0.02; 0.40]; 0.080
Walking ability (T25-FW [seconds][e])							
ULTIMATE I	97	6.86 (5.81)	0.13 [-0.19; 0.45]	90	6.33 (3.47)	0.16 [-0.16; 0.48]	-0.03 [-0.40; 0.34]
ULTIMATE II	75	7.12 (5.56)	-0.18 [-0.76; 0.40]	93	6.69 (4.05)	-0.22 [-0.75; 0.32]	0.04 [-0.67; 0.74]
Total[d]							0.01 [-0.38; 0.40]
Coordination (9-HPT [seconds][e])							
ULTIMATE I	97	0.04 (0.01)	0.002 [0.001; 0.004]	90	0.04 (0.01)	0.001 [-0.001; 0.002]	0.001 [-0.000; 0.003]
ULTIMATE II	75	0.05 (0.01)	0.003 [0.001; 0.005]	93	0.05 (0.01)	0.000 [-0.001; 0.002]	0.003 [0.001; 0.004]
Total[d]							0.002 [0.001; 0.003]
Cognition (PASAT-3 [correct answers][c])							
ULTIMATE I	97	46.80 (9.65)	4.84 [2.84; 6.85]	90	45.93 (11.27)	3.67 [1.68; 5.66]	1.18 [-0.83; 3.19]
ULTIMATE II	75	46.68 (12.40)	4.68 [2.66; 6.71]	93	46.52 (12.01)	5.17 [3.30; 7.04]	-0.48 [-2.39; 1.43]
Total[d]							0.35 [-1.11; 1.81]

a. Number of patients taken into account in the analysis for calculating the effect estimation; baseline values may rest on different patient numbers.
b. Effect, CI and p-value: MMRM without imputation strategy for missing values (with unstructured covariance matrix, restricted maximum likelihood estimation and Satterthwaite approximation), adjusted for region, EDSS strata, time of analysis, interaction between treatment and time of analysis, baseline value.
c. Higher (increasing) values indicate improved symptoms; positive effects (intervention minus control) indicate an advantage for ublituximab.
d. Calculated from meta-analysis.
e. Lower (decreasing) values indicate improved symptoms; negative effects (intervention minus control) indicate an advantage for ublituximab.

Table 9: Results (morbidity, continuous) – RCT, direct comparison: ublituximab vs. teriflunomide (multipage table)

Outcome category outcome study	Ublituximab			Teriflunomide			Ublituximab vs. teriflunomide
	N[a]	values at baseline mean (SD)	change at Week 96 mean [95 % CI]	N[a]	values at baseline mean (SD)	change at Week 96 mean [95 % CI]	MD [95% CI]; p-value[b]
9-HPT: 9-Hole Peg Test; CI: confidence interval; MD: mean difference; MMRM: mixed-effects model with repeated measures; MSFC: Multiple Sclerosis Functional Composite; N: number of analysed patients; PASAT-3: Paced Auditory Serial Addition Test-3; RCT: randomized controlled trial; SD: standard deviation; T25-FW: Timed 25-Foot Walk							

On the basis of the available information, at most proof, e.g. of an added benefit, can be determined for all outcomes.

Mortality

All-cause mortality

The results on all-cause mortality are based on data on fatal AEs. For the outcome of all-cause mortality, there was altogether one event in the ublituximab arm of the ULTIMATE I study. There was no hint of an added benefit of ublituximab in comparison with teriflunomide; an added benefit is therefore not proven.

Morbidity

Confirmed relapses

The meta-analysis shows a statistically significant difference between the treatment groups in favour of ublituximab for the outcome of confirmed relapses, operationalized using the annualized relapse rate. However, there was an effect modification by the characteristic “sex" for this outcome (see Section 2.3.4). For men, there is proof of an added benefit of ublituximab in comparison with teriflunomide. For women, there is no hint of an added benefit of ublituximab in comparison with teriflunomide; an added benefit is therefore not proven for women.

Confirmed disability progression (EDSS-based)

The meta-analysis showed no statistically significant difference between the treatment groups for the outcome "confirmed disability progression (EDSS-based)". There is no hint of an added benefit of ublituximab in comparison with teriflunomide; an added benefit is therefore not proven.

Disability severity (MSFC)

The meta-analysis showed no statistically significant difference between treatment groups for the outcome “severity of disability”, recorded using the MSFC-z score. There is no hint of an added benefit of ublituximab in comparison with teriflunomide; an added benefit is therefore not proven.

Fatigue (FIS)

The meta-analysis showed no statistically significant difference between the treatment groups for the outcome “fatigue” (analyses on improvement and deterioration of the FIS total score compared to baseline). There is no hint of an added benefit of ublituximab in comparison with teriflunomide; an added benefit is therefore not proven.

Health-related quality of life (MSQoL-54)

The meta-analysis shows a statistically significant difference between the treatment groups in favour of ublituximab for the MSQoL-54 PHCS (analyses on the improvement and deterioration from baseline). There is proof of an added benefit of ublituximab in comparison with teriflunomide.

The meta-analysis showed no statistically significant difference between the treatment groups for the MSQoL-54 MHCS (analyses on improvement and deterioration compared to baseline). There is no hint of an added benefit of ublituximab in comparison with teriflunomide; an added benefit is therefore not proven.

Side effects

SAEs

For the outcome of SAEs, the meta-analysis does not show any statistically significant differences between treatment groups. However, there was an effect modification by the characteristic “sex" for this outcome (see Section 2.3.4). For men, there was no hint of greater or lesser harm from ublituximab in comparison with teriflunomide; greater or lesser harm is therefore not proven for men. For women, there was a proof of greater harm from ublituximab in comparison with teriflunomide.

Severe AEs and discontinuation due to AEs

The meta-analysis showed no statistically significant difference between treatment groups for the outcomes of severe AEs and discontinuation due to AEs. In each case, there was no hint of greater or lesser harm from ublituximab in comparison with teriflunomide; greater or lesser harm is therefore not proven.

Specific AEs

Infusion-related reactions (AEs), reduced lymphocyte count (severe AEs)

The meta-analysis shows a statistically significant difference between the treatment groups to the disadvantage of ublituximab for the outcomes of both infusion-related reactions (AEs) and lymphocyte count decreased (severe AEs). In each case, there is proof of greater harm from ublituximab in comparison with teriflunomide.

Infections and infestations (SAEs)

The meta-analysis showed no statistically significant difference between the treatment groups for the outcome "infections and infestations (SAEs)". There was no hint of greater or lesser harm from ublituximab in comparison with teriflunomide; greater or lesser harm is therefore not proven.

Alopecia (AEs)

A statistically significant difference between treatment groups in favour of ublituximab was shown for the outcome of alopecia (AEs). There is proof of lesser harm from ublituximab in comparison with teriflunomide.

2.3.4 Subgroups and other effect modifiers

The following potential effect modifiers were taken into account for the present benefit assessment:

- age (< 38 years versus ≥ 38 years)
- sex (women versus men)
- EDSS at baseline (≤ 3.5 vs. > 3.5)

The selected characteristics were defined by the company before the start of the study. In the studies ULTIMATE I and ULTIMATE II, subgroup analyses were only predefined for the primary outcome of annual relapse rate. With its subsequently submitted analyses, the company presented post hoc subgroup analyses for the relevant subpopulation for all relevant outcomes.

Interaction tests are performed when at least 10 patients per subgroup are included in the analysis. For binary data, there must also be at least 10 events in at least one subgroup.

In the present assessment, a test based on the Q-test (using the meta-analytically summarized relative risks according to Mantel and Haenszel and the associated standard errors) is performed for binary outcomes in addition to the interaction test of the company, provided that the company's approach had produced a statistically significant effect modification at the level of 0.1. There were no further significant effect modifications at the level of 0.05.

Only the results with an effect modification with a statistically significant interaction between treatment and subgroup characteristic (p-value < 0.05) are presented. In addition, subgroup results are presented only if there is a statistically significant and relevant effect in at least one subgroup.

Table 10 and Table 11 summarize the subgroup results for the relevant subpopulation for the comparison of ublituximab with teriflunomide. Where necessary, calculations conducted by the Institute are provided in addition to the data from the documents subsequently submitted by the company. Forest plots for the Institute's calculation are shown in Appendix B.

Table 10: Subgroups (morbidity, confirmed relapses) – RCT, direct comparison: ublituximab vs. teriflunomide

Outcome category outcome characteristic study subgroup	Ublituximab			Teriflunomide			Ublituximab vs. teriflunomide
	N	n_E	annualized relapse rate [95% CI]	N	n_E	annualized relapse rate [95% CI]	rate ratio [95% CI]; p-value
Morbidity							
Confirmed relapses (EDSS-based)							
Annualized relapse rate							
Sex							
ULTIMATE I[a]							
Men	42	4	0.05 [ND]	35	11	0.18 [ND]	0.29 [0.07; 0.98]; 0.024
Women	55	9	0.10 [ND]	55	8	0.08 [ND]	1.17 [0.4; 3.5]; 0.741
ULTIMATE II[a]							
Men	32	0	0.00 [ND]	36	12	0.19 [ND]	ND; = 0.001
Women	43	5	0.06 [ND]	57	12	0.12 [ND]	0.54 [0.15; 1.64]; 0.238
Total						Interaction:	0.033[b]
Men[a]	74	4	0.03 [ND]	71	23	0.19 [ND]	0.16 [0.04; 0.47]; < 0.001
Women[c]	98	14	0.07 [0.02; 0.20]	112	20	0.09 [0.03; 0.25]	0.74 [0.19; 1.29]; 0.425

a. Annual relapse rate: unadjusted; p-value: Wald test.
b. For the p-value of the interaction: negative binomial model analogous to footnote c, additionally sex and corresponding interaction term (sex* treatment group); information on the methods of the statistical test is not available. According to the company, Cochran's Q-test (presumably based on the two subgroup-specific unadjusted rate ratios) would result in a p-value of 0.012 for this interaction.
c. Annualized relapse rate (LS means) and CI (per treatment arm) as well as rate ratio with CI and p-value (group comparison): negative binomial model, adjusted for prespecified stratification factors (EDSS strata and region) and logarithm of treatment duration as offset variable. Unadjusted rate ratio, 95% CI and p-value: 0.81 [0.38; 1.68]; 0.543

CI: confidence interval; EDSS: Expanded Disability Status Scale; LS: least squares; N: number of analysed patients; n_E: number of events (several events per patient possible); ND: no data; RCT: randomized controlled trial

Table 11: Subgroups (side effects, dichotomous) – RCT, direct comparison: ublituximab vs. teriflunomide

Outcome category outcome characteristic study subgroup	Ublituximab		Teriflunomide		Ublituximab vs. teriflunomide	
	N	patients with event n (%)	N	patients with event n (%)	RR [95% CI]	p-value
Side effects						
SAEs						
Sex						
ULTIMATE I						
Men	43	1 (2.3)	35	5 (14.3)	0.16 [0.02; 1.33][a]	0.048[a]
Women	56	4 (7.1)	56	2 (3.6)	2.00 [0.38; 10.48][a]	0.531[a]
ULTIMATE II						
Men	32	1 (3.1)	37	1 (2.7)	1.16 [0.08; 17.75][a]	0.993[a]
Women	43	9 (20.9)	57	4 (7.0)	2.98 [0.98; 9.04][a]	0.043[a]
Total					Interaction:	0.018[b]
Men	75	2 (2.7)	72	6 (8.3)	0.31 [0.07; 1.40][c]	0.126[c]
Women	99	13 (13.1)	113	6 (5.3)	2.62 [1.05; 6.56][c]	0.040[c]

a. Institute's calculation of RR, CI (asymptotic) and p-value (unconditional exact test, CSZ method according to [14]). Discrepancy between p-value (exact) and CI (asymptotic) is possible due to different calculation methods.
b. Institute's calculation by means of Cochran's Q test.
c. Institute's calculation of RR, CI (asymptotic) and p-value (meta-analysis according to Mantel and Haenszel).

CI: confidence interval; n: number of patients with (at least one) event; N: number of analysed patients; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event

According to the company, no effect estimate could be calculated for the subgroup of men for the outcome of confirmed relapses due to the low number of events and the non-converging regression model. With the analyses presented following the oral hearing, the company subsequently provided subgroup analyses for the outcome of confirmed disease relapses for the characteristic "sex" by means of unadjusted analyses. Due to the similarity of the adjusted and unadjusted analyses in the subgroup of women, the unadjusted analyses are used for the assessment of the subgroup of men in the present data situation.

Morbidity

Confirmed relapses

For the outcome of confirmed relapses, operationalized through the annualized relapse rate, there was an effect modification by the characteristic of sex. For men, the meta-analysis showed a statistically significant difference in favour of ublituximab. For men, there is proof of an added benefit of ublituximab in comparison with teriflunomide.

For women, the meta-analysis showed no statistically significant difference between the treatment groups. For women, there is no hint of an added benefit of ublituximab in comparison with teriflunomide; an added benefit is therefore not proven.

Side effects

SAEs

For the outcome of SAEs, there is an effect modification by the characteristic of sex. For men, the meta-analysis showed no statistically significant difference between the treatment groups. For men, there was no hint of greater or lesser harm from ublituximab in comparison with teriflunomide; greater or lesser harm is therefore not proven.

For women, the meta-analysis showed a statistically significant difference between the treatment groups to the disadvantage of ublituximab. For women, there was a proof of greater harm from ublituximab in comparison with teriflunomide.

Consideration of effect modification by the characteristic of sex when deriving an overall conclusion

In the total population of the pooled ULTIMATE studies presented in the original dossier and in the relevant subpopulation presented by the company with the comments, effect modifications for the primary outcome "confirmed relapses" (operationalized via the annual relapse rate) were shown by the characteristics “age” and “sex”. In the total population of the pooled ULTIMATE studies, there was an effect modification by the characteristic of age (< 38 years vs. ≥ 38 years). Younger patients aged < 38 years benefit from a significantly lower occurrence of disease relapses per year under treatment with ublituximab, while there is no such effect for the older age group (≥ 38 years). However, the described effect modification by age in the total population of the pooled ULTIMATE studies is barely no longer significant in the relevant subpopulation, which comprises only about 30% of the total population. In contrast, the relevant subpopulation of the pooled ULTIMATE studies shows an effect modification by the characteristic of sex (see above for a detailed description of the effects). It is striking that the not statistically significant effect of the therapy for women described in the section above is also due to better results under teriflunomide (annualized relapse rate: 0.09 for women vs. 0.19 for men in the pooled ULTIMATE studies; the situation is similar within the two studies, see Table 10). Again, the effect modification by the characteristic of sex is barely not significant in the total population of the pooled ULTIMATE studies.

For the outcome of SAEs, there was a similar constellation regarding an effect modification by the characteristics of age and of sex. In the total population of the pooled ULTIMATE studies, there was a statistically significant effect modification by the characteristic of age (< 38 years vs. ≥ 38 years). In contrast to the older age group (≥ 38 years), younger patients aged < 38 years showed a significantly higher occurrence of SAEs under treatment with ublituximab.

However, this effect modification by age in the total population of the pooled ULTIMATE studies was no longer significant in the relevant subpopulation. Instead, the relevant subpopulation of the pooled ULTIMATE studies showed an effect modification by the characteristic of sex (see above for a detailed description of the effects). This, in turn, is not significant in the total population of the pooled ULTIMATE studies.

In summary, the described data constellation indicates that sex and/or age could be potential effect modifiers for the morbidity outcome of confirmed relapses (operationalized via the annualized relapse rate) and the outcome of SAEs. It could be inferred from the oral hearing [15] that no sex-specific differences in the efficacy of cluster of differentiation 20 (CD20) antibodies were observed in clinical practice, but that postmenopause could possibly have an effect on the disease activity in women with RMS. However, to date, this relation has not yet been confirmed by clinical experience. Overall, however, the results of the present subgroup analyses support the consideration of the charcteristic “sex” as an effect modifier when deriving an added benefit of ublituximab in the relevant subpopulation (see Section 2.4.2).

2.4 Probability and extent of added benefit

The probability and extent of added benefit at outcome level are derived below, taking into account the different outcome categories and effect sizes. The methods used for this purpose are explained in the IQWiG *General Methods* [16].

The approach for deriving an overall conclusion on the added benefit based on the aggregation of conclusions derived at outcome level is a proposal by IQWiG. The G-BA decides on the added benefit.

2.4.1 Assessment of added benefit at outcome level

The extent of the respective added benefit at outcome level was estimated from the results presented in Sections 2.3.3 and 2.3.4 (see Table 12).

Determination of the outcome category for symptom outcomes

It cannot be inferred from the dossier or the subsequently submitted documents whether the following symptoms outcome is serious/severe or non-serious/non-severe. The classification of this outcome is explained below.

Confirmed relapses

For the outcome of confirmed relapses, data available to categorize the severity category as serious/severe are insufficient. This outcome was therefore assigned to the outcome category "non-serious/non-severe symptoms".

Table 12: Extent of added benefit at outcome level: ublituximab vs. teriflunomide (multipage table)

Outcome category **outcome** **effect modifier** **subgroup**	**Ublituximab vs. teriflunomide** **median time to event (months) or proportion of events (%) or annual rate** **effect estimation [95% CI];** **p-value** **probability**[a]	**Derivation of extent**[b]
Mortality		
All-cause mortality	0.0–1.0% vs. 0.0–-0.0%[c] RR: –[d]	Lesser/added benefit not proven
Morbidity		
Confirmed relapses (annual relapse rate)		
Sex		
Men	Annual rate: 0.00–0.05 vs. 0.18–0.19[c] Rate ratio: 0.16 [0.04; 0.47]; p < 0.001 probability: “proof”	Outcome category: non-serious/non-severe symptoms/late complications added benefit; extent: “considerable”
Women	Annual rate: 0.06–0.10 vs. 0.08–0.12[c] rate ratio: 0.74 [0.19; 1.29]; p = 0.425	Lesser/added benefit not proven
Confirmed disability progression (EDSS-based)	Median: NR vs. NR[c] HR: 0.52 [0.16; 1.72]; p = 0.276	Lesser/added benefit not proven
Disability severity (MSFC z-score)	Change at Week 96: 0.64-0.66 vs. 0.39-0.54[c] MD: 0.19 [-0.02; 0.40]; p = 0.080	Lesser/added benefit not proven
Fatigue (FIS total score)		
Improvement (decrease by ≥ 24 points)	17.5–20.0 % vs. 10.0–12.9 %[c] RR: 1.64 [0.99; 2.74]; p = 0.057	Lesser/added benefit not proven
Deterioration (increase by ≥ 24 points)	8.0–12.4 % vs. 9.7–11.1 %[c] RR: 0.99 [0.53; 1.83]; p = 0.970	Lesser/added benefit not proven
Health-related quality of life		
MSQoL-54, PHCS sum score		
Improvement (increase by ≥ 15 points)	14.7–24.7 % vs. 10.8–13.3 %[c] RR: 1.65 [1.01; 2.70] RR: 0.61 [0.37; 0.99][e]; p = 0.047 probability: “proof”	Outcome category: health-related quality of life $0.90 \leq CI_u < 1.00$ added benefit, extent: “minor”

Table 12: Extent of added benefit at outcome level: ublituximab vs. teriflunomide (multipage table)

Outcome category **outcome** **effect modifier** **subgroup**	**Ublituximab vs. teriflunomide** **median time to event (months) or proportion of events (%) or annual rate** **effect estimation [95% CI];** **p-value** **probability**[a]	**Derivation of extent**[b]
Deterioration (decrease by ≥ 15 points)	1.3–5.2 % vs. 7.8–10.8 %[c] RR: 0.37 [0.14; 0.93]; p = 0.035 probability: "proof"	Outcome category: health-related quality of life $0.90 \leq CI_u < 1.00$ added benefit, extent: "minor"
MSQoL-54, MHCS sum score		
Improvement (increase by ≥ 15 points)	20.6–25.3 % vs. 16.7–18.3 %[c] RR: 1.31 [0.86; 1.99]; p = 0.205	Lesser/added benefit not proven
Deterioration (decrease by ≥ 15 points)	6.7–7.2 % vs. 7.8–17.2 %[c] RR: 0.57 [0.29; 1.12]; p = 0.104	Lesser/added benefit not proven
Side effects		
SAEs Sex		
Men	2.3–3.1 % vs. 2.7–14.3 %[c] RR: 0.31 [0.07; 1.40]; p = 0.126	Greater/lesser harm not proven
Women	7.1–20.9 % vs. 3.6–7.0 %[c] RR: 2.62 [1.05; 6.56] RR: 0.38 [0.15; 0.95][e]; p = 0.040 probability: "proof"	Outcome category: serious/severe side effects $0.90 \leq CI_u < 1.00$ greater harm, extent: "minor"
Severe AEs	16.0–17.2 % vs. 4.3–14.3 %[c] RR: 1.73 [0.9996; 3.01]; p = 0.0502	Greater/lesser harm not proven
Discontinuation due to AEs	1.3–6.1% vs. 0–0.0%[c] RR: 8.18 [0.99; 67.83]; p = 0.051	Greater/lesser harm not proven
Infusion-related reactions (AEs)	40.0–44.4 % vs. 11.0–11.7 %[c] RR: 3.74 [2.41; 5.82] RR: 0.27 [0.17; 0.41][e]; p < 0.001 probability: "proof"	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ greater harm; extent: "considerable"

Table 12: Extent of added benefit at outcome level: ublituximab vs. teriflunomide (multipage table)

Outcome category **outcome** **effect modifier** **subgroup**	**Ublituximab vs. teriflunomide** **median time to event (months) or proportion of events (%) or annual rate** **effect estimation [95% CI];** **p-value** **probability**[a]	**Derivation of extent**[b]
Infections and infestations (SAEs)	2.7–4.0 % vs. 2.2–3.2 %[c] RR: 1.28 [0.39; 4.20]; p = 0.688	Greater/lesser harm not proven
Lymphocyte count decreased (severe AEs)	6.1–6.7% vs. 0–0.0%[c] RR: 12.78 [1.68; 97.37] RR: 0.08 [0.01; 0.60][e]; p = 0.014 probability: “proof”	Outcome category: serious/severe side effects CI_u < 0.75, risk ≥ 5 % greater harm, extent: “major”
Alopecia (AEs)	1.0–5.3 % vs. 11.0–18.1 %[c] RR: 0.21 [0.09; 0.53]; p < 0.001 probability: “proof”	Outcome category: non-serious/non-severe side effects CI_u < 0.80 lesser harm, extent: “considerable”

a. Probability provided if statistically significant differences are present.
b. Depending on the outcome category, the effect size is estimated using different limits based on the upper limit of the confidence interval (CI_u).
c. Minimum and maximum proportions of events or median time to event or mean change at Week 96 or annualized rate per treatment arm in the studies included.
d. An effect estimate (including confidence interval and p-value) was not performed due to the low number of events.
e. Institute’s calculation; inverse direction of effect to enable use of limits to derive the extent of the added benefit.

AE: adverse event; CI: confidence interval; CI_u: upper limit of the confidence interval; FIS: Fatigue Impact Scale; MD: mean difference; MHCS: mental health composite score; MSFC: Multiple Sclerosis Functional Composite; MSQoL-54: Multiple Sclerosis Quality of Life-54; NA: not achieved; ND: no data; PHCS: physical health composite score; RR: relative risk; SAE: serious adverse event

2.4.2 Overall conclusion on added benefit

Table 13 summarizes the results taken into account in the overall conclusion on the extent of added benefit.

Table 13: Positive and negative effects from the assessment of ublituximab in comparison with teriflunomide

Positive effects	Negative effects
Non-serious/non-severe symptoms/late complications ▪ confirmed relapses (annual relapse rate): ▫ men: proof of added benefit – extent "considerable"	–
Health-related quality of life ▪ MSQoL-54, PHCS sum score (improvement and deterioration): proof of added benefit - Extent: "minor"	–
–	Serious/severe side effects ▪ SAEs ▫ women: proof of greater harm – extent: "minor" ▪ lymphocyte count decreased (severe AEs): proof of greater harm – extent: "major"
Non-serious/non-severe side effects ▪ alopecia (AEs): proof of lesser harm – extent: "considerable"	Non-serious/non-severe side effects ▪ infusion-related reactions (AEs): proof of greater harm – extent: "considerable"
AE: adverse event; MSQoL-54: Multiple Sclerosis Quality of Life-54; PHCS: physical health composite score; SAE: serious adverse event	

Overall, for adults with RMS who have not yet received disease-modifying therapy and have no signs of a severe course of disease, there are both positive and negative effects for ublituximab compared to teriflunomide. Due to the effect modification in the morbidity outcome of confirmed relapses by the characteristic of sex, the results on the added benefit of ublituximab compared to teriflunomide are derived separately by sex in the following (see also Section 2.3.4).

Men

For men, there is proof of a considerable added benefit in the morbidity outcome (confirmed relapses). Positive effects were also shown in health-related quality of life, measured using the MSQoL-54, with the extent "minor", and in the category of side effects (non-serious/non-severe) for the outcome "alopecia (AEs)" with the extent "considerable".

This was offset by 2 negative effects in the side effects category (here in different severity categories). For the outcome "lymphocyte count decreased (severe AEs)", there is proof of greater harm with the extent " major"; for the outcome "infusion-related reactions (AEs)", there is proof of greater harm with the extent "considerable". Overall, however, these negative effects are not expected to challenge the benefits in the outcomes on morbidity (confirmed relapses) and health-related quality of life (MSQoL-54).

For men with RMS who have not yet received disease-modifying therapy and have no signs of a severe course of disease, there is overall proof of considerable added benefit of ublituximab compared to teriflunomide.

Women

For women, on the other hand, there is no hint of an added benefit for the morbidity outcome of confirmed disease relapses. Positive effects were shown in health-related quality of life, measured using the MSQoL-54, with the extent “minor”, and in the side effects category (non-serious/non-severe) for the outcome “alopecia (AEs)” with the extent “considerable“.

This was offset by 3 negative effects for the side effects category. Here, proof of greater harm with the extent “minor” in the overall rate of SAEs is only shown for women. Furthermore, analogous to the men, there is proof of greater harm with the extent “major” for the outcome of lymphocyte count decreased (severe AEs), as well as proof of greater harm with the extent “considerable” for the outcome of infusion-related reactions (AEs). Overall, it is assumed that the positive effects for women are offset by the negative effects.

In summary, for women with RMS who have not yet received disease-modifying therapy and have no signs of a severe course of disease, there is no hint of an added benefit of ublituximab over teriflunomide, an added benefit is therefore not proven for women.

2.5 Summary

The data subsequently submitted by the company in the commenting procedure change the conclusion on the added benefit of ublituximab from dossier assessment A24-13 for research question 1: For men with RMS who have not yet received disease-modifying therapy and show no signs of a severe course of disease, there is proof of a considerable added benefit of ublituximab compared with teriflunomide. For women with RMS who have not yet received disease-modifying therapy and have no signs of a severe course of disease, there is no hint of an added benefit of ublituximab compared to teriflunomide. For research question 2, there is no change from dossier assessment A24-13.

Table 14 below shows the result of the benefit assessment of ublituximab, taking into account dossier assessment A24-13 and the present addendum.

Table 14: Ublituximab – probability and extent of added benefit

Research question	Therapeutic indication[a]	ACT[b]	Probability and extent of added benefit
1	Adults with RMS who have not yet received disease-modifying therapy and show no evidence of a severe course of disease	Dimethyl fumarate or diroximel fumarate or glatiramer acetate or IFN-β1a or IFN-β1b or teriflunomide	▪ Men: proof of considerable added benefit ▪ women: added benefit not proven
2	Adults with RMS who have not yet received disease-modifying therapy and show evidence of a severe course of disease and adults who show an active course of disease despite treatment with a disease-modifying therapy	Individualized therapy[c, d] taking into account the disease activity and prognostic factors[e] choosing from the following drugs: ▪ fingolimod, natalizumab, ocrelizumab, ofatumumab, ozanimod and ponesimod	Added benefit not proven

b. In analogy to the treatment algorithm recommended in the guidelines, a distinction is principally made between the patient populations with regard to previous therapy (treatment-naive or pretreated) and severity of the disease.
b. Presentation of the respective ACT specified by the G-BA.
c. For the implementation of individualized therapy in a study of direct comparison, the investigator is expected to have a selection of several treatment options at disposal to permit an individualized treatment decision taking into account the listed criteria (multicomparator study). A rationale must be provided for the choice and any limitation of treatment options. In the present indication, the specified appropriate comparator therapy offers the possibility that a single comparator study can also be presented in the benefit assessment and, if applicable, an added benefit can be derived for a part of the therapeutic indication.
d. An unchanged continuation of the prior therapy is not considered an appropriate implementation of the ACT if there is a therapeutic indication to change the disease-modifying therapy.
e. E.g. young age, polysymptomatic onset, poor regression of the relapse, high lesion load, spinal or infratentorial lesions, quantitative intrathecal immunoglobulin synthesis (IgG and IgM).

G-BA: Federal Joint Committee; IFN: interferon; Ig: immunoglobulin; RMS: relapsing multiple sclerosis

The G-BA decides on the added benefit.

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Appendix A Kaplan-Meier curves

A.1 Morbidity

Confirmed disability progression (EDSS-based)

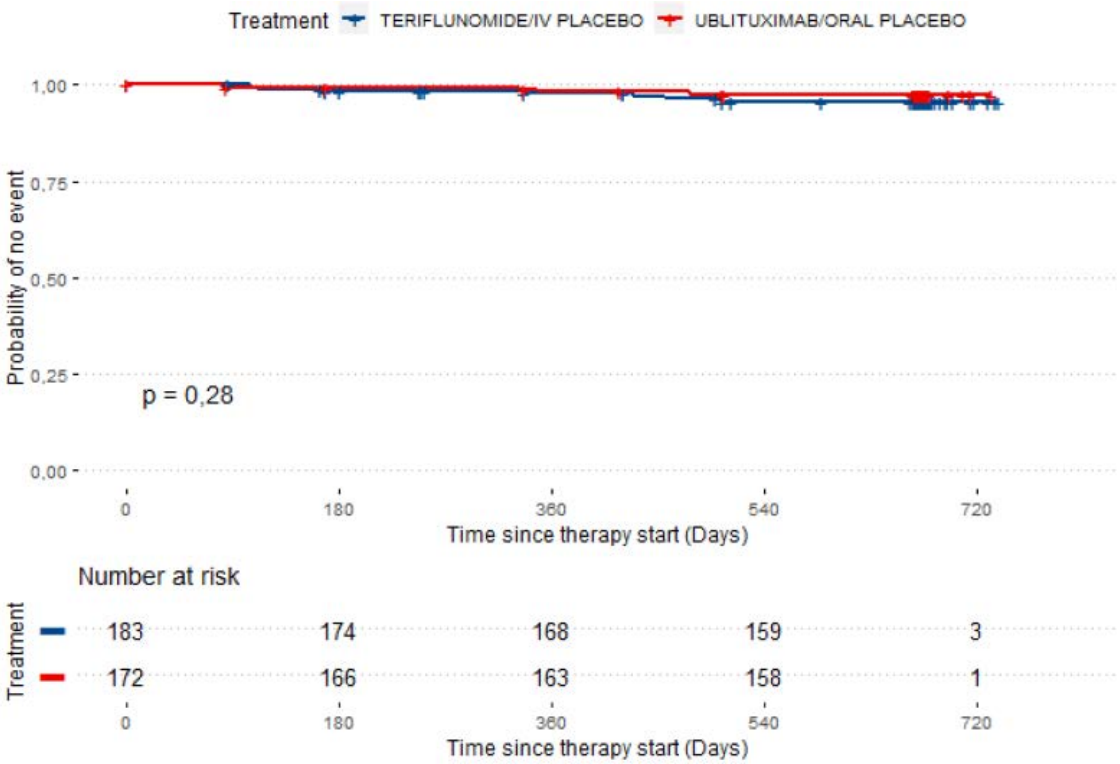

Figure 1: Kaplan-Meier curve for the outcome of confirmed disability progression (EDSS-based), meta-analysis of the studies ULTIMATE I and ULTIMATE II

Appendix B Forest plots for the Institute's calculations

B.1 Morbidity

Fatigue

Total score (FIS) - improvement from Week 96

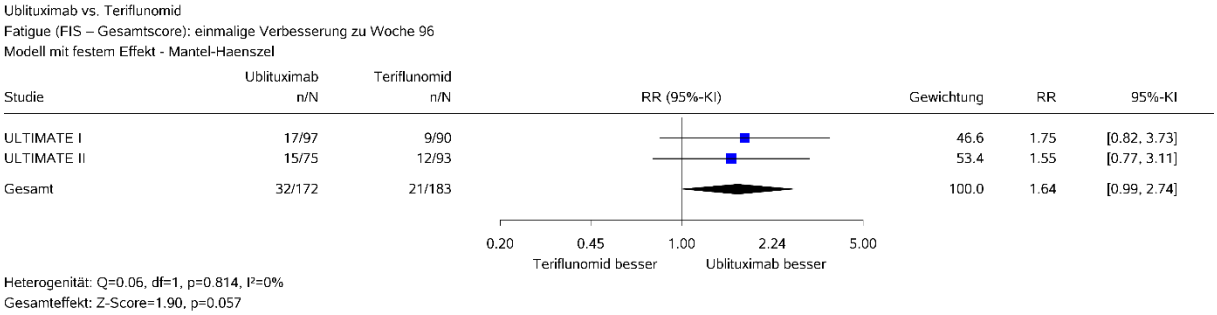

Figure 2: Meta-analysis for the outcome of fatigue (FIS - total score: improvement at Week 96), relevant subpopulation of the studies ULTIMATE I and ULTIMATE II

Total score (FIS) - deterioration at Week 96

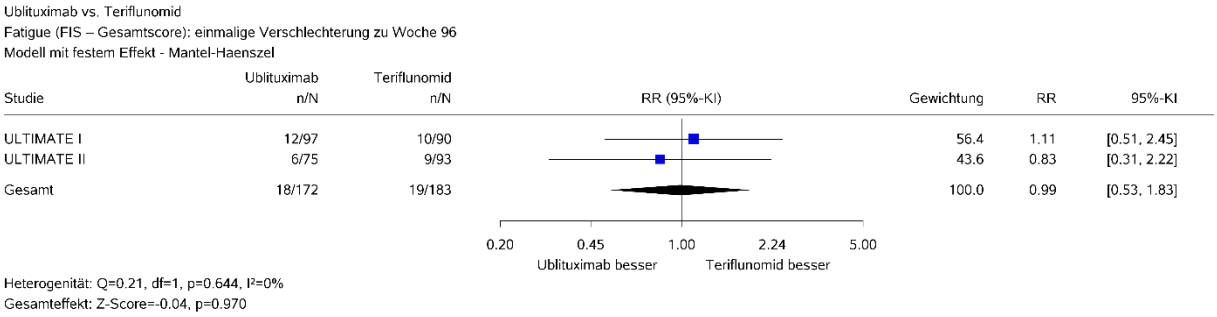

Figure 3: Meta-analysis for the outcome of fatigue (FIS - total score: deterioration at Week 96), relevant subpopulation of the studies ULTIMATE I and ULTIMATE II

Cognitive domain (FIS) - improvement at Week 96

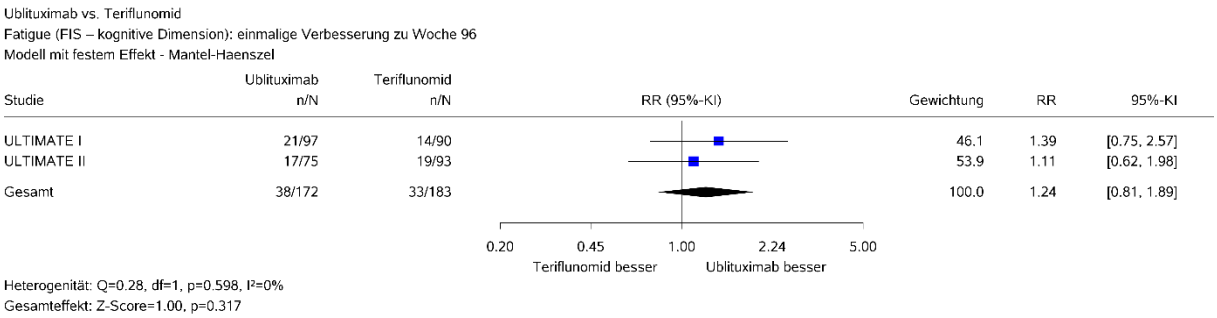

Figure 4: Meta-analysis for the outcome of fatigue (FIS - cognitive domain: improvement at Week 96), relevant subpopulation of the studies ULTIMATE I and ULTIMATE II

Cognitive domain (FIS) - deterioration at Week 96

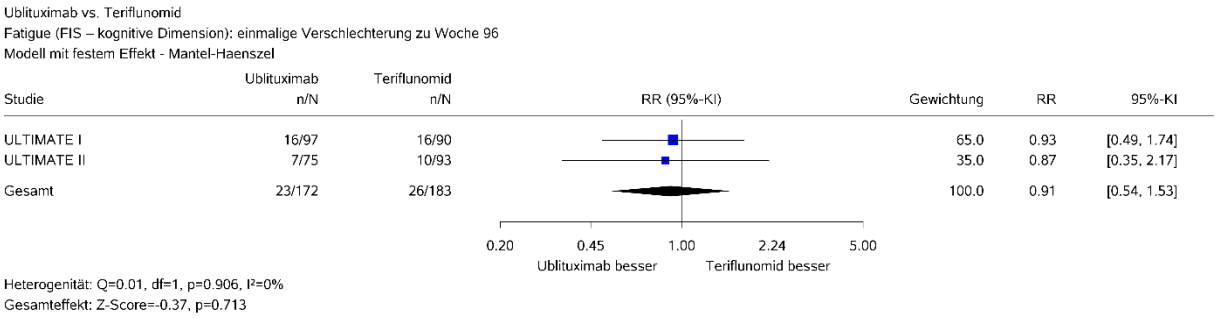

Figure 5: Meta-analysis for the outcome of fatigue (FIS - cognitive domain: deterioration at Week 96), relevant subpopulation of the studies ULTIMATE I and ULTIMATE II

Physical domain (FIS) - improvement at Week 96

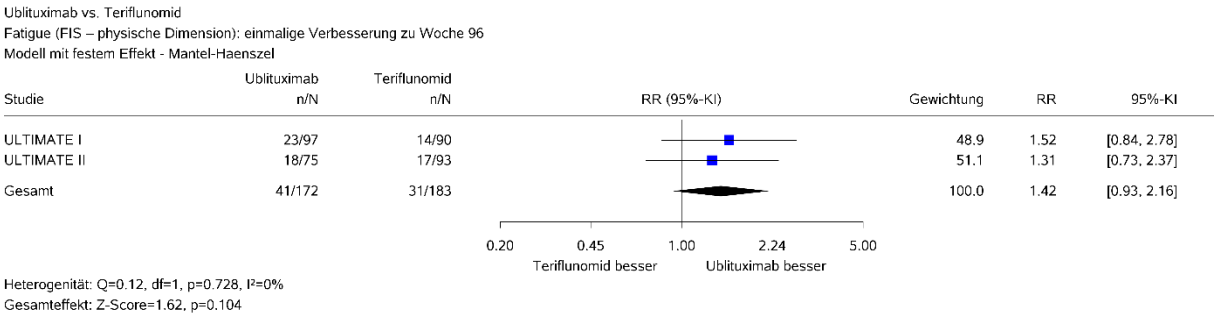

Figure 6: Meta-analysis for the outcome of fatigue (FIS - physical domain: improvement at Week 96), relevant subpopulation of the studies ULTIMATE I and ULTIMATE II

Physical domain (FIS) - deterioration at Week 96

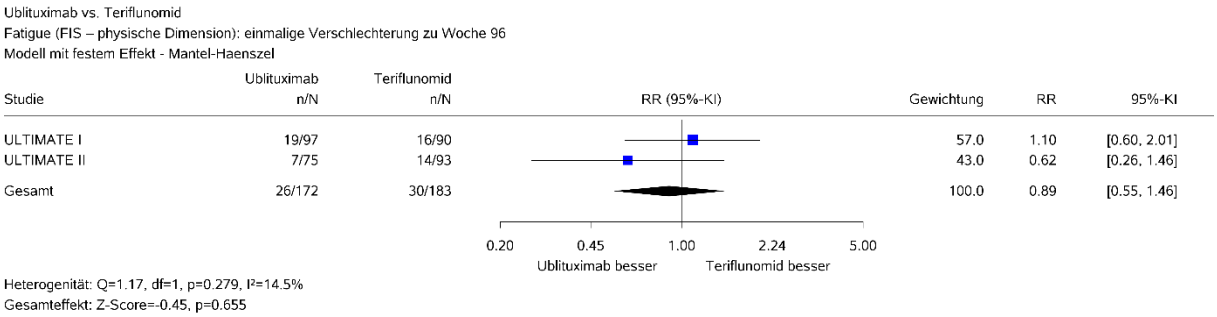

Figure 7: Meta-analysis for the outcome of fatigue (FIS - physical domain: deterioration at Week 96), relevant subpopulation of the studies ULTIMATE I and ULTIMATE II

Social domain (FIS) - improvement at Week 96

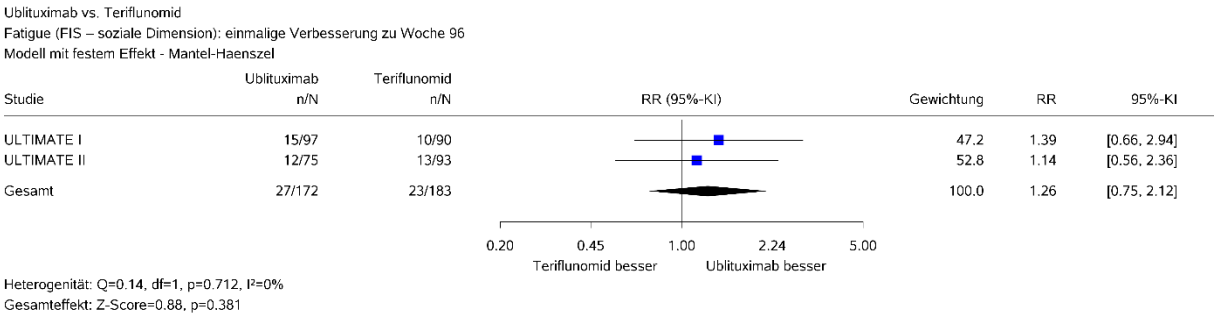

Figure 8: Meta-analysis for the outcome of fatigue (FIS - social domain: improvement at Week 96), relevant subpopulation of the studies ULTIMATE I and ULTIMATE II

Social domain – (FIS) - deterioration at Week 96

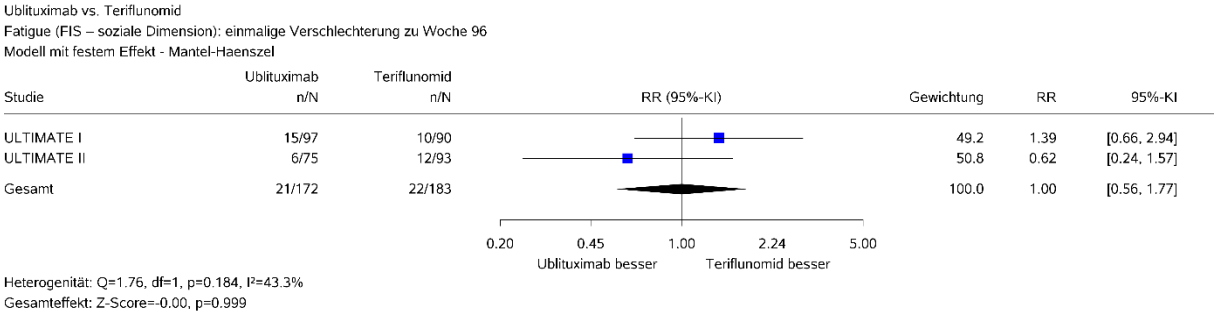

Figure 9: Meta-analysis for the outcome of fatigue (FIS - social domain: deterioration at Week 96), relevant subpopulation of the studies ULTIMATE I and ULTIMATE II

B.2 Health-related quality of life

MSQoL-54

Physical Component Summary (PHCS) - improvement at Week 96

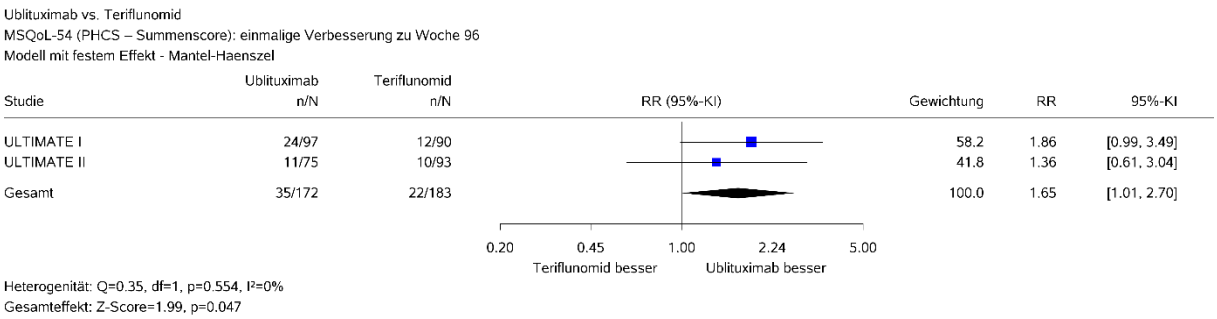

Figure 10: Meta-analysis for the outcome of health-related quality of life (MSQoL-54 – PCS: improvement at Week 96), relevant subpopulation of the studies ULTIMATE I and ULTIMATE II

Physical Component Summary (PHCS) - deterioration at Week 96

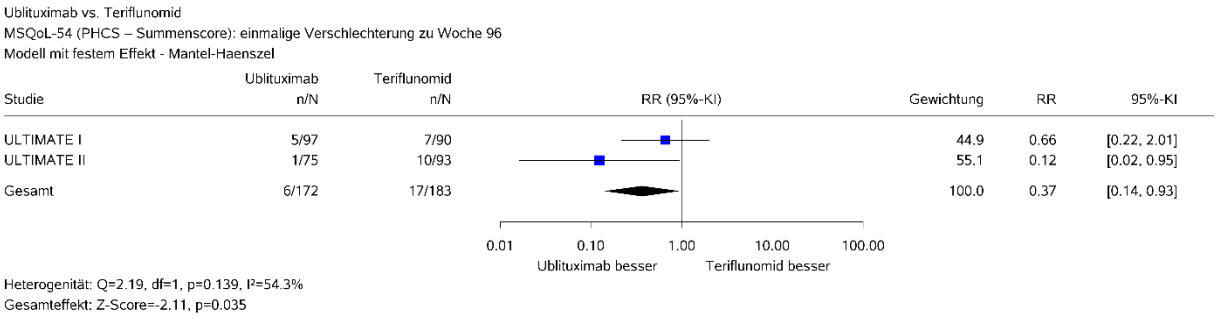

Figure 11: Meta-analysis for the outcome of health-related quality of life (MSQoL-54 – PCS: deterioration at Week 96), relevant subpopulation of the studies ULTIMATE I and ULTIMATE II

Mental Component Summary (MCS) - improvement at Week 96

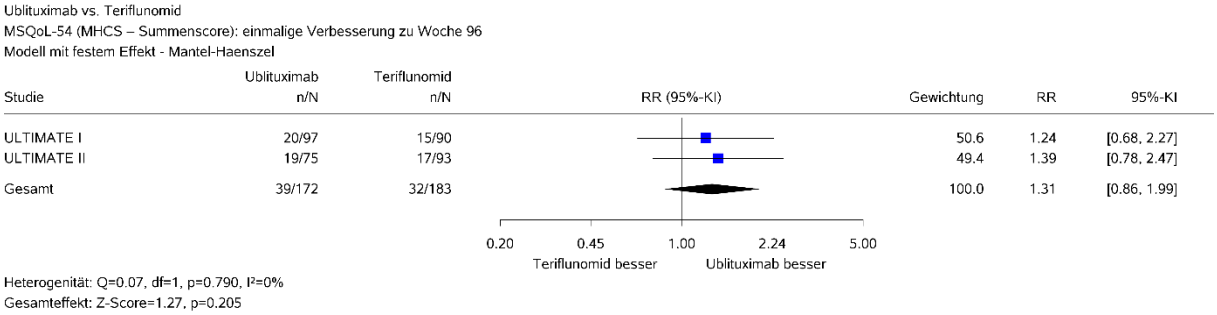

Figure 12: Meta-analysis for the outcome of health-related quality of life (MSQoL-54 – MCS: improvement at Week 96), relevant subpopulation of the studies ULTIMATE I and ULTIMATE II

Mental Component Summary (MCS) - deterioration at Week 96

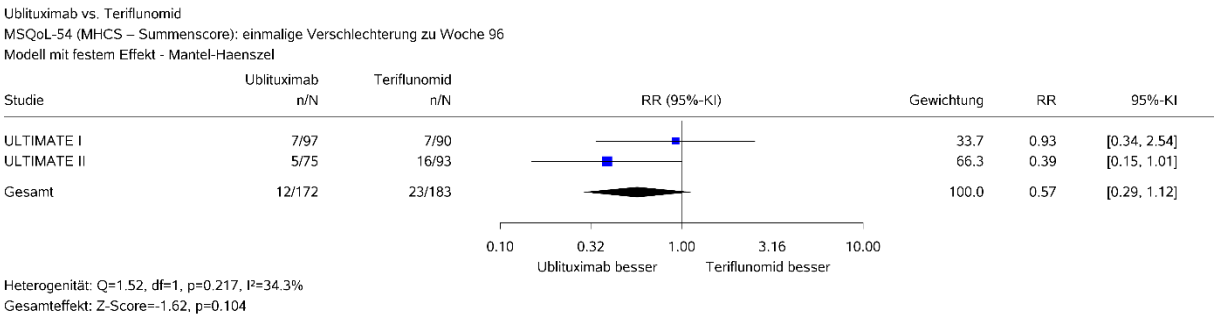

Figure 13: Meta-analysis for the outcome of health-related quality of life (MSQoL-54 – MCS: deterioration at Week 96), relevant subpopulation of the studies ULTIMATE I and ULTIMATE II

Physical health (subdomain of the PHCS) - improvement at Week 96

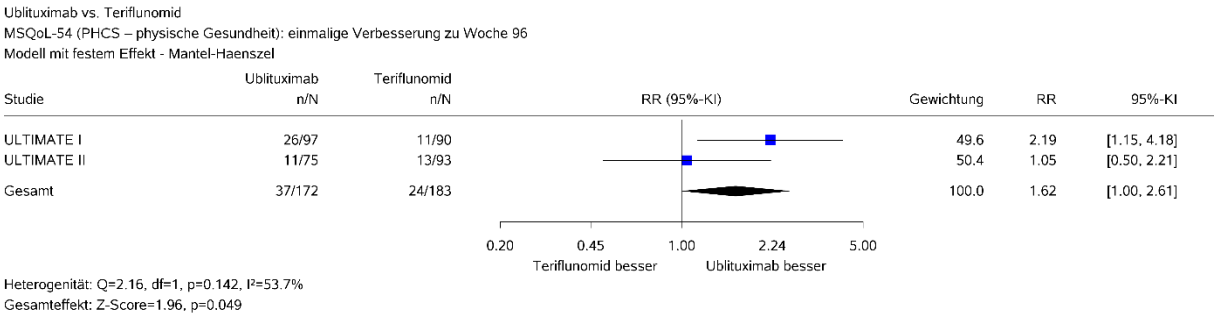

Figure 14: Meta-analysis for the outcome of health-related quality of life (MSQoL-54 – physical health: improvement at Week 96), relevant subpopulation of the studies ULTIMATE I and ULTIMATE II

Physical health (subdomain of the PHCS) - deterioration at Week 96

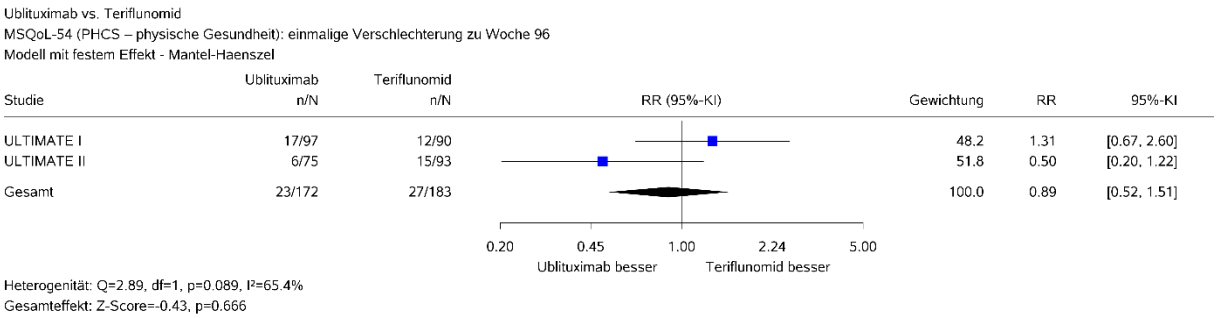

Figure 15: Meta-analysis for the outcome of health-related quality of life (MSQoL-54 – physical health: deterioration at Week 96), relevant subpopulation of the studies ULTIMATE I and ULTIMATE II

Health perception (subdomain of the PHCS) - improvement at Week 96

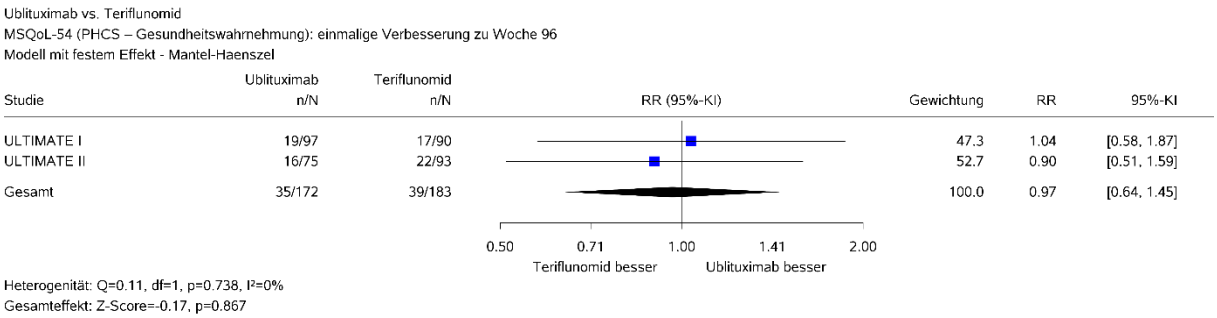

Figure 16: Meta-analysis for the outcome of health-related quality of life (MSQoL-54 – health perception: improvement at Week 96), relevant subpopulation of the studies ULTIMATE I and ULTIMATE II

Health perception (subdomain of the PHCS) - deterioration at Week 96

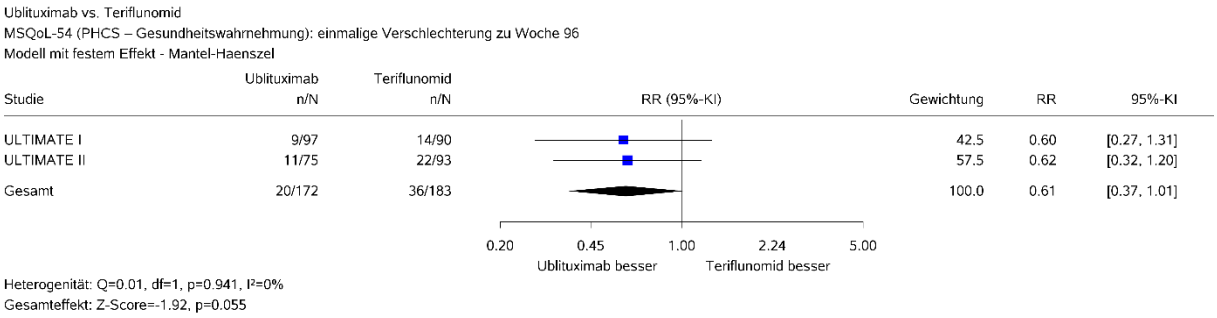

Figure 17: Meta-analysis for the outcome of health-related quality of life (MSQoL-54 – health perception: deterioration at Week 96), relevant subpopulation of the studies ULTIMATE I and ULTIMATE II

Energy (subdomain of the PHCS) - improvement at Week 96

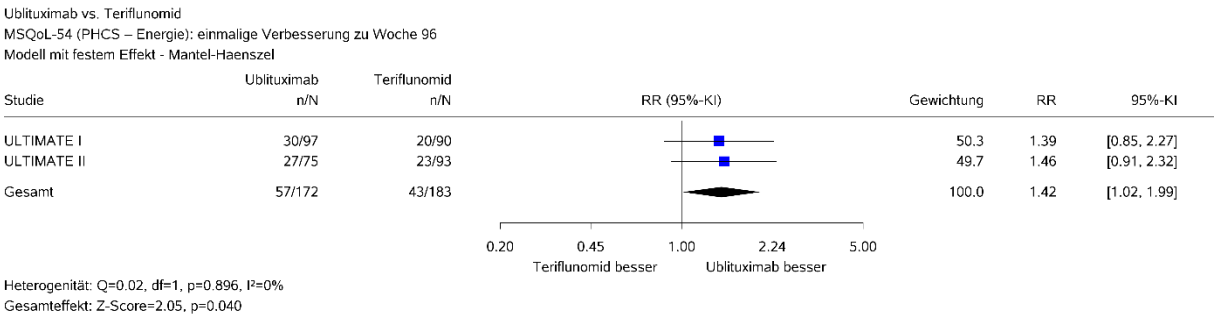

Figure 18: Meta-analysis for the outcome of health-related quality of life (MSQoL-54 – energy: improvement at Week 96), relevant subpopulation of the studies ULTIMATE I and ULTIMATE II

Energy (subdomain of the PHCS) - deterioration at Week 96

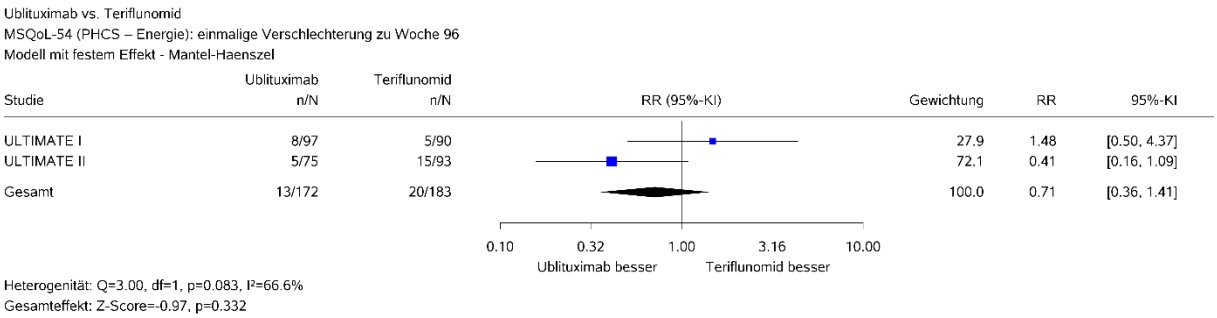

Figure 19: Meta-analysis for the outcome of health-related quality of life (MSQoL-54 – energy: deterioration at Week 96), relevant subpopulation of the studies ULTIMATE I and ULTIMATE II

Physical role restrictions (subdomain of the PHCS) - improvement at Week 96

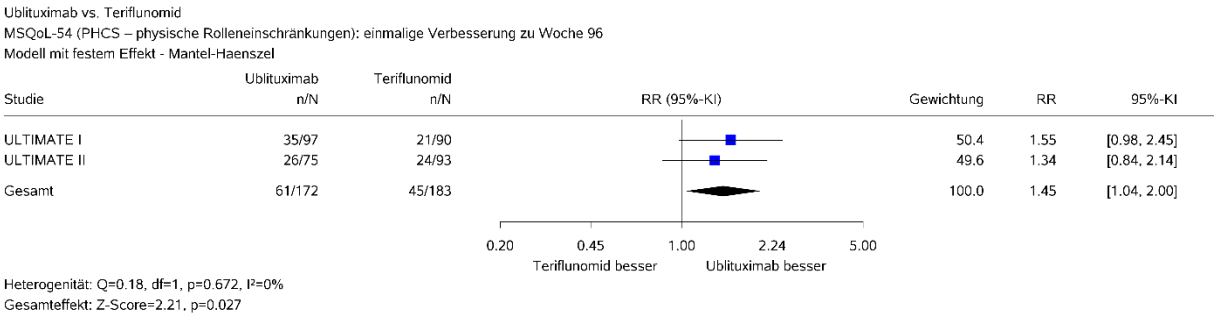

Figure 20: Meta-analysis for the outcome of health-related quality of life (MSQoL-54 – physical role restrictions: improvement at Week 96), relevant subpopulation of the studies ULTIMATE I and ULTIMATE II

Physical role restrictions (subdomain of the PHCS) - deterioration at Week 96

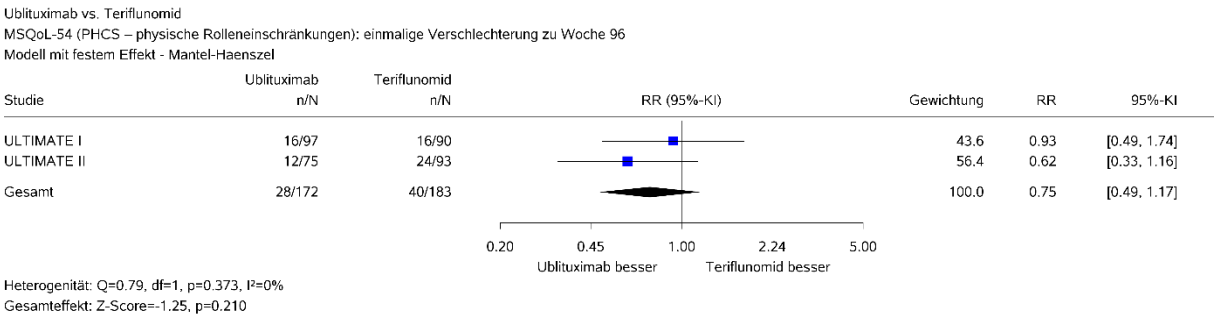

Figure 21: Meta-analysis for the outcome of health-related quality of life (MSQoL-54 – physical role restrictions: deterioration at Week 96), relevant subpopulation of the studies ULTIMATE I and ULTIMATE II

Social functioning (subdomain of the PHCS) - improvement at Week 96

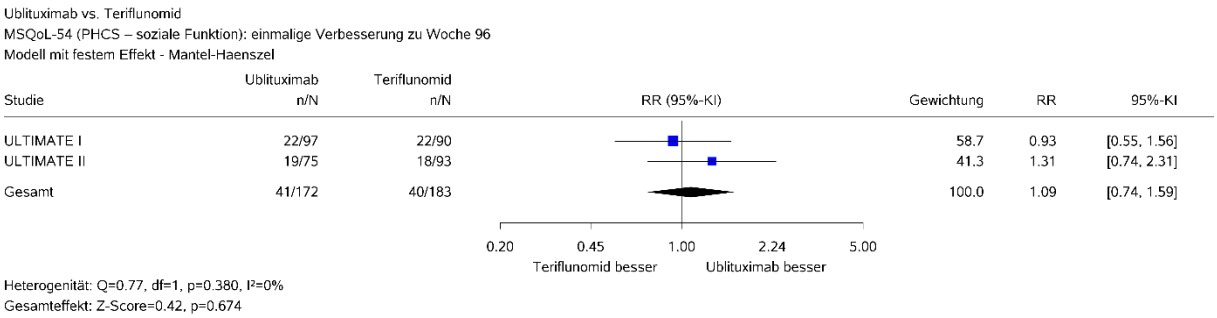

Figure 22: Meta-analysis for the outcome of health-related quality of life (MSQoL-54 – social functioning: improvement at Week 96), relevant subpopulation of the studies ULTIMATE I and ULTIMATE II

Social functioning (subdomain of the PHCS) - deterioration at Week 96

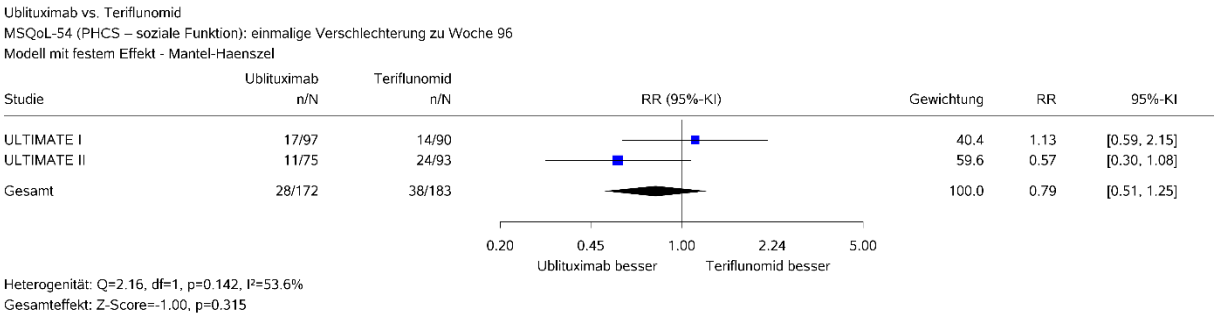

Figure 23: Meta-analysis for the outcome of health-related quality of life (MSQoL-54 – social functioning: deterioration at Week 96), relevant subpopulation of the studies ULTIMATE I and ULTIMATE II

Pain (subdomain of the PHCS) - improvement at Week 96

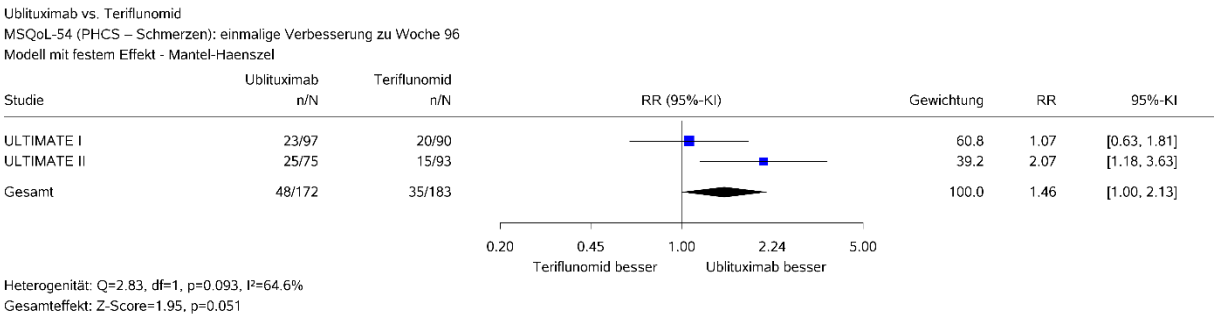

Figure 24: Meta-analysis for the outcome of health-related quality of life (MSQoL-54 – pain: improvement at Week 96), relevant subpopulation of the studies ULTIMATE I and ULTIMATE II

Pain (subdomain of the PHCS) - deterioration at Week 96

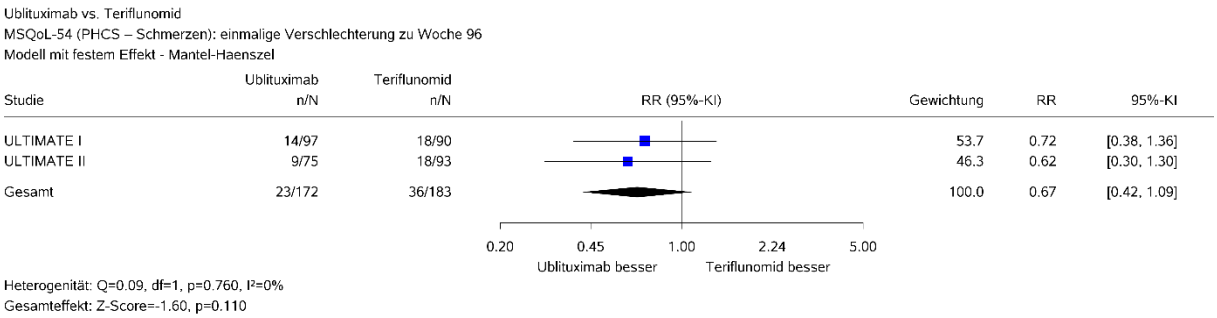

Figure 25: Meta-analysis for the outcome of health-related quality of life (MSQoL-54 – pain: deterioration at Week 96), relevant subpopulation of the studies ULTIMATE I and ULTIMATE II

Emotional wellbeing (subdomain of the MHCS) - improvement at Week 96

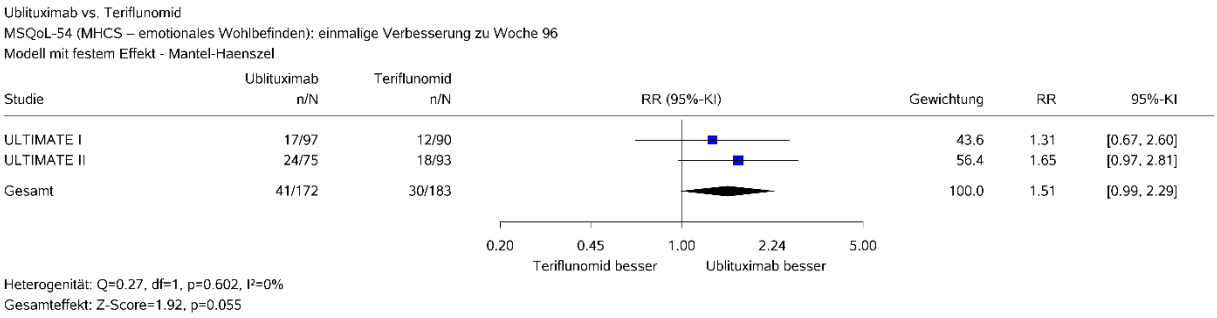

Figure 26: Meta-analysis for the outcome of health-related quality of life (MSQoL-54 – emotional wellbeing: improvement at Week 96), relevant subpopulation of the studies ULTIMATE I and ULTIMATE II

Emotional wellbeing (subdomain of the MHCS) - deterioration at Week 96

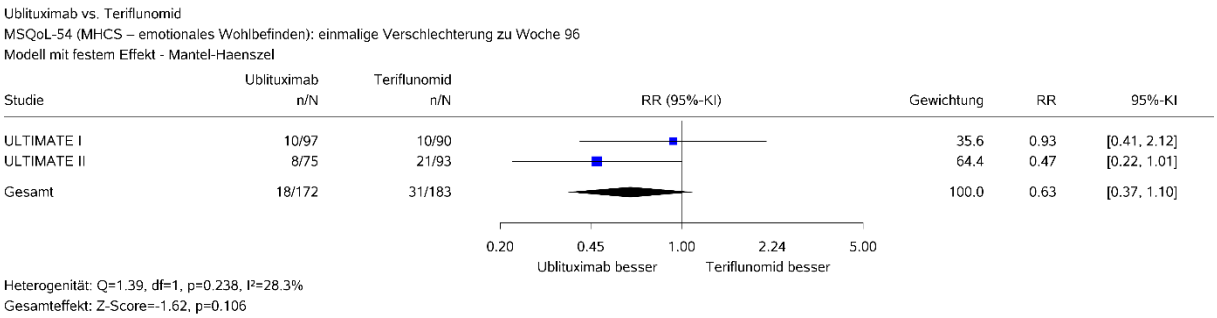

Figure 27: Meta-analysis for the outcome of health-related quality of life (MSQoL-54 – emotional wellbeing: deterioration at Week 96), relevant subpopulation of the studies ULTIMATE I and ULTIMATE II

Emotional role restrictions (subdomain of the MHCS) - improvement at Week 96

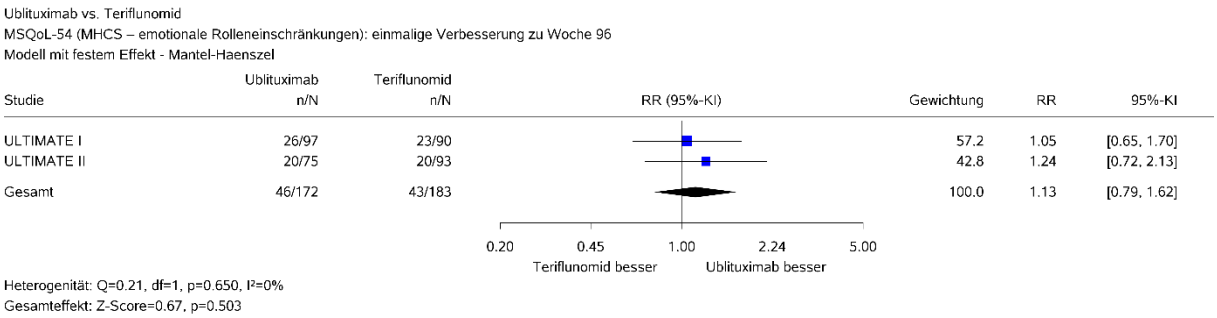

Figure 28: Meta-analysis for the outcome of health-related quality of life (MSQoL-54 – emotional role restrictions: improvement at Week 96), relevant subpopulation of the studies ULTIMATE I and ULTIMATE II

Emotional role restrictions (subdomain of the MHCS) - deterioration at Week 96

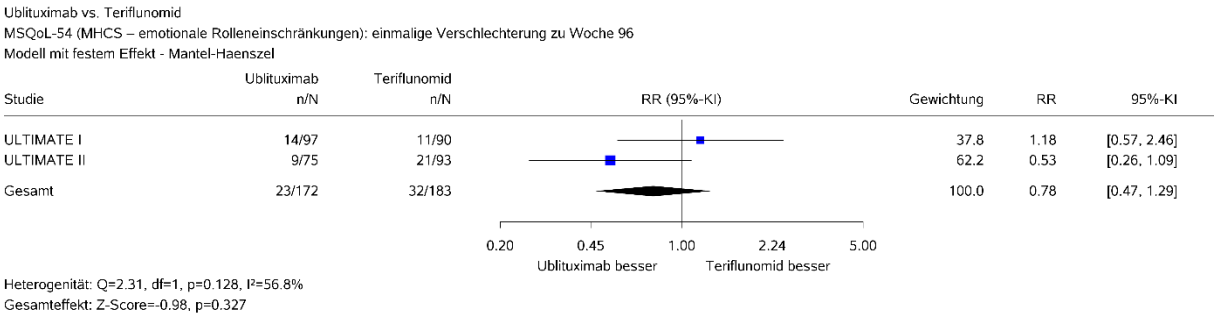

Figure 29: Meta-analysis for the outcome of health-related quality of life (MSQoL-54 – emotional role restrictions: deterioration at Week 96), relevant subpopulation of the studies ULTIMATE I and ULTIMATE II

Cognitive functioning (subdomain of the MHCS) - improvement at Week 96

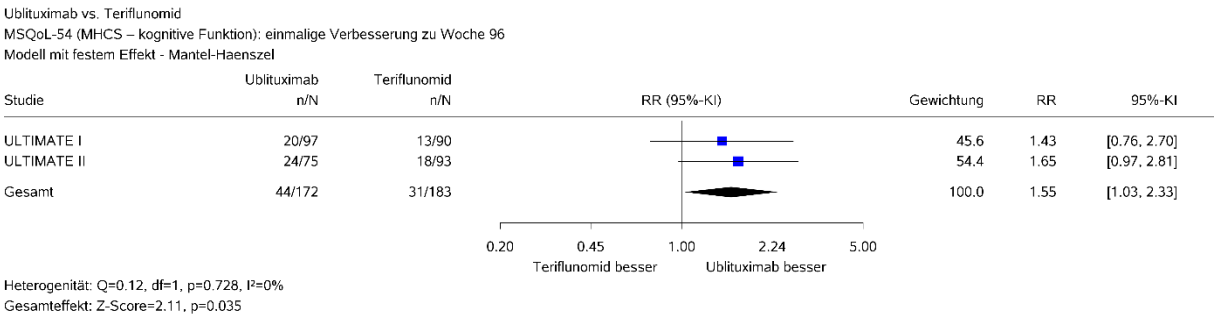

Figure 30: Meta-analysis for the outcome of health-related quality of life (MSQoL-54 – cognitive functioning: improvement at Week 96), relevant subpopulation of the studies ULTIMATE I and ULTIMATE II

Cognitive functioning (subdomain of the MHCS) - deterioration at Week 96

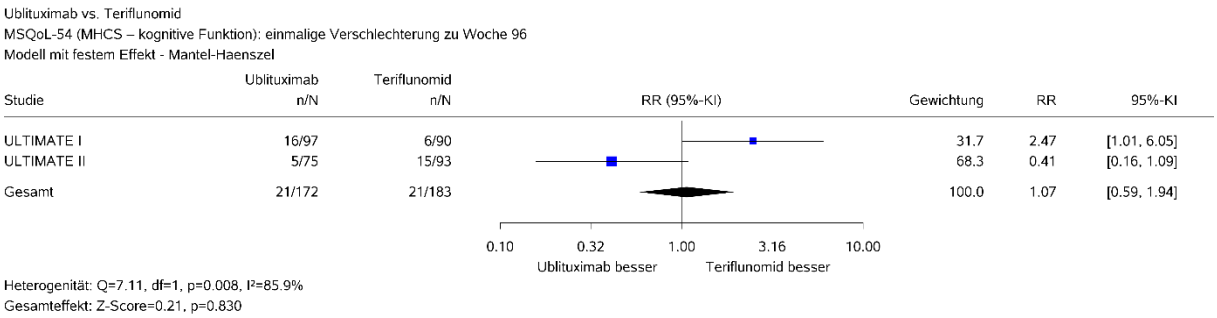

Figure 31: Meta-analysis for the outcome of health-related quality of life (MSQoL-54 – cognitive functioning: deterioration at Week 96), relevant subpopulation of the studies ULTIMATE I and ULTIMATE II

Sexual functioning (subdomain of the PHCS) - improvement at Week 96

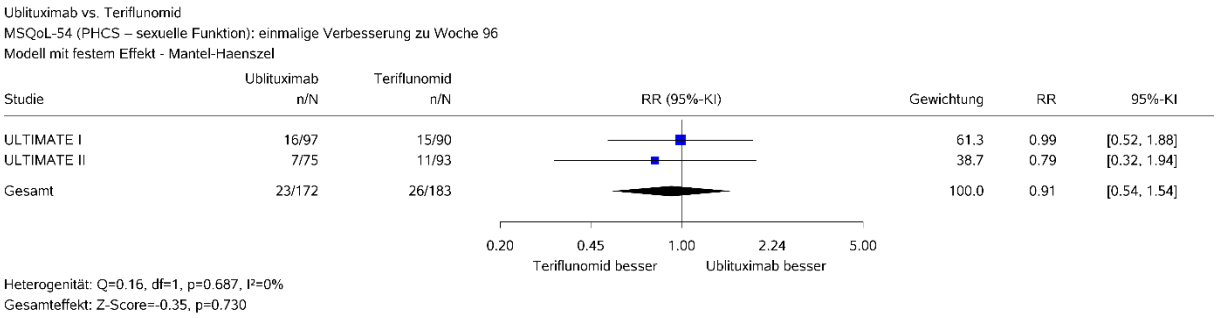

Figure 32: Meta-analysis for the outcome of health-related quality of life (MSQoL-54 – sexual functioning: improvement at Week 96), relevant subpopulation of the studies ULTIMATE I and ULTIMATE II

Sexual functioning (subdomain of the PHCS) - deterioration at Week 96

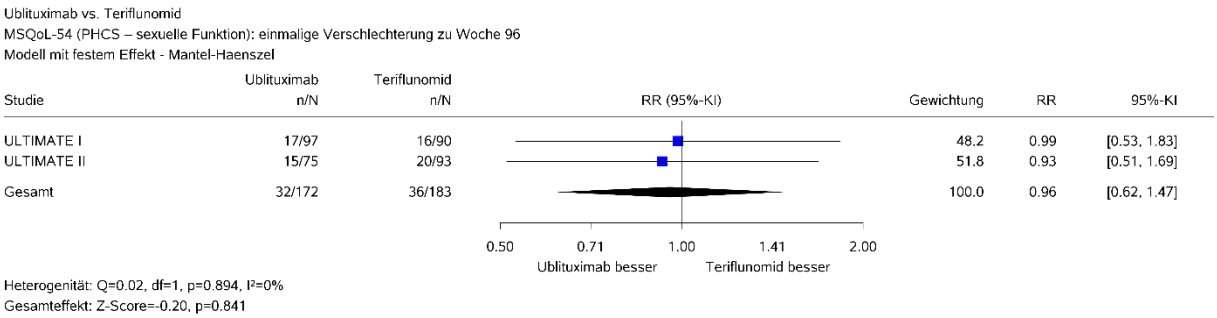

Figure 33: Meta-analysis for the outcome of health-related quality of life (MSQoL-54 – sexual functioning: deterioration at Week 96), relevant subpopulation of the studies ULTIMATE I and ULTIMATE II

Health burden (subdomain of the PHCS) - improvement at Week 96

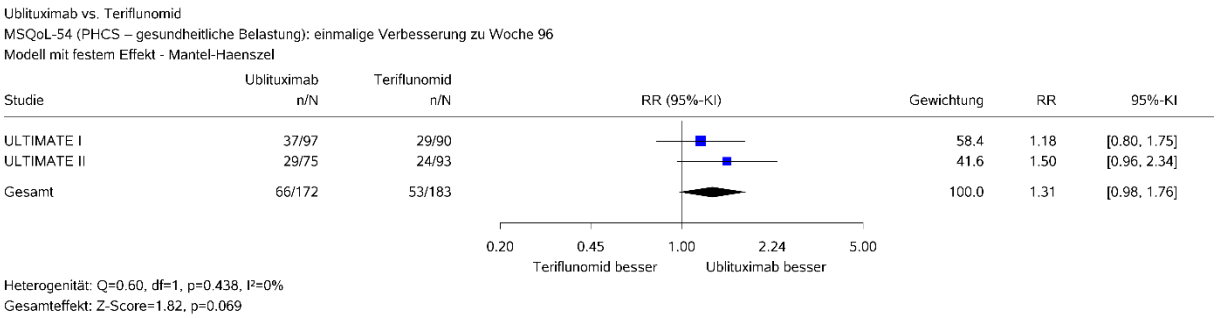

Figure 34: Meta-analysis for the outcome of health-related quality of life (MSQoL-54 – health burden: improvement at Week 96), relevant subpopulation of the studies ULTIMATE I and ULTIMATE II

Health burden (subdomain of the PHCS) - deterioration at Week 96

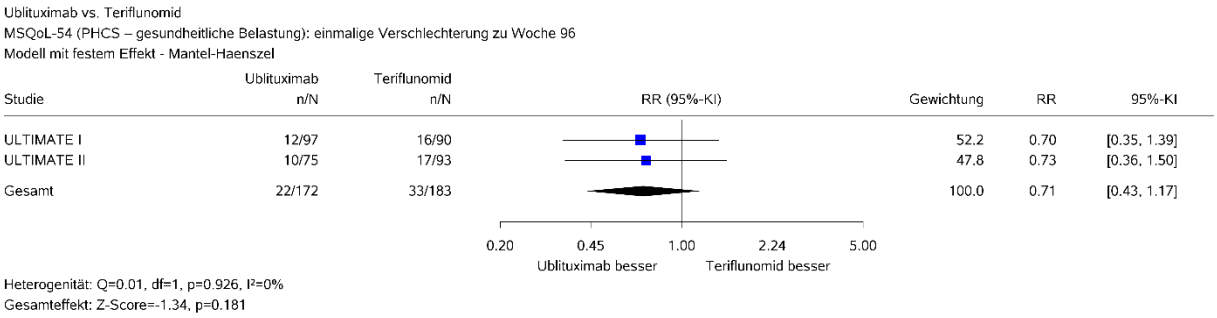

Figure 35: Meta-analysis for the outcome of health-related quality of life (MSQoL-54 – health burden: deterioration at Week 96), relevant subpopulation of the studies ULTIMATE I and ULTIMATE II

General quality of life (subdomain of the MHCS) - improvement at Week 96

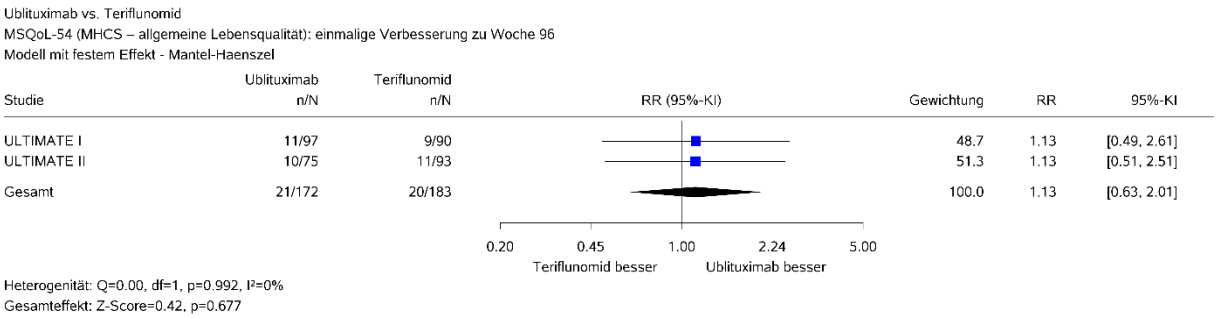

Figure 36: Meta-analysis for the outcome of health-related quality of life (MSQoL-54 – general quality of life: improvement at Week 96), relevant subpopulation of the studies ULTIMATE I and ULTIMATE II

General quality of life (subdomain of the MHCS) - deterioration at Week 96

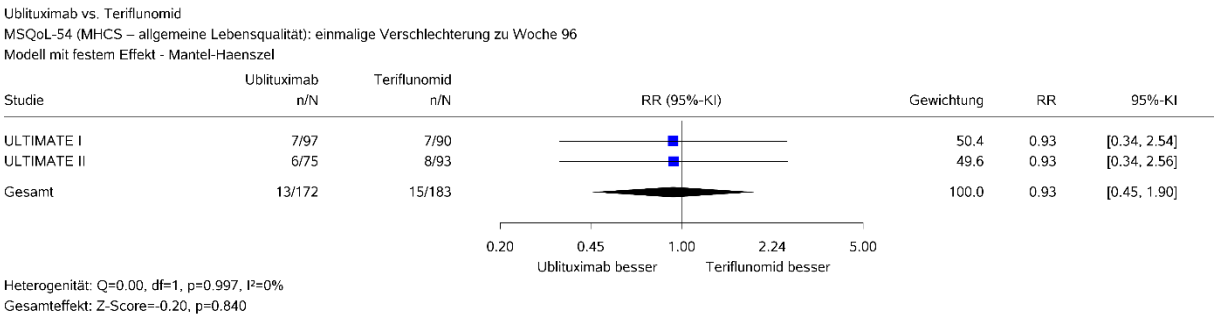

Figure 37: Meta-analysis for the outcome of health-related quality of life (MSQoL-54 – general quality of life: deterioration at Week 96), relevant subpopulation of the studies ULTIMATE I and ULTIMATE II

Change in health status (individual item, supplementary information) - improvement at Week 96

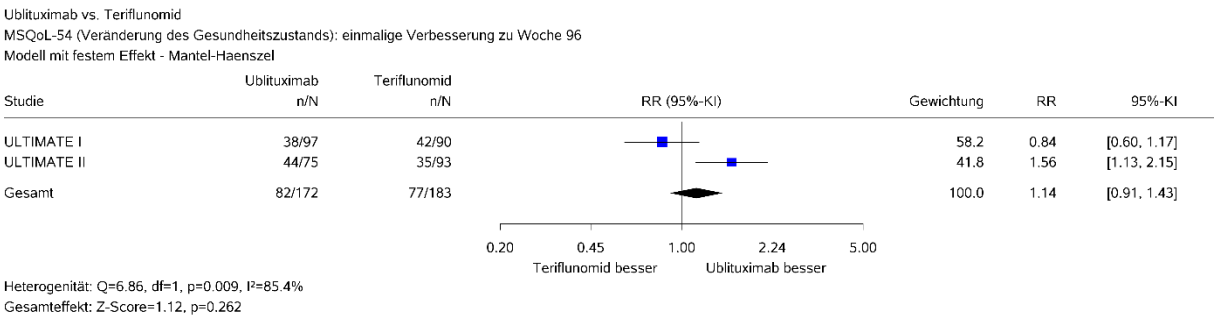

Figure 38: Meta-analysis for the outcome of health-related quality of life (MSQoL-54 – change in health status: improvement at Week 96), relevant subpopulation of the studies ULTIMATE I and ULTIMATE II

Change in health status (individual item, supplementary information) - deterioration at week 96

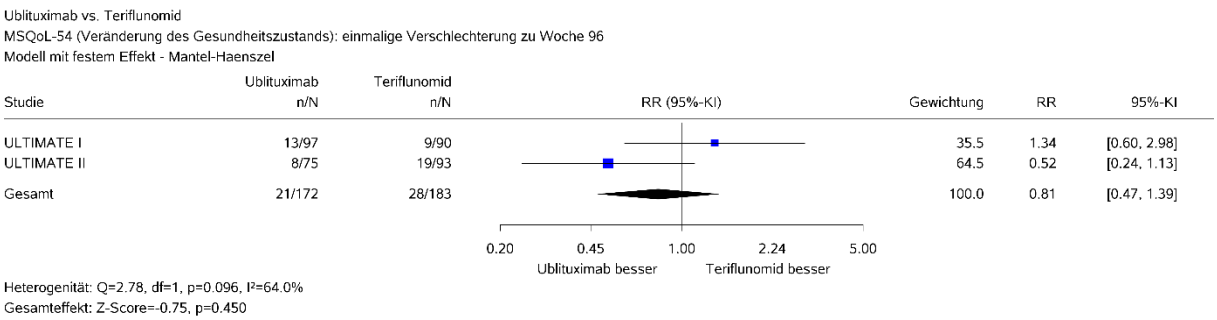

Figure 39: Meta-analysis for the outcome of health-related quality of life (MSQoL-54 – change in health status: deterioration at Week 96), relevant subpopulation of the studies ULTIMATE I and ULTIMATE II

Satisfaction with sexual functioning (individual item, supplementary information) - improvement at Week 96

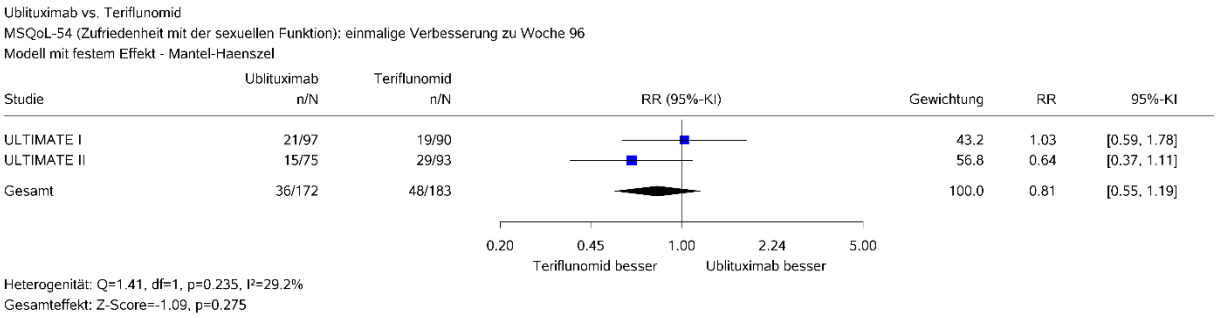

Figure 40: Meta-analysis for the outcome of health-related quality of life (MSQoL-54 – satisfaction with sexual functioning: improvement at Week 96), relevant subpopulation of the studies ULTIMATE I and ULTIMATE II

Satisfaction with sexual functioning (individual item, supplementary information) - deterioration at Week 96

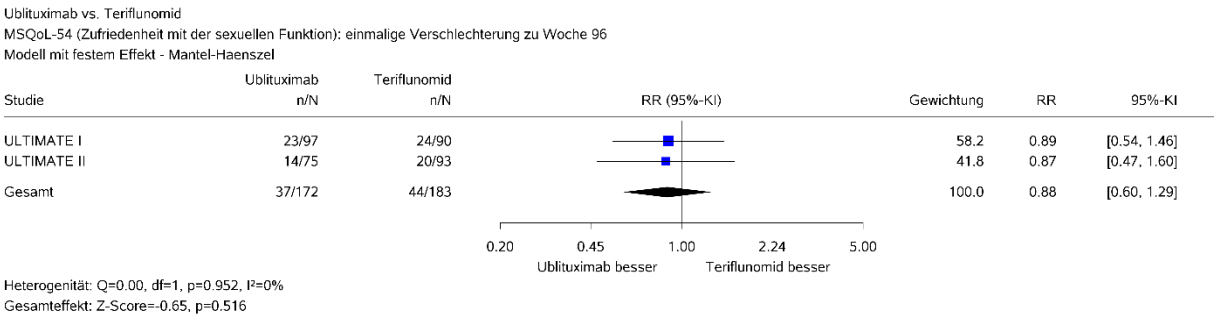

Figure 41: Meta-analysis for the outcome of health-related quality of life (MSQoL-54 – satisfaction with sexual functioning: deterioration at Week 96), relevant subpopulation of the studies ULTIMATE I and ULTIMATE II

B.3 Side effects

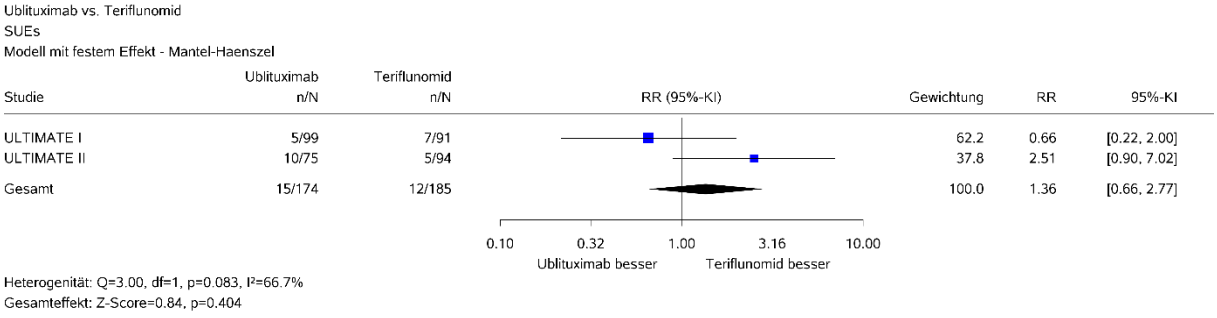

Figure 42: Meta-analysis for the outcome of SAEs, relevant subpopulation of the studies ULTIMATE I and ULTIMATE II

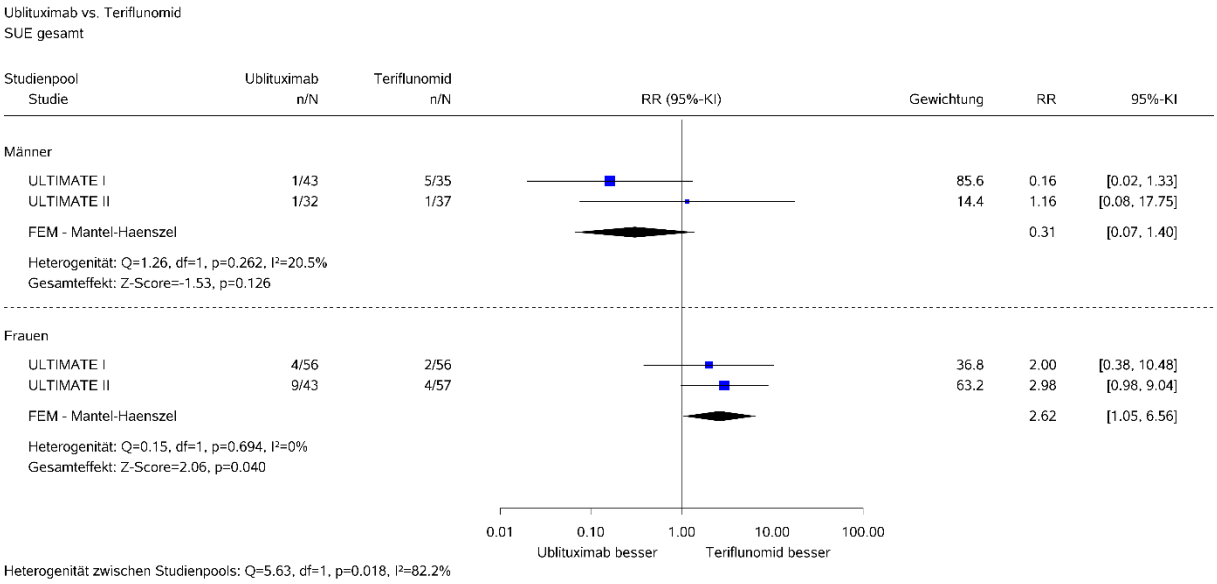

Figure 43: Meta-analysis for the subgroup characteristic “sex” (women vs. men) for the outcome of SAEs, relevant subpopulation of the studies ULTIMATE I and ULTIMATE II

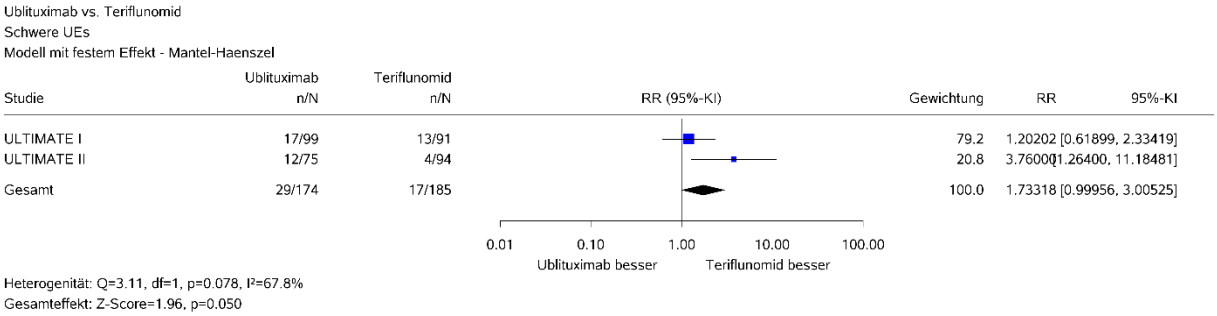

Figure 44: Meta-analysis for the outcome of severe AEs, relevant subpopulation of the studies ULTIMATE I and ULTIMATE II

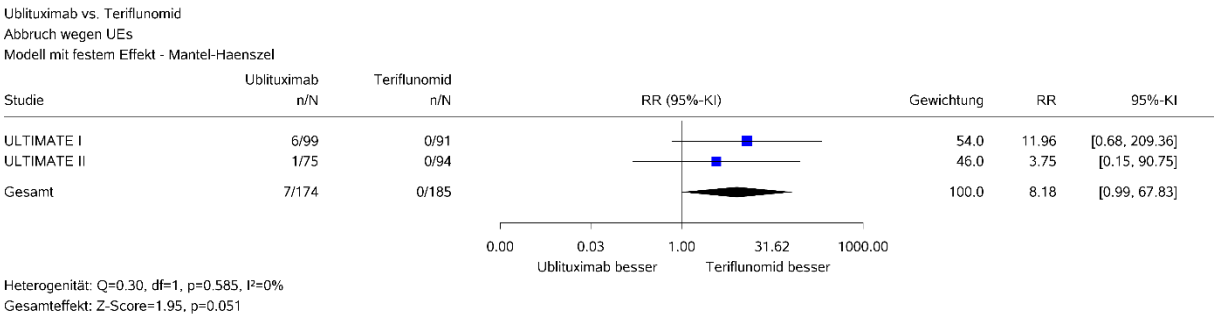

Figure 45: Meta-analysis for the outcome of discontinuation due to AEs, relevant subpopulation of the studies ULTIMATE I and ULTIMATE II

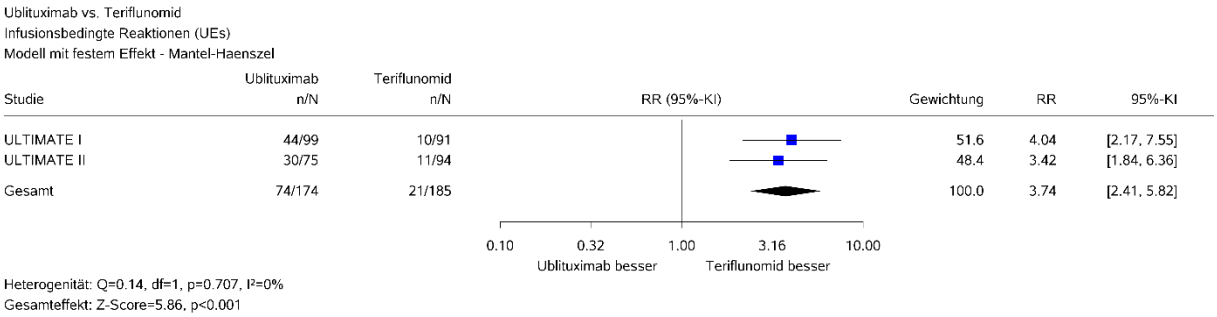

Figure 46: Meta-analysis for the outcome of infusion-related reactions (AEs), relevant subpopulation of the studies ULTIMATE I and ULTIMATE II

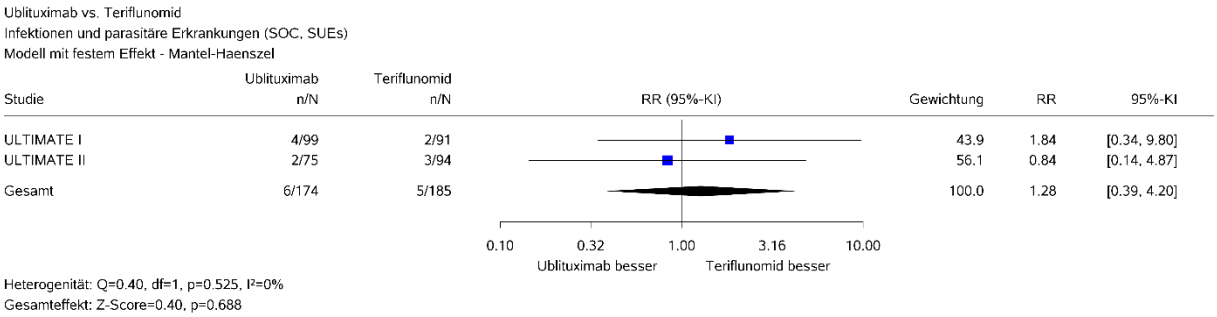

Figure 47: Meta-analysis for the outcome of infections and infestations (SOC, SAEs), relevant subpopulation of the studies ULTIMATE I and ULTIMATE II

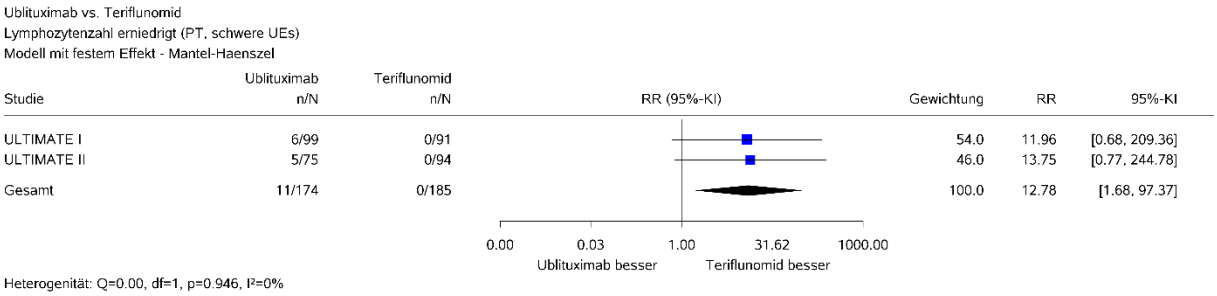

Figure 48: Meta-analysis for the outcome of lymphocyte count decreased (PT, severe AEs), relevant subpopulation of the studies ULTIMATE I and ULTIMATE II

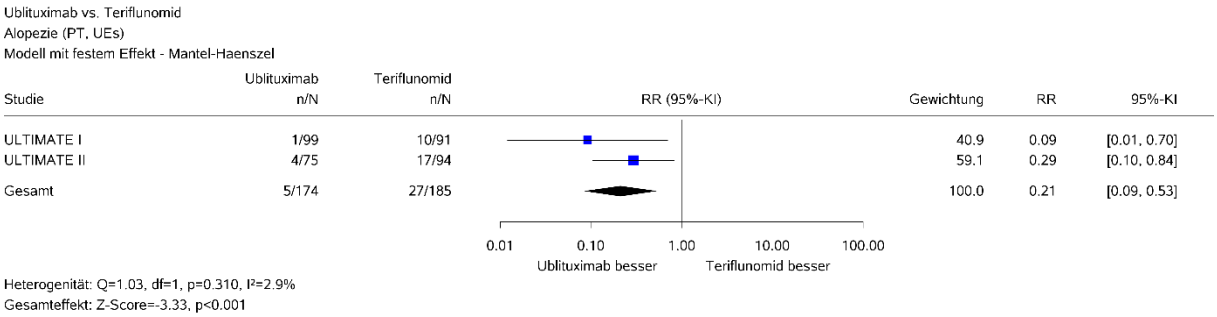

Figure 49: Meta-analysis for the outcome of alopecia (PT, AEs), relevant subpopulation of the studies ULTIMATE I and ULTIMATE II

Appendix C Results on side effects

For the overall rates of AEs, SAEs and severe AEs (e.g. CTCAE grade ≥ 3), the following tables present events for SOCs and PTs as per MedDRA, each based on the following criteria:

- overall rate of AEs (irrespective of severity): events which occurred in at least 10% of patients in one study arm
- overall rate of severe AEs (e.g. CTCAE grade ≥ 3) and SAEs: events which occurred in at least 5% of patients in 1 study arm
- in addition, for all events irrespective of severity: events which occurred in at least 10 patients and in at least 1% of patients in 1 study arm

A complete presentation of all events (SOCs/PTs) that resulted in discontinuation is provided for the outcome of discontinuation due to AEs.

Table 15: Common AEsa - RCT, direct comparison: ublituximab vs. teriflunomide, ULTIMATE I study

Study	Patients with event n (%)	
SOC[b] PT[b]	ublituximab N = 99	teriflunomide N = 91
ULTIMATE I		
Overall AE rate	81 (81.8)	76 (83.5)
Blood and lymphatic system disorders	12 (12.1)	11 (12.1)
Cardiac disorders	11 (11.1)	6 (6.6)
Gastrointestinal disorders	29 (29.3)	21 (23.1)
Nausea	11 (11.1)	3 (3.3)
General disorders and administration site conditions	30 (30.3)	16 (17.6)
Pyrexia	16 (16.2)	7 (7.7)
Infections and infestations	35 (35.4)	41 (45.1)
Nasopharyngitis	9 (9.1)	18 (19.8)
Injury, poisoning and procedural complications	7 (7.1)	12 (13.2)
Investigations	31 (31.3)	19 (20.9)
Lymphocyte count decreased	12 (12.1)	2 (2.2)
Musculoskeletal and connective tissue disorders	13 (13.1)	23 (25.3)
Back pain	4 (4)	13 (14.3)
Nervous system disorders	37 (37.4)	27 (29.7)
Headache	31 (31.3)	19 (20.9)
Respiratory, thoracic and mediastinal disorders	14 (14.1)	10 (11)
Skin and subcutaneous tissue disorders	13 (13.1)	16 (17.6)
Alopecia	1 (1)	10 (11)

a. Events which occurred in ≥ 10% of the patients in at least 1 study arm.
b. MedDRA version 23.0; SOC and PT notation taken without adaptation from the documents subsequently submitted.

AE: adverse event; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least one event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class

Table 16: Common SAEsa - RCT, direct comparison: ublituximab vs. teriflunomide, ULTIMATE I study

Study	Patients with event n (%)	
SOC **PT**	**ublituximab** **N = 99**	**teriflunomide** **N = 91**
ULTIMATE I		
Overall rate of SAEs[b]	5 (5.1)	7 (7.7)

a. Events that occurred in ≥ 5% of the patients in at least one study arm.
b. For SAEs, no MedDRA SOCs and PTs met the criterion for presentation.

MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least one event; N: number of analysed patients; PT: Preferred Term; SAE: serious adverse event; SOC: System Organ Class

Table 17: Common severe AEsa (CTCAE grade ≥ 3) - RCT, direct comparison: ublituximab vs. teriflunomide, ULTIMATE I study

Study	Patients with event n (%)	
SOC[b] **PT[b]**	**ublituximab** **N = 99**	**teriflunomide** **N = 91**
ULTIMATE I		
Overall rate of severe AEs (CTCAE grade ≥ 3)	17 (17.2)	13 (14.3)
Blood and lymphatic system disorders	5 (5.1)	3 (3.3)
Lymphopenia	5 (5.1)	0 (0)
Investigations	8 (8.1)	3 (3.3)
Lymphocyte count decreased	6 (6.1)	0 (0)

a. Events that occurred in ≥ 5% of the patients in at least one study arm.
b. MedDRA version 23.0; SOC and PT notation taken without adaptation from the documents subsequently submitted.

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least 1 event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class

Table 18; Discontinuations due to AEs - RCT, direct comparison: ublituximab vs. teriflunomide, ULTIMATE I study

Study	**Patients with event n (%)**	
SOC[a] **PT[a]**	**ublituximab** **N = 99**	**teriflunomide** **N = 91**
ULTIMATE I		
Overall rate of discontinuations due to AEs	6 (6.1)	0 (0)
Cardiac disorders	2 (2.0)	0 (0)
Myocardial ischaemia	1 (1.0)	0 (0)
Palpitations	1 (1.0)	0 (0)
Infections and infestations	2 (2.0)	0 (0)
Central nervous system enteroviral infection	1 (1.0)	0 (0)
Encephalitis	1 (1.0)	0 (0)
Injury, poisoning and procedural complications	1 (1.0)	0 (0)
Infusion-related reaction	1 (1.0)	0 (0)
Skin and subcutaneous tissue disorders	1 (1.0)	0 (0)
Toxic skin eruption	1 (1.0)	0 (0)

a. MedDRA version 23.0; SOC and PT notation taken without adaptation from the documents subsequently submitted.

AE: adverse event; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least one event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class

Table 19: Common AEsa - RCT, direct comparison: ublituximab vs. teriflunomide, ULTIMATE II study

Study	Patients with event n (%)	
SOC[b] PT[b]	ublituximab N = 75	teriflunomide N = 94
ULTIMATE II		
Overall AE rate	63 (84.0)	85 (90.4)
Blood and lymphatic system disorders	9 (12)	8 (8.5)
Cardiac disorders	9 (12)	12 (12.8)
Gastrointestinal disorders	22 (29.3)	32 (34)
General disorders and administration site conditions	29 (38.7)	12 (12.8)
Influenza-like illness	8 (10.7)	2 (2.1)
Pyrexia	11 (14.7)	3 (3.2)
Infections and infestations	39 (52)	53 (56.4)
Nasopharyngitis	21 (28)	16 (17)
Oral herpes	5 (6.7)	10 (10.6)
Pharyngitis	8 (10.7)	1 (1.1)
Respiratory Tract Infection	3 (4)	13 (13.8)
Upper respiratory tract infection	4 (5.3)	13 (13.8)
Injury, poisoning and procedural complications	14 (18.7)	12 (12.8)
Investigations	23 (30.7)	10 (10.6)
Musculoskeletal and connective tissue disorders	22 (29.3)	21 (22.3)
Back pain	10 (13.3)	8 (8.5)
Nervous system disorders	30 (40)	39 (41.5)
Headache	25 (33.3)	29 (30.9)
Psychiatric disorders	13 (17.3)	8 (8.5)
Reproductive system and breast disorders	9 (12)	7 (7.4)
Respiratory, thoracic and mediastinal disorders	12 (16)	10 (10.6)
Skin and subcutaneous tissue disorders	11 (14.7)	26 (27.7)
Alopecia	4 (5.3)	17 (18.1)

a. Events that occurred in ≥ 10% of the patients in at least one study arm.
b. MedDRA version 23.0; SOC and PT notation taken without adaptation from the documents subsequently submitted.

AE: adverse event; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least one event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class

Table 20: Common AEsa - RCT, direct comparison: ublituximab vs. teriflunomide, ULTIMATE II study

Study	Patients with event n (%)	
SOC[b] PT[b]	ublituximab N = 75	teriflunomide N = 94
ULTIMATE II		
Overall rate of SAEs[b]	10 (13.3)	5 (5.3)

a. Events that occurred in ≥ 5% of the patients in at least one study arm.
b. For SAEs, no MedDRA SOCs and PTs met the criterion for presentation.

MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least one event; N: number of analysed patients; PT: Preferred Term; SAE: serious adverse event; SOC: System Organ Class

Table 21: Common severe AEsa (CTCAE grade ≥ 3) - RCT, direct comparison: ublituximab vs. teriflunomide, ULTIMATE II study

Study	Patients with event n (%)	
SOC[b] PT[b]	ublituximab N = 75	teriflunomide N = 94
ULTIMATE II		
Overall rate of severe AEs (CTCAE grade ≥ 3)	12 (16.0)	4 (4.3)
Investigations	7 (9.3)	0 (0)
Lymphocyte count decreased	5 (6.7)	0 (0)

a. Events that occurred in ≥ 5% of the patients in at least one study arm.
b. MedDRA version 23.0; SOC and PT notation taken without adaptation from the documents subsequently submitted.

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least 1 event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class

Table 22: Discontinuations due to AEs - RCT, direct comparison: ublituximab vs. teriflunomide, ULTIMATE II study

Study	**Patients with event n (%)**	
SOC[b] **PT[b]**	**ublituximab** **N = 75**	**teriflunomide** **N = 94**
ULTIMATE II		
Overall rate of discontinuations due to AEs	1 (1.3)	0 (0)
General disorders and administration site conditions	1 (1.3)	0 (0)
Decreased Activity	1 (1.3)	0 (0)
Fatigue	1 (1.3)	0 (0)
Musculoskeletal and connective tissue disorders	1 (1.3)	0 (0)
Muscular weakness	1 (1.3)	0 (0)
Nervous system disorders	1 (1.3)	0 (0)
Dysaesthesia	1 (1.3)	0 (0)

a. MedDRA version 23.0; SOC and PT notation taken without adaptation from the documents subsequently submitted.

AE: adverse event; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least one event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class