IQWiG Reports – Commission No. A21-87

Acalabrutinib (pretreated chronic lymphocytic leukaemia) –

3rd Addendum to Commission A20-105[1]

Addendum

Commission: A21-87
Version: 1.0
Status: 9 July 2021

[1] Translation of addendum A21-87 *Acalabrutinib (vorbehandelte chronische lymphatische Leukämie) – Addendum zum Auftrag A20-105* (Version 1.0; Status: 9 July 2021). Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

Publishing details

Publisher
Institute for Quality and Efficiency in Health Care

Topic
Acalabrutinib (pretreated chronic lymphocytic leukaemia) – 3rd Addendum to Commission A20-105

Commissioning agency
Federal Joint Committee

Commission awarded on
22 June 2021

Internal Commission No.
A21-87

Address of publisher
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Keywords: Acalabrutinib, Leukemia – Lymphocytic – Chronic – B-Cell, Benefit Assessment, NCT02970318

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List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
CLL	chronic lymphocytic leukaemia
CTCAE	Common Terminology Criteria for Adverse Events
FACIT	Functional Assessment of Chronic Illness Therapy
EORTC	European Organisation for Research and Treatment of Cancer
EQ-5D	European Quality of Life-5 Dimensions
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
QLQ-C30	Quality of Life Questionnaire-Core 30
SGB	Sozialgesetzbuch (Social Code Book)
SPC	Summary of Product Characteristics
TP53 mutation	mutation of the tumour protein p53
VAS	visual analogue scale

1 Background

On 22 June 2021, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Commission A20-105 (Acalabrutinib – Benefit assessment according to §35a Social Code Book V) [1].

In its dossier [2], the pharmaceutical company (hereinafter referred to as "the company") presented the results of the randomized controlled trial (RCT) ASCEND for the benefit assessment of acalabrutinib in adult patients with chronic lymphocytic leukaemia (CLL) who have received at least one prior therapy. It investigated 2 research questions in its dossier and accordingly presented analyses on 2 subpopulations of the ASCEND study. The G-BA's appropriate comparator therapy (ACT) updated in November 2020 resulted in 3 research questions, however. In the commenting procedure, the company subsequently submitted analyses of the ASCEND study, in which it investigated the 3 research questions arising from the updated ACT of the G-BA [3,4]. On 27 April 2021, the G-BA commissioned IQWiG with the assessment of the analyses of the ASCEND study presented by the company in the commenting procedure with regard to the research questions of the current ACT. As the ACT (a patient-specific therapy) was not implemented in 2 of the 3 research questions, the analyses for these research questions could not be used for the benefit assessment [1,5].

At the meeting of the pharmaceuticals subcommittee on 22 June 2021, the G-BA commissioned IQWiG with the assessment of the analyses of the ASCEND study subsequently submitted by the company in the commenting procedure with regard to the following patient populations:

- Research question 1: adult patients with CLL after one prior therapy who have no 17p deletion or mutation of the tumour protein p53 (TP53 mutation) and for whom chemo-immunotherapy is indicated
- Research question 3: adult patients with CLL after at least 2 prior therapies

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

2 Presentation of the results for research question 1 (adults with CLL; one prior therapy; chemo-immunotherapy suitable) and research question 3 (adults with CLL; ≥ 2 prior therapies)

Information on the study design of the ASCEND study can be found in dossier assessment A20-105 [1] and in addendum A21-54 [5].

2.1 Research question 1: adults with CLL; one prior therapy; chemo-immunotherapy suitable

2.1.1 Study characteristics

Table 1 describes the intervention of the ASCEND study.

Table 1: Characteristics of the intervention – RCT, direct comparison: acalabrutinib vs. bendamustine + rituximab/idelalisib + rituximab

Study	Intervention	Comparison
ASCEND	Acalabrutinib 200 mg (100 mg twice daily) orally until disease progression or unacceptable toxicity	Bendamustine IV for a maximum of 6 cycles[a] ▪ 70 mg/m² BSA on day 1 and 2 of each cycle + rituximab IV for 6 cycles[a] ▪ cycle 1: 375 mg/m² BSA on day 1 ▪ cycle 2–6: 500 mg/m² BSA on day 1 or idelalisib 300 mg (150 mg twice daily) orally until disease progression or unacceptable toxicity + rituximab IV, 8 infusions in total ▪ 375 mg/m² BSA on day 1 of cycle 1[a] ▪ 500 mg/m² BSA every 2 weeks for 4 doses ▪ 500 mg/m² BSA every 4 weeks for 3 doses
	Treatment interruptions and dose adjustments ▪ Treatment interruptions ≤ 28 days and dose adjustments due to toxicity were allowed (dose adjustments for rituximab were not allowed) ▪ If the respective study medication was discontinued, the other study medication could be continued in the case of the combination therapies.	
	Allowed prior and concomitant treatment ▪ steroids ≤ 2 weeks (> 20 mg/day) as premedication for administration of the study medication, and corticosteroids > 2 weeks to treat idelalisib-related AEs were possible ▪ prophylaxis for *Pneumocystis jirovecii* pneumonia (PJP) during treatment with idelalisib ▪ antiemetics for clinical indication ▪ standard supportive medication ▪ haematopoietic growth factors **Non-permitted concomitant treatment** ▪ any other therapies for treating CLL ▪ warfarin or an equivalent vitamin K antagonist	

a. A treatment cycle comprises 28 days.

AE: adverse event; BSA: body surface area; CLL: chronic lymphocytic leukaemia; PJP: *Pneumocystis jirovecii* pneumonia; RCT: randomized controlled trial

Treatment with acalabrutinib was in compliance with the Summary of Product Characteristics (SPC) [6]. Bendamustine was administered in combination with rituximab for a maximum of 6 cycles. According to the SPC, bendamustine in CLL is used as primary therapy (monotherapy) [7]. The dosage specified in the SPC is 100 mg/m² body surface area on days 1 and 2, every 4 weeks, for up to 6 cycles. Treatment with idelalisib in combination with rituximab followed an established dosing regimen [8].

Information on the planned duration of follow-up observation and on the data cut-offs can be found in addendum A21-54 [5].

Characteristics of the relevant subpopulation

Table 2 shows the characteristics of the patients of research questions 1 in the study included.

Table 2: Patient characteristics – RCT, direct comparison: acalabrutinib vs. bendamustine + rituximab (adults with CLL; one prior therapy; chemo-immunotherapy suitable) (multipage table)

Study Characteristic Category	Acalabrutinib N = 17	Bendamustine + rituximab N = 19
ASCEND		
Age [years], mean (SD)	67 (10)	71 (9)
Sex [F/M], %	24/76	42/58
Region, n (%)		
North America	2 (12)	2 (11)
Western Europe	3 (18)	5 (26)
Central/Eastern Europe	8 (47)	10 (53)
Australia/New Zealand	4 (24)	2 (11)
Family origin, n (%)		
White	17 (100)	17 (89)
Other[a]	0 (0)	2 (11)[b]
ECOG PS, n (%)		
0	5 (29)	8 (42)
1	6 (35)	7 (37)
2	6 (35)	4 (21)
Disease duration: time between first diagnosis and randomization [months], median [min; max]	72.2 [25.0; 183.0]	77.0 [7.0; 174.4]
Bulky disease[c], n (%)		
< 5 cm	10 (59)	11 (58)
≥ 5 cm	7 (41)	8 (42)
Rai stage, n (%)		
0/I/II	11 (65)[b]	9 (47)[b]
III/IV	6 (35)[b]	10 (53)[b]
Binet stage, n (%)		
A	2 (12)	7 (37)
B	9 (53)	9 (47)
C	5 (29)	2 (11)
Missing	1 (6)	1 (5)
Beta 2 microglobulin, n (%)		
> 3.5 mg/L	9 (53)	13 (68)
≤ 3.5 mg/L	7 (41)	4 (21)
Missing	1 (6)	2 (11)

Table 2: Patient characteristics – RCT, direct comparison: acalabrutinib vs. bendamustine + rituximab (adults with CLL; one prior therapy; chemo-immunotherapy suitable) (multipage table)

Study Characteristic Category	Acalabrutinib N = 17	Bendamustine + rituximab N = 19
Cytopenia[d], n (%)	8 (47)	9 (47)
Disease-related symptoms[e], n (%)	9 (53)	9 (47)
Chromosome anomaly, n (%)		
17p deletion	1 (6)	0 (0)
11q deletion	4 (24)	5 (26)
TP53 mutation	1 (6)	0 (0)
17p deletion and TP53 mutation	1 (6)	0 (0)
IGHV status, n (%)		
Mutated	7 (41)	3 (16)
Unmutated	10 (59)	16 (84)
Complex karyotype[f], n (%)		
Yes	5 (29)	0 (0)
No	12 (71)	18 (95)
Undetermined	0 (0)	1 (5)
Treatment discontinuation, n (%)	2 (12)	18 (95)
Study discontinuation, n (%)	2 (12)	4 (21)

a. Composed of Pacific Island family origin or not reported.
b. Institute's calculation.
c. The assessment was made by the investigator.
d. Neutrophil count ≤ 1.5 x 10^9/L, haemoglobin ≤ 110 g/L or platelet count ≤ 100 x 10^9/L.
e. At least one of the following symptoms: weight loss, fever, night sweats, fatigue.
f. Defined as the presence of 3 or more cytogenetic abnormalities based on karyotyping by a central laboratory.
g. According to the company, discontinuation of the randomized therapy.

11q deletion: deletion of the long arm of chromosome 11; 17p deletion: deletion of the short arm of chromosome 17; CLL: chronic lymphocytic leukaemia; ECOG PS: Eastern Cooperative Oncology Performance Status; F: female; IGHV: immunoglobulin heavy-chain variable region; M: male; max.: maximum; min.: minimum; n: number of patients in the category; N: number of randomized patients; RCT: randomized controlled trial; SD: standard deviation; TP53 mutation: mutation of the tumour protein p53

Patient characteristics were largely balanced between the treatment arms. Notable differences were shown regarding treatment discontinuations. Almost all patients in the comparator arm (95%), but only 12% in the intervention arm discontinued treatment.

Information on the course of the study

Table 3 shows the mean/median treatment durations of the patients and the mean/median observation periods for individual outcomes.

Table 3: Information on the course of the study – RCT, direct comparison: acalabrutinib vs. bendamustine + rituximab (adults with CLL; one prior therapy; chemo-immunotherapy suitable)

Study **Duration of the study phase** **Outcome category**	**Acalabrutinib** **N = 17**	**Bendamustine + rituximab** **N = 19**
ASCEND		
Treatment duration[a] [months]		
Median [min; max]	22.6 [8.0; 27.9]	5.6 [5.5; 7.1][b]
Mean (SD)	22.10 (4.79)	5.75 (0.41)[b]
Observation period[c] [months]		
Overall survival		
Median [min; max]	22.60 [ND]	21.68 [ND]
Mean (SD)	ND	ND
Morbidity		
Health status (EQ-5D VAS), fatigue (FACIT-Fatigue), symptoms (EORTC QLQ-C30)		
Median [min; max]	11.73 [ND]	11.24 [ND]
Mean (SD)	ND	ND
Disease-specific symptoms[d]	No usable data available[e]	
Health-related quality of life (EORTC QLQ-C30)		
Median [min; max]	11.73 [ND]	11.24 [ND]
Mean (SD)	ND	ND
Side effects[a]		
Median [min; max]	22.6 [ND]	5.7 [ND]
Mean (SD)	ND	ND

a. Data refer to the safety analysis set: 16 vs. 18 patients who received at least one dose of the study medication, analysed according to the first study medication actually taken.
b. Data for bendamustine; the median [min; max] treatment duration with rituximab was 5.5 [0.9; 7.1] months.
c. For the outcomes of the outcome categories of morbidity and health-related quality of life, the data are based on the data cut-off of 15 January 2019, for overall survival and side effects on the data cut-off of 1 August 2019.
d. Weight loss, fatigue, fever, night sweats.
e. The analysed population contains only a maximum of 50% of the randomized patients.

CLL: chronic lymphocytic leukaemia; EORTC: European Organisation for Research and Treatment of Cancer; EQ-5D: European Quality of Life-5 Dimensions; FACIT: Functional Assessment of Chronic Illness Therapy; max.: maximum; min: minimum; N: number of randomized patients; ND: no data; QLQ-C30: Quality of Life Questionnaire-Core 30; RCT: randomized controlled trial; SD: standard deviation; VAS: visual analogue scale

Based on the data, it can be seen that the treatment in the intervention arm of the relevant subpopulation was 4 times longer than in the comparator arm.

The median observation period is comparable between the 2 study arms for the outcomes of the categories of mortality, morbidity and health-related quality of life. Observation of side effects was about 4 times longer in the intervention arm than in the comparator arm. This is due to the fact that the follow-up observation for side effects was only planned up to 30 days after the last dose of the study medication and there were differences in the treatment durations between the study arms.

Table 4 shows which subsequent therapies patients received after discontinuing the study medication.

Table 4: Information on subsequent antineoplastic therapies – RCT, direct comparison: acalabrutinib vs. bendamustine + rituximab (adults with CLL; one prior therapy; chemo-immunotherapy suitable)

Study Drug	Patients with subsequent therapy n (%)	
	Acalabrutinib N = 17	Bendamustine + rituximab N = 19
ASCEND		
Total	1 (5.9)	4 (21.1)
Acalabrutinib	0 (0)	3 (15.8)
Purine analogues	0 (0)	0 (0)
Alkylating agents other than bendamustine	1 (5.9)	1 (5.3)
Bendamustine	0 (0)	0 (0)
Anti-CD20 monoclonal antibodies	1 (5.9)	1 (5.3)
Ibrutinib	0 (0)	1 (5.3)
Venetoclax	0 (0)	0 (0)
Other	0 (0)	0 (0)

CD: cluster of differentiation; CLL: chronic lymphocytic leukaemia; n: number of patients with subsequent therapy; N: number of randomized patients; RCT: randomised controlled trial

Subsequent therapy was allowed for patients in both study arms after disease progression. Patients from the comparator arm with confirmed disease progression could receive acalabrutinib at the discretion of the investigator. In the relevant subpopulation, a total of one patient in the relevant intervention arm and 4 patients in the comparator arm received subsequent therapy. The most common subsequent therapy administered was acalabrutinib. This is an approved use because acalabrutinib can also be administered to patients with CLL who have received more than one pretreatment.

Risk of bias across outcomes (study level)

The assessment of the risk of bias across outcomes (risk of bias at study level) can be found in addendum A21-54 [5].

2.1.2 Results

2.1.2.1 Outcomes included and risk of bias

An overview of the included outcomes can be found in addendum A21-54 [5]. The risk of bias for all outcomes, except for “overall survival”, was rated as high. For reasons, see addendum A21-54 [5].

2.1.2.2 Results

Table 5 summarizes the results of the comparison of acalabrutinib with bendamustine + rituximab in adult patients with CLL after one prior therapy who have no 17p deletion or TP53 mutation and for whom chemo-immunotherapy is indicated.

Results presented as supplementary information can be found in Appendix A. Kaplan-Meier curves on the event time analyses are presented in Appendix C. The results on the common adverse events (AEs), serious AEs (SAEs), severe AEs, and on all AEs that led to treatment discontinuation are presented in Appendix E.

Table 5: Results (mortality, morbidity, health-related quality of life and side effects) – RCT, direct comparison: acalabrutinib vs. bendamustine + rituximab (adults with CLL; one prior therapy; chemo-immunotherapy suitable)
(multipage table)

Study Outcome category Outcome	Acalabrutinib		Bendamustine + rituximab		Acalabrutinib vs. bendamustine + rituximab
	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]
ASCEND					
Mortality (data cut-off: 1 August 2019)					
Overall survival	17	NA 1 (5.9)	19	NA 2 (10.5)	0.58 [0.03; 6.01]; 0.648
Morbidity (data cut-off: 15 January 2019)					
Fatigue (FACIT-Fatigue, deterioration[b])	17	NA 3 (17.6)	19	NA 4 (21.1)	0.79 [0.16; 3.59]; 0.770
Disease-related symptoms	No usable data available[c]				
EORTC QLQ-C30 (deterioration[d])					
Fatigue	17	NA 2 (11.8)	19	NA 3 (15.8)	0.78 [0.10; 4.70]; 0.784
Nausea and vomiting	17	NA 2 (11.8)	19	NA 5 (26.3)	0.42 [0.06; 1.96]; 0.294
Pain	17	13.9 [1.1; NC] 7 (41.2)	19	16.8 [2.1; NC] 6 (31.6)	1.53 [0.48; 5.21]; 0.463
Appetite loss	17	NA 1 (5.9)	19	NA 5 (26.3)	0.21 [0.01; 1.30]; 0.116
Diarrhoea	17	NA 2 (11.8)	19	11.3 [1.0; NC] 7 (36.8)	0.29 [0.04; 1.18]; 0.096
Dyspnoea	17	NA 5 (29.4)	19	NA 4 (21.1)	1.77 [0.47; 7.16]; 0.390
Insomnia	17	NA 5 (29.4)	19	12.0 [1.9; NC] 8 (42.1)	0.64 [0.19; 1.92]; 0.433
Constipation	17	NA 4 (23.5)	19	NA 6 (31.6)	0.78 [0.20; 2.75]; 0.704
Health status (EQ-5D VAS, deterioration[e])	17	NA 1 (5.9)	19	NA 3 (15.8)	0.36 [0.02; 2.80]; 0.354

Table 5: Results (mortality, morbidity, health-related quality of life and side effects) – RCT, direct comparison: acalabrutinib vs. bendamustine + rituximab (adults with CLL; one prior therapy; chemo-immunotherapy suitable)
(multipage table)

Study Outcome category Outcome	Acalabrutinib		Bendamustine + rituximab		Acalabrutinib vs. bendamustine + rituximab
	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]
Health-related quality of life (data cut-off: 15 January 2019)					
EORTC QLQ-C30 (deterioration[e])					
Global health status	17	NA 2 (11.8)	19	NA 5 (26.3)	0.39 [0.06; 1.82]; 0.252
Physical functioning	17	NA 3 (17.6)	19	NA 2 (10.5)	1.81 [0.30; 13.80]; 0.508
Role functioning	17	NA 3 (17.6)	19	NA 5 (26.3)	0.62 [0.13; 2.52]; 0.514
Cognitive functioning	17	NA 5 (29.4)	19	NA 4 (21.1)	1.80 [0.48; 7.28]; 0.376
Emotional functioning	17	NA 4 (23.5)	19	NA 4 (21.1)	1.11 [0.26; 4.69]; 0.886
Social functioning	17	NA 4 (23.5)	19	3.7 [1.0; NC] 9 (47.4)	0.47 [0.13; 1.44]; 0.199
Side effects (data cut-off: 1 August 2019)					
AEs (supplementary information)	16	0.2 [0.1; 0.5] 16 (100)	18	0.2 [0.0; 0.3] 15 (83.3)	–
SAEs	16	NA 4 (25.0)	18	NA 5 (27.8)	0.44 [0.08; 1.95]; 0.289
Severe AEs[f]	16	NA 5 (31.3)	18	NA 8 (44.4)	0.35 [0.08; 1.20]; 0.103
Discontinuation due to AEs (≥ 1 component)	16	NA 0 (0)	18	NA 1 (5.6)	NC; 0.346
Cardiac disorders (SOC, AE)	16	ND	18	ND	–
Infections and infestations (SOC, severe AE[f])	16	NA 3 (18.8)	18	NA 2 (11.1)	0.53 [0.02; 5.54]; 0.599
Haemorrhages[g] (severe AE[f])	16	NA 0 (0)	18	NA 0 (0)	NC; NC
Diarrhoea (PT, AE)	16	NA 0 (0)	18	NA 4 (22.2)	NC; 0.049

Table 5: Results (mortality, morbidity, health-related quality of life and side effects) – RCT, direct comparison: acalabrutinib vs. bendamustine + rituximab (adults with CLL; one prior therapy; chemo-immunotherapy suitable)
(multipage table)

Study Outcome category Outcome	Acalabrutinib		Bendamustine + rituximab		Acalabrutinib vs. bendamustine + rituximab
	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]
Headache (PT, AE)	16	NA 7 (43.8)	18	NA 0 (0)	NC; 0.002
Neutropenia (PT, severe AE[f])	16	NA 0 (0)	18	6.5 [3.7; 6.5] 6 (33.3)	NC; 0.003

a. HR (incl. 95% CI) calculated using Cox proportional hazards model; p-value based on a log-rank test. According to the company, no adjustment or stratification was carried out.
b. The (first) clinically relevant deterioration is defined as a decrease by ≥ 7.8 points on a scale of 0 to 52 points.
c. The analysed population contains only a maximum of 50% of the randomized patients.
d. Clinically relevant deterioration is defined as an increase by ≥ 15 points on a scale of 0 to 100 points.
e. Clinically relevant deterioration is defined as a decrease by ≥ 15 points on a scale of 0 to 100 points.
f. Operationalized as CTCAE grade ≥ 3.
g. No information on which bleeding episodes are included in the AE of special clinical interest.

AE: adverse event; CI: confidence interval; CLL: chronic lymphocytic leukaemia; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; EQ-5D: European Quality of Life-5 Dimensions; FACIT: Functional Assessment of Chronic Illness Therapy; HR: hazard ratio; n: number of patients with (at least one) event; N: number of analysed patients, for analyses of efficacy all as randomized, for side effects according to the first study medication actually taken; NA: not achieved; NC: not calculable; ND: no data; PT: Preferred Term; QLQ-C30: Quality of Life Questionnaire-Core 30; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale

Mortality

Overall survival

No statistically significant difference between the treatment groups was shown for the outcome "overall survival".

Morbidity

Fatigue (Functional Assessment of Chronic Illness Therapy [FACIT]-Fatigue])

No statistically significant difference between the treatment groups was shown for the outcome "fatigue" (FACIT-Fatigue).

Disease-related symptoms

There are no usable data for the outcome "disease-related symptoms".

Symptoms (European Organisation for Research and Treatment of Cancer [EORTC] Quality of Life Questionnaire-Core 30 [QLQ-C30])

No statistically significant difference between the treatment groups was shown for any of the following outcomes: fatigue, nausea and vomiting, pain, appetite loss, diarrhoea, dyspnoea, insomnia, and constipation.

Health status (European Quality of Life-5 Dimensions [EQ-5D] visual analogue scale [VAS])

No statistically significant difference between the treatment groups was shown for the outcome "health status" (EQ-5D VAS).

Health-related quality of life

EORTC QLQ-C30

No statistically significant difference between the treatment groups was shown for any of the following outcomes: global health status, physical functioning, role functioning, emotional functioning, cognitive functioning, and social functioning.

Side effects

SAEs, severe AEs (Common Terminology Criteria for Adverse Events [CTCAE] grade ≥ 3) and discontinuation due to AEs

No statistically significant difference between the treatment groups was shown for the outcomes "SAEs", "severe AEs" (CTCAE grade ≥ 3) and "discontinuation due to AEs".

Cardiac disorders

No usable data are available for the outcome "cardiac disorders".

Infections and infestations and haemorrhages

No statistically significant difference between the treatment groups was shown for either of the outcomes "infections and infestations" and "haemorrhages".

Diarrhoea and neutropenia

A statistically significant difference in favour of acalabrutinib was shown for each of the outcomes "diarrhoea" and "neutropenia".

Headache

A statistically significant difference to the disadvantage of acalabrutinib was shown for the outcome "headache".

2.1.2.3 Subgroups and other effect modifiers

The following subgroup characteristics were considered in the present assessment:

- age (< 75 years, ≥ 75 years)
- sex (male, female)
- Rai stage at baseline (0/I/II versus III/IV)

Interaction tests were performed when at least 10 patients per subgroup were included in the analysis. Moreover, for binary data, there must be 10 events in at least one subgroup.

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 only presented if there is a statistically significant and relevant effect in at least one subgroup.

In accordance with the methods described, no relevant effect modification by age, sex or Rai stage at baseline was identified for the outcomes used.

2.2 Research question 3: adults with CLL; ≥ 2 prior therapies

2.2.1 Study characteristics

Information on the intervention can be found in Section 2.1.1.

Characteristics of the relevant subpopulation

Table 6 shows the characteristics of the patients of research questions 3 in the study included.

Table 6: Characteristics of the study population – RCT, direct comparison: acalabrutinib vs. bendamustine + rituximab/idelalisib + rituximab (adults with CLL; ≥ 2 prior therapies) (multipage table)

Study Characteristic Category	**Acalabrutinib N = 73**	**Bendamustine + rituximab/idelalisib + rituximab N = 88**
ASCEND		
Age [years], mean (SD)	68 (10)	66 (9)
Sex [F/M], %	29/71	34/66
Region, n (%)		
North America	3 (4)	4 (5)
Western Europe	13 (18)	18 (21)
Central/Eastern Europe	50 (69)	56 (64)
Australia/New Zealand	4 (6)	4 (5)
Asia	3 (4)	6 (7)
Family origin, n (%)		
White	69 (95)	79 (90)
Other[a]	4 (6)[b]	9 (10)[b]
ECOG PS, n (%)		
0	24 (33)	27 (31)
1	41 (56)	49 (56)
2	8 (11)	12 (14)
Disease duration: time between first diagnosis and randomization [months], median [min; max]	100.8 [19.8; 314.4]	93.6 [16.0; 254.2]
Bulky disease[c], n (%)		
< 5 cm	35 (48)	48 (55)
≥ 5 cm	38 (52)	40 (46)
Rai stage, n (%)		
0/I/II	41 (56)[b]	48 (55)[b]
III/IV/missing	32 (44)[b]	40 (45)[b]
Binet stage, n (%)		
A	16 (22)	9 (10)
B	29 (40)	30 (34)
C	22 (30)	39 (44)
Missing	6 (8)	10 (11)
Beta 2 microglobulin, n (%)		
> 3.5 mg/L	59 (81)	75 (85)
≤ 3.5 mg/L	13 (18)	12 (14)
Missing	1 (1)	1 (1)
Cytopenia[d], n (%)	45 (62)	51 (58)
Disease-related symptoms[e], n (%)	47 (64)	57 (65)

Table 6: Characteristics of the study population – RCT, direct comparison: acalabrutinib vs. bendamustine + rituximab/idelalisib + rituximab (adults with CLL; ≥ 2 prior therapies) (multipage table)

Study Characteristic Category	Acalabrutinib N = 73	Bendamustine + rituximab/idelalisib + rituximab N = 88
Chromosome anomaly, n (%)		
17p deletion	16 (22)	15 (17)
11q deletion	17 (23)	25 (28)
TP53 mutation	24 (33)	24 (27)
17p deletion and TP53 mutation	14 (19)	10 (11)
IGHV status, n (%)		
Mutated	15 (21)	15 (17)
Unmutated	55 (75)	73 (83)
Not determined	3 (4)	0 (0)
Complex karyotype[f]		
Yes	30 (41)	31 (35)
No	40 (55)	47 (53)
Undetermined	3 (4)	10 (11)
Treatment discontinuation, n (%)	26 (36)	74 (84)
Study discontinuation, n (%)	14 (19)	21 (24)

a. Composed of Asian family origin or not reported.
b. Institute's calculation.
c. The assessment was made by the investigator.
d. Neutrophil count ≤ 1.5 x 10^9/L, haemoglobin ≤ 110 g/L or platelet count ≤ 100 x 10^9/L.
e. At least one of the following symptoms: weight loss, fever, night sweats, fatigue.
f. Defined as the presence of 3 or more cytogenetic abnormalities based on karyotyping by a central laboratory.

11q deletion: deletion of the long arm of chromosome 11; 17p deletion: deletion of the short arm of chromosome 17; CLL: chronic lymphocytic leukaemia; ECOG PS: Eastern Cooperative Oncology Performance Status; F: female; IGHV: immunoglobulin heavy-chain variable region; M: male; max.: maximum; min.: minimum; n: number of patients in the category; N: number of randomized patients; RCT: randomized controlled trial; SD: standard deviation; TP53 mutation: mutation of the tumour protein p53

Patient characteristics were sufficiently balanced between the treatment arms.

Information on the course of the study

Table 7 shows the mean/median treatment duration of the patients and the mean/median observation period for individual outcomes.

Table 7: Information on the course of the study – RCT, direct comparison: acalabrutinib vs. bendamustine + rituximab/idelalisib + rituximab (adults with CLL; ≥ 2 prior therapies)

Study **Duration of the study phase** **Outcome category**	**Acalabrutinib** **N = 73**	**Bendamustine + rituximab/ idelalisib + rituximab** **N = 88**
ASCEND		
Treatment duration [months]		
Median [min; max]	22.0 [1.1; 27.9]	5.6 [1.0; 6.7][a]
Mean (SD)	19.39 (7.19)	4.67 (1.87)[a]
Observation period[b] [months]		
Overall survival		
Median [min; max]	22.41 [ND]	22.60 [ND]
Mean (SD)	ND	ND
Morbidity		
Health status (EQ-5D VAS), fatigue (FACIT-Fatigue), symptoms (EORTC QLQ-C30)		
Median [min; max]	11.20 [ND]	10; 71 [ND]
Mean (SD)	ND	ND
Disease-specific symptoms[c]	No usable data available[d]	
Health-related quality of life		
Median [min; max]	11.20 [ND]	10; 71 [ND]
Mean (SD)	ND	ND
Side effects		
Median [min; max]	22.0 [ND]	9.2 [ND]
Mean (SD)	ND	ND

a. Data for bendamustine; the median [min; max] treatment duration with rituximab was 5.5 [0.9; 6.7] months and 5.5 [0.9; 7.3] months, respectively, and with idelalisib 11.6 [0.2; 27.2] months.
b. For the outcomes of the outcome categories of morbidity and health-related quality of life, the data are based on the data cut-off of 15 January 2019, for overall survival and side effects on the data cut-off of 1 August 2019.
c. Weight loss, fatigue, fever, night sweats.
d. The analysed population contains only a maximum of 65% of the randomized patients.

CLL: chronic lymphocytic leukaemia; EORTC: European Organisation for Research and Treatment of Cancer; EQ-5D: European Quality of Life-5 Dimensions; FACIT: Functional Assessment of Chronic Illness Therapy; max.: maximum; min: minimum; N: number of randomized patients; ND: no data; QLQ-C30: Quality of Life Questionnaire-Core 30; RCT: randomized controlled trial; SD: standard deviation; VAS: visual analogue scale

Based on the data, it can be seen that the treatment in the intervention arm of the relevant subpopulation was about 4 times longer than for bendamustine + rituximab, and about twice as long as for idelalisib in the comparator arm.

The median observation period is comparable between the 2 study arms for the outcomes of the categories of mortality, morbidity and health-related quality of life. Observation of side effects was 2.4 times longer in the intervention arm than in the comparator arm. This is due to the fact that the follow-up observation for side effects was only planned up to 30 days after the last dose

of the study medication and there were differences in the treatment durations between the study arms.

Data on subsequent antineoplastic therapies are not available for the subpopulation for research question 3.

Risk of bias across outcomes (study level)

The assessment of the risk of bias across outcomes (risk of bias at study level) can be found in addendum A21-54 [5].

2.2.2 Results on added benefit

2.2.2.1 Outcomes included and risk of bias

An overview of the included outcomes can be found in addendum A21-54 [5]. The risk of bias for all outcomes, except for "overall survival", was rated as high. For reasons, see addendum A21-54 [5].

2.2.2.2 Results

Table 8 summarizes the results of the comparison of acalabrutinib with bendamustine + rituximab/idelalisib + rituximab in adult patients with CLL after ≥ 2 prior therapies.

Results presented as supplementary information can be found in Appendix B. Kaplan-Meier curves on the event time analyses are presented in Appendix D. The results on the common AEs, SAEs, severe AEs, as well as on all AEs that led to treatment discontinuation are presented in Appendix E.

Table 8: Results for mortality, morbidity, health-related quality of life and side effects – RCT, direct comparison: acalabrutinib vs. bendamustine + rituximab/idelalisib + rituximab (adults with CLL; ≥ 2 prior therapies) (multipage table)

Study Outcome category Outcome	Acalabrutinib		Bendamustine + rituximab/ idelalisib + rituximab		Acalabrutinib vs. bendamustine + rituximab/idelalisib + rituximab
	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]
ASCEND					
Mortality (data cut-off: 1 August 2019)					
Overall survival	73	NA 14 (19.2)	88	NA 17 (19.3)	0.97 [0.47; 1.98]; 0.929
Morbidity (data cut-off: 15 January 2019)					
Fatigue (FACIT-Fatigue, deterioration[b])	73	NA 20 (27.4)	88	NA 18 (20.5)	1.27 [0.66; 2.43]; 0.475
Disease-related symptoms	No usable data available[c]				
EORTC QLQ-C30 (deterioration[d])					
Fatigue	73	NA 29 (39.7)	88	NA 20 (22.7)	1.92 [1.09; 3.45]; 0.026
Nausea and vomiting	73	NA 17 (23.3)	88	NA 33 (37.5)	0.49 [0.27; 0.87]; 0.017
Pain	73	3.7 [2.0; 4.8] 43 (58.9)	88	NA 32 (36.4)	1.85 [1.17; 2.96]; 0.009
Appetite loss	73	NA 19 (26.0)	88	NA 28 (31.8)	0.65 [0.35 1.17]; 0.156
Diarrhoea	73	NA 20 (27.4)	88	NA 27 (30.7)	0.67 [0.37; 1.21]; 0.188
Dyspnoea	73	NA 26 (35.6)	88	NA 22 (25.0)	1.33 [0.75; 2.38]; 0.332
Insomnia	73	11.2 [2.9; NC] 35 (47.9)	88	NA 22 (25.0)	1.99 [1.17; 3.46]; 0.011
Constipation	73	NA 18 (24.7)	88	NA 20 (22.7)	0.99 [0.51; 1.87]; 0.954
Health status (EQ-5D VAS, deterioration[e])	73	NA 24 (32.9)	88	NA 26 (29.5)	1.05 [0.60; 1.85]; 0.849

Table 8: Results for mortality, morbidity, health-related quality of life and side effects – RCT, direct comparison: acalabrutinib vs. bendamustine + rituximab/idelalisib + rituximab (adults with CLL; ≥ 2 prior therapies) (multipage table)

Study Outcome category Outcome	Acalabrutinib		Bendamustine + rituximab/ idelalisib + rituximab		Acalabrutinib vs. bendamustine + rituximab/idelalisib + rituximab
	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]
Health-related quality of life (data cut-off: 15 January 2019)					
EORTC QLQ-C30 (deterioration[e])					
Global health status	73	16.8 [5.6; NC] 29 (39.7)	88	NA 28 (31.8)	1.12 [0.67; 1.90]; 0.665
Physical functioning	73	NA 22 (30.1)	88	NA 13 (14.8)	2.01 [1.02; 4.13]; 0.045
Role functioning	73	4.8 [2.8; NC] 40 (54.8)	88	9.0 [2.8; 16.9] 42 (47.7)	1.13 [0.73; 1.75]; 0.606
Cognitive functioning	73	6.0 [2.8; NC] 36 (49.3)	88	11.0 [3.7; NC] 39 (44.3)	1.06 [0.67; 1.68]; 0.814
Emotional functioning	73	16.9 [5.7; NC] 29 (39.7)	88	NA 27 (30.7)	1.22 [0.72; 2.09]; 0.451
Social functioning	73	16.8 [2.9; NC] 35 (47.9)	88	8.4 [2.8; NC] 39 (44.3)	0.97 [0.61; 1.53]; 0.894
Side effects (data cut-off: 1 August 2019)					
AEs (supplementary information)	73	0.4 [0.3; 1.0] 70 (95.9)	88	0.5 [0.2; 0.7] 83 (94.3)	–
SAEs	73	NA 27 (37.0)	88	10.5 [6.8; NC] 42 (47.7)	0.54 [0.32; 0.88]; 0.014
Severe AEs[f]	73	10.2 [2.8; 19.1] 46 (63.0)	88	1.9 [1.0; 2.8] 71 (80.7)	0.45 [0.30; 0.67] < 0.001
Discontinuation due to AEs (≥ 1 component)	73	NA 14 (19.2)	88	12.1 [8.4; 16.5] 48 (54.5)	0.19 [0.10; 0.34]; < 0.001
Cardiac disorders (SOC, AEs)	73	NA 11 (15.1)	88	NA 8 (9.1)	1.36 [0.54; 3.58]; 0.514
Infections and infestations (SOC, severe AEs[f])	73	NA 14 (19.2)	88	NA 22 (25.0)	0.48 [0.23; 0.98]; 0.046
Haemorrhages[g] (severe AEs[f])	73	NA 4 (5.5)	88	NA 3 (3.4)	1.01 [0.22; 5.20]; 0.991
Headache (PT, AEs)	73	NA 14 (19.2)	88	NA 6 (6.8)	3.16 [1.26; 8.98]; 0.014

Table 8: Results for mortality, morbidity, health-related quality of life and side effects – RCT, direct comparison: acalabrutinib vs. bendamustine + rituximab/idelalisib + rituximab (adults with CLL; ≥ 2 prior therapies) (multipage table)

Study Outcome category Outcome	Acalabrutinib		Bendamustine + rituximab/ idelalisib + rituximab		Acalabrutinib vs. bendamustine + rituximab/idelalisib + rituximab
	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]
Blood and lymphatic system disorders (SOC, severe AE[f])	73	NA 24 (32.9)	88	NA 42 (47.7)	0.55 [0.32; 0.91]; 0.023
Gastrointestinal disorders (SOC, severe AE[f])	73	NA 6 (8.2)	88	NA 18 (20.5)	0.20 [0.07; 0.49]; < 0.001
Investigations (SOC, severe AE[f])	73	NA 5 (6.8)	88	NA 18 (20.5)	0.23 [0.08; 0.59]; 0.002

a. HR (incl. 95% CI) calculated using Cox proportional hazards model; p-value based on a log-rank test. According to the company, adjustment or stratification according to 17p deletion status (yes vs. no) and number of prior therapies (2 or 3 vs. ≥ 4).
b. The (first) clinically relevant deterioration is defined as a decrease by ≥ 7.8 points on a scale of 0 to 52 points.
c. The analysed population contains only a maximum of 65% of the randomized patients.
d. Clinically relevant deterioration is defined as an increase by ≥ 15 points on a scale of 0 to 100 points.
e. Clinically relevant deterioration is defined as a decrease by ≥ 15 points on a scale of 0 to 100 points.
f. Operationalized as CTCAE grade ≥ 3.
g. No information on which bleeding episodes are included in the AE of special clinical interest.

AE: adverse event; CI: confidence interval; CLL: chronic lymphocytic leukaemia; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; EQ-5D: European Quality of Life-5 Dimensions; FACIT: Functional Assessment of Chronic Illness Therapy; HR: hazard ratio; n: number of patients with (at least one) event; N: number of analysed patients; NA: not achieved; NC: not calculable; PT: Preferred Term; QLQ-C30: Quality of Life Questionnaire-Core 30; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale

Mortality

Overall survival

No statistically significant difference between the treatment groups was shown for the outcome "overall survival".

Morbidity

Fatigue (FACIT-Fatigue)

No statistically significant difference between the treatment groups was shown for the outcome "fatigue" (FACIT-Fatigue).

Disease-related symptoms

There are no usable data for the outcome "disease-related symptoms".

Symptoms (EORTC QLQ-C30)

No statistically significant difference between the treatment groups was shown for any of the following outcomes: appetite loss, diarrhoea, dyspnoea and constipation.

Fatigue, pain, insomnia

A statistically significant disadvantage of acalabrutinib was shown for each of the outcomes "fatigue", "pain" and "insomnia".

Nausea and vomiting

A statistically significant advantage of acalabrutinib was shown for the outcome "nausea and vomiting".

Health status (EQ-5D VAS)

No statistically significant difference between the treatment groups was shown for the outcome "health status" (EQ-5D VAS).

Health-related quality of life

EORTC QLQ-C30

No statistically significant difference between the treatment groups was shown for any of the following outcomes: global health status, role functioning, emotional functioning, cognitive functioning, and social functioning.

Physical functioning

A statistically significant disadvantage of acalabrutinib was shown for the outcome "physical functioning".

Side effects

SAEs, severe AEs (CTCAE grade ≥ 3) and discontinuation due to AEs

A statistically significant advantage of acalabrutinib was shown for each of the outcomes "SAEs", "severe AEs" (CTCAE grade ≥ 3) and "discontinuation due to AEs".

Infections and infestations, blood and lymphatic system disorders, gastrointestinal disorders, and investigations

A statistically significant advantage of acalabrutinib was shown for each of the following outcomes: infections and infestations, blood and lymphatic system disorders, gastrointestinal disorders, and investigations.

Cardiac disorders

No usable data are available for the outcome "cardiac disorders".

Haemorrhages

No statistically significant difference between the treatment groups was shown for the outcome "haemorrhages".

Headache

A statistically significant disadvantage of acalabrutinib was shown for the outcome "headache".

2.2.2.3 Subgroups and other effect modifiers

The following subgroup characteristics were considered in the present assessment:

- age (< 75 years, ≥ 75 years)
- sex (male, female)
- Rai stage at baseline (0/I/II versus III/IV)

Interaction tests were performed when at least 10 patients per subgroup were included in the analysis. Moreover, for binary data, there had to be 10 events in at least one subgroup.

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 only presented if there is a statistically significant and relevant effect in at least one subgroup.

Table 9 shows the results of the subgroup analyses. Kaplan-Meier curves on the event time analyses for the subgroups are presented in Appendix D.

Table 9: Subgroups (side effects) – RCT, direct comparison: acalabrutinib vs. bendamustine + rituximab/idelalisib + rituximab (adults with CLL; ≥ 2 prior therapies)

Study Outcome category Outcome Characteristic Subgroup	Acalabrutinib		Bendamustine + rituximab/idelalisib + rituximab		Acalabrutinib vs. bendamustine + rituximab/idelalisib + rituximab	
	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][a]	p-value[b]
ASCEND						
Side effects						
Discontinuation due to AEs (≥ 1 component)						
Rai stage						
0–II	41	NA 5 (12.2)	48	9.7 [5.5; 15.2] 28 (58.3)	0.10 [0.03; 0.25]	< 0.001
III–IV	32	NA 9 (28.1)	39	15.4 [8.7; NC] 19 (48.7)	0.39 [0.17; 0.85]	0.017
Total					Interaction:	0.030

a. HR (incl. 95% CI) according to the company calculated using Cox proportional hazards model with the factors treatment, subgroup characteristic, and interaction between treatment and subgroup characteristic.
a. p-values according to the company from likelihood ratio test based on unstratified Cox proportional hazards model with the factors treatment, subgroup characteristic, and interaction between treatment and subgroup characteristic.

AE: adverse event; CI: confidence interval; CLL: chronic lymphocytic leukaemia; HR: hazard ratio; n: number of patients with event; N: number of analysed patients; NA: not achieved; NC: not calculable; RCT: randomized controlled trial

Side effects

Discontinuation due to AEs

There was an effect modification by the characteristic of Rai stage for the outcome "discontinuation due to AE". Both for RAI stages 0 to II and for III to IV, there was a statistically significant advantage of acalabrutinib.

3 Summary

The assessed data have not changed the conclusion on the added benefit from addendum A21-54 [5], an added benefit is therefore still not proven. As explained in the addendum, the data presented by the company are neither relevant for research question 1 (patients with CLL after one prior therapy who have no 17p deletion or TP53 mutation and for whom chemo-immunotherapy is indicated) nor for research question 3 (adult patients with CLL after at least 2 prior therapies), as the ACT was not implemented.

4 References

The reference list contains citations provided by the company in which bibliographical information may be missing.

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Appendix A – Results presented as supplementary information: adults with CLL; one prior therapy; chemo-immunotherapy suitable

A.1 – Results on the EORTC QLQ-C30 (continuous)

Table 10: Results (morbidity, health-related quality of life, continuous – supplementary presentation on the EORTC QLQ-C30) – RCT, direct comparison: acalabrutinib vs. bendamustine + rituximab (adults with CLL; one prior therapy; chemo-immunotherapy suitable) (multipage table)

Study Outcome category Outcome	Acalabrutinib			Bendamustine + rituximab			Acalabrutinib vs. bendamustine + rituximab
	N[a]	Values at baseline mean (SD)	Mean change in the course of the study mean (SE)[b]	N[a]	Values at baseline mean (SD)	Mean change in the course of the study mean (SE)[b]	MD [95% CI]; p-value[b]
ASCEND							
Morbidity							
EORTC QLQ-C30 – symptom scales[c]							
Fatigue	13	42.74 (27.91)	−19.07 (3.80)	15	41.48 (21.19)	−10.81 (3.55)	−8.26 [−18.97; 2.45]; 0.125
Nausea and vomiting	13	5.13 (8.01)	−1.92 (4.31)	15	3.33 (6.90)	2.12 (10.76)	−4.04 [−46.38; 38.29]; 0.754
Pain	13	11.54 (19.70)	−7.31 (3.60)	15	15.56 (25.56)	−4.16 (3.39)	−3.15 [−13.46; 7.17]; 0.532
Appetite loss	13	23.08 (21.01)	−11.00 (3.14)	15	8.89 (15.26)	−4.72 (2.95)	−6.28 [−15.53; 2.97]; 0.173
Diarrhoea	13	5.13 (12.52)	2.43 (3.83)	15	0 (0)	7.20 (3.53)	−4.77 [−15.79; 6.25]; 0.379
Dyspnoea	13	15.38 (32.25)	−5.09 (4.40)	15	20.00 (27.60)	−8.18 (4.10)	3.09 [−9.32; 15.49]; 0.613
Insomnia	13	30.77 (25.32)	−6.81 (5.28)	15	22.22 (27.22)	−4.07 (4.86)	−2.74 [−17.59; 12.11]; 0.707
Constipation	13	5.13 (12.52)	0.78 (3.15)	15	8.89 (15.26)	−1.22 (2.92)	1.99 [−6.91; 10.89]; 0.649
Health-related quality of life							
EORTC QLQ-C30 – functional scales[d]							
Global health status	13	55.77 (15.73)	18.19 (3.30)	15	56.11 (18.22)	7.01 (3.07)	11.18 [1.91; 20.45]; 0.020
Physical functioning	13	79.49 (17.74)	10.52 (3.23)	15	66.67 (20.63)	7.46 (2.99)	3.06 [−6.25; 12.37]; 0.504
Role functioning	13	70.51 (28.18)	13.76 (4.74)	15	63.33 (25.36)	11.37 (4.41)	2.39 [−10.99; 15.77]; 0.717
Cognitive functioning	13	85.90 (17.80)	6.56 (3.09)	15	75.56 (27.36)	8.01 (2.90)	−1.45 [−10.29; 7.39]; 0.738
Emotional functioning	13	82.05 (17.95)	10.58 (3.05)	15	67.78 (23.54)	10.32 (2.84)	0.26 [−8.56; 9.08]; 0.953
Social functioning	13	78.21 (19.70)	9.24 (4.60)	15	73.33 (33.21)	6.20 (4.27)	3.04 [−9.92; 16.00]; 0.633

Table 10: Results (morbidity, health-related quality of life, continuous – supplementary presentation on the EORTC QLQ-C30) – RCT, direct comparison: acalabrutinib vs. bendamustine + rituximab (adults with CLL; one prior therapy; chemo-immunotherapy suitable) (multipage table)

Study Outcome category Outcome	Acalabrutinib			Bendamustine + rituximab			Acalabrutinib vs. bendamustine + rituximab
	N[a]	Values at baseline mean (SD)	Mean change in the course of the study mean (SE)[b]	N[a]	Values at baseline mean (SD)	Mean change in the course of the study mean (SE)[b]	MD [95% CI]; p-value[b]

a. Number of patients with a value at baseline and at least one value from a subsequent visit; the values at baseline may be based on other patient numbers.
b. From MMRM; effect presents the difference between the treatment groups of the changes averaged over the course of the study between the respective time point of measurement and the start of the study.
c. Lower values indicate better symptoms; negative effects (acalabrutinib minus bendamustine + rituximab) indicate an advantage for acalabrutinib.
d. Higher values indicate better quality of life; positive effects (acalabrutinib minus bendamustine + rituximab) indicate an advantage for acalabrutinib.

CI: confidence interval; CLL: chronic lymphocytic leukaemia; EORTC: European Organisation for Research and Treatment of Cancer; MD: mean difference; MMRM: mixed-effects model with repeated measures; N: number of analysed patients; QLQ-C30: Quality of Life Questionnaire-Core 30; RCT: randomized controlled trial; SD: standard deviation; SE: standard error

A.2 – Results on the outcome "disease-related symptoms"

Table 11: Results (morbidity – supplementary presentation on the outcome "disease-related symptoms", data cut-off from 1 August 2019) – RCT, direct comparison: acalabrutinib vs. bendamustine + rituximab (adults with CLL; one prior therapy; chemo-immunotherapy suitable)

Study Outcome category Outcome	Acalabrutinib		Bendamustine + rituximab		Acalabrutinib vs. bendamustine + rituximab
	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]
ASCEND					
Morbidity					
Patients with at least one disease-related symptom[b] at baseline					
Time to first absence of any disease-related symptoms	9	1.0 [1.0; 1.1] 8 (88.9)	9	1.0 [0.9; 1.1] 9 (100.0)	1.03 [0.38; 2.82]; 0.936

a. HR (incl. 95% CI) calculated using Cox proportional hazards model; p-value using log-rank test.
b. Unintentional weight loss ≥ 10% within the previous 6 months, significant fatigue (e.g. ECOG PS ≥ 2; inability to work or perform usual activities), fever > 38°C for more than 2 weeks without evidence of infection, night sweats for more than 1 month without evidence of infection.

CI: confidence interval; CLL: chronic lymphocytic leukaemia; ECOG PS: Eastern Cooperative Oncology Group Performance Status; HR: hazard ratio; n: number of patients with (at least one) event; N: number of analysed patients; RCT: randomized controlled trial

Appendix B – Results presented as supplementary information: adults with CLL; ≥ 2 prior therapies

B.1 – Results on the EORTC QLQ-C30 (continuous)

Table 12: Results (morbidity, health-related quality of life, continuous – supplementary presentation on the EORTC QLQ-C30) – RCT, direct comparison: acalabrutinib vs. bendamustine + rituximab/idelalisib + rituximab (adults with CLL; ≥ 2 prior therapies) (multipage table)

Study Outcome category Outcome	Acalabrutinib			Bendamustine + rituximab/idelalisib + rituximab			Acalabrutinib vs. bendamustine + rituximab/idelalisib + rituximab
	N[a]	Values at baseline mean (SD)	Mean change in the course of the study mean (SE)[b]	N[a]	Values at baseline mean (SD)	Mean change in the course of the study mean (SE)[b]	MD [95% CI]; p-value[b]
ASCEND							
Morbidity							
EORTC QLQ-C30 – symptom scales[c]							
Fatigue	71	35.21 (21.50)	−4.25 (2.15)	79	37.83 (21.76)	−6.87 (2.14)	2.62 [−2.15; 7.39]; 0.280
Nausea and vomiting	71	4.69 (10.23)	−2.10 (0.82)	79	5.91 (12.24)	−1.82 (0.80)	−0.28 [−2.14; 1.58]; 0.766
Pain	71	15.26 (23.70)	6.62 (2.18)	79	16.46 (19.88)	0.28 (2.18)	6.35 [1.43; 11.26]; 0.012
Appetite loss	71	16.90 (27.53)	−6.48 (1.71)	79	13.92 (19.69)	−5.25 (1.73)	−1.23 [−5.19; 2.74]; 0.542
Diarrhoea	71	11.27 (21.78)	−2.93 (1.66)	79	7.59 (16.84)	−1.65 (1.66)	−1.29 [−5.04; 2.47]; 0.500
Dyspnoea	71	23.94 (29.38)	−8.88 (2.30)	79	27.85 (28.46)	−8.05 (2.30)	−0.83 [−6.02; 4.36]; 0.753
Insomnia	71	24.41 (31.85)	−3.04 (2.81)	79	29.96 (29.52)	−7.18 (2.79)	4.14 [−2.21; 10.48]; 0.199
Constipation	71	7.51 (16.13)	−0.98 (1.57)	79	6.75 (16.35)	0.95 (1.53)	−1.93 [−5.51; 1.65]; 0.288
Health-related quality of life							
EORTC QLQ-C30 – functional scales[d]							
Global health status	71	57.75 (18.11)	7.04 (1.88)	79	58.02 (17.73)	8.25 (1.87)	−1.21 [−5.35; 2.92]; 0.563
Physical functioning	71	76.34 (18.30)	1.35 (1.83)	79	76.20 (15.35)	5.50 (1.81)	−4.16 [−8.42; 0.11]; 0.056
Role functioning	71	75.35 (25.95)	1.94 (2.26)	79	76.58 (24.54)	3.36 (2.22)	−1.42 [−6.55; 3.71]; 0.585
Cognitive functioning	71	85.92 (19.03)	−3.02 (1.83)	79	85.44 (16.75)	1.94 (1.82)	−4.96 [−9.14; −0.78]; 0.021

Table 12: Results (morbidity, health-related quality of life, continuous – supplementary presentation on the EORTC QLQ-C30) – RCT, direct comparison: acalabrutinib vs. bendamustine + rituximab/idelalisib + rituximab (adults with CLL; ≥ 2 prior therapies) (multipage table)

Study Outcome category Outcome	Acalabrutinib			Bendamustine + rituximab/idelalisib + rituximab			Acalabrutinib vs. bendamustine + rituximab/idelalisib + rituximab
	N[a]	Values at baseline mean (SD)	Mean change in the course of the study mean (SE)[b]	N[a]	Values at baseline mean (SD)	Mean change in the course of the study mean (SE)[b]	MD [95% CI]; p-value[b]
Emotional functioning	71	79.23 (22.00)	2.57 (1.85)	79	78.59 (20.49)	5.50 (1.84)	−2.92 [−7.15; 1.30]; 0.173
Social functioning	71	81.22 (23.89)	−1.24 (2.39)	79	81.65 (22.42)	0.58 (2.37)	−1.82 [−7.35; 3.71]; 0.516

a. Number of patients with a value at baseline and at least one value from a subsequent visit; the values at baseline may be based on other patient numbers.
b. From MMRM; effect presents the difference between the treatment groups of the changes averaged over the course of the study between the respective time point of measurement and the start of the study.
c. Lower values indicate better symptoms; negative effects (acalabrutinib minus bendamustine + rituximab/idelalisib + rituximab) indicate an advantage for acalabrutinib.
d. Higher values indicate better quality of life; positive effects (acalabrutinib minus bendamustine + rituximab/idelalisib + rituximab) indicate an advantage for acalabrutinib.

CI: confidence interval; CLL: chronic lymphocytic leukaemia; EORTC: European Organisation for Research and Treatment of Cancer; MD: mean difference; MMRM: mixed-effects model with repeated measures; N: number of analysed patients; QLQ-C30: Quality of Life Questionnaire-Core 30; RCT: randomized controlled trial; SD: standard deviation; SE: standard error

B.2 – Results on the outcome "disease-related symptoms"

Table 13: Results (morbidity – supplementary presentation on the outcome "disease-related symptoms", data cut-off from 1 August 2019) – RCT, direct comparison: acalabrutinib vs. bendamustine + rituximab/idelalisib + rituximab (adults with CLL; ≥ 2 prior therapies)

Study Outcome category Outcome	Acalabrutinib		Bendamustine + rituximab/ idelalisib + rituximab		Acalabrutinib vs. bendamustine + rituximab/ idelalisib + rituximab
	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]
ASCEND					
Morbidity					
Patients with at least one disease-related symptom[b] at baseline					
Time to first absence of any disease-related symptoms	47	1.1 [1.0; 1.1] 45 (95.7)	57	1.2 [1.0; 1.4] 53 (93.0)	1.46 [0.95; 2.24]; 0.108

a. HR (incl. 95% CI) calculated using Cox proportional hazards model stratified by 17p deletion status (yes vs. no) and number of prior therapies (2 or 3 vs. ≥ 4); p-value calculated using stratified log-rank test.
b. Unintentional weight loss ≥ 10% within the previous 6 months, significant fatigue (e.g. ECOG PS ≥ 2; inability to work or perform usual activities), fever > 38°C for more than 2 weeks without evidence of infection, night sweats for more than 1 month without evidence of infection.

CI: confidence interval; CLL: chronic lymphocytic leukaemia; ECOG PS: Eastern Cooperative Oncology Group Performance Status; HR: hazard ratio; n: number of patients with (at least one) event; N: number of analysed patients; RCT: randomized controlled trial

Appendix C – Kaplan-Meier curves: adults with CLL; one prior therapy; chemo-immunotherapy suitable

C.1 – Mortality

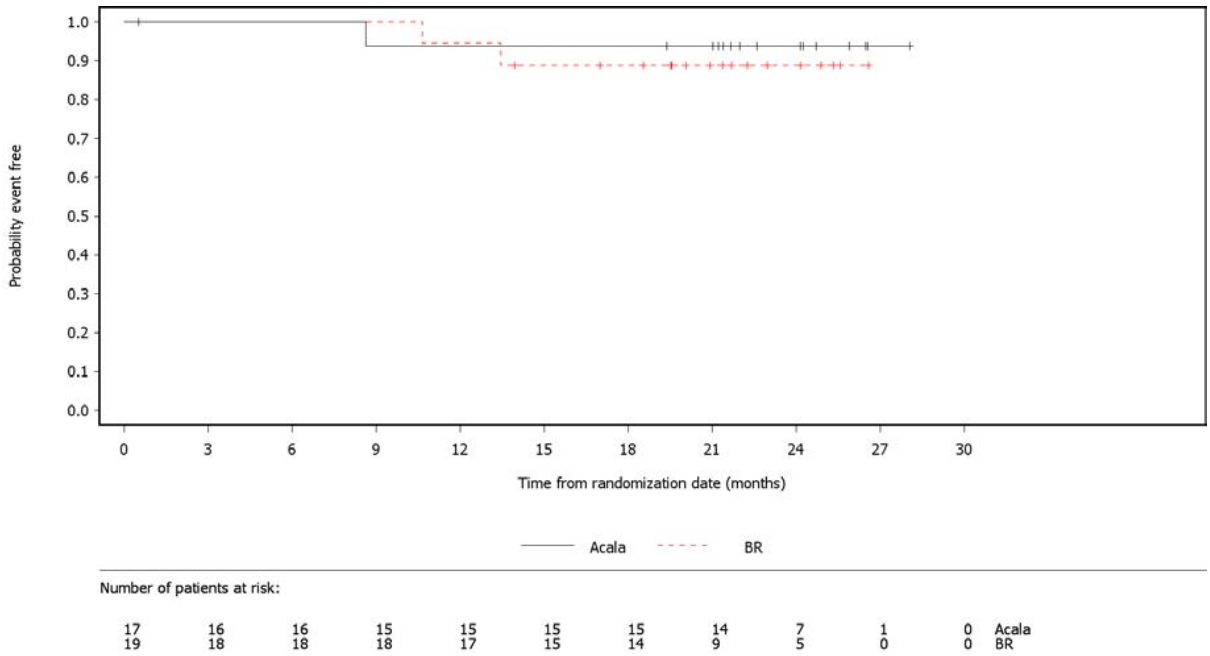

Figure 1: Kaplan-Meier curves, outcome "overall survival", ASCEND study, data cut-off from 1 August 2019

C.2 – Morbidity

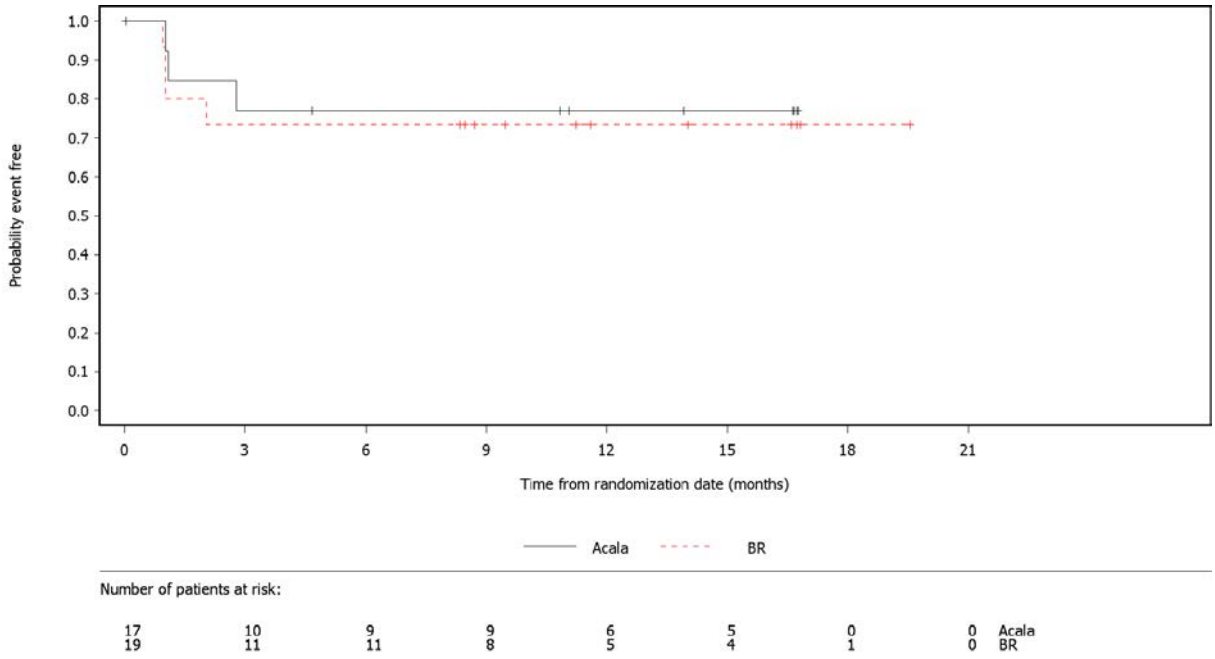

Figure 2: Kaplan-Meier-curves for symptoms, outcome "fatigue" (FACIT-Fatigue, time to clinically relevant deterioration by ≥ 7.8 points), ASCEND study, data cut-off from 15 January 2019

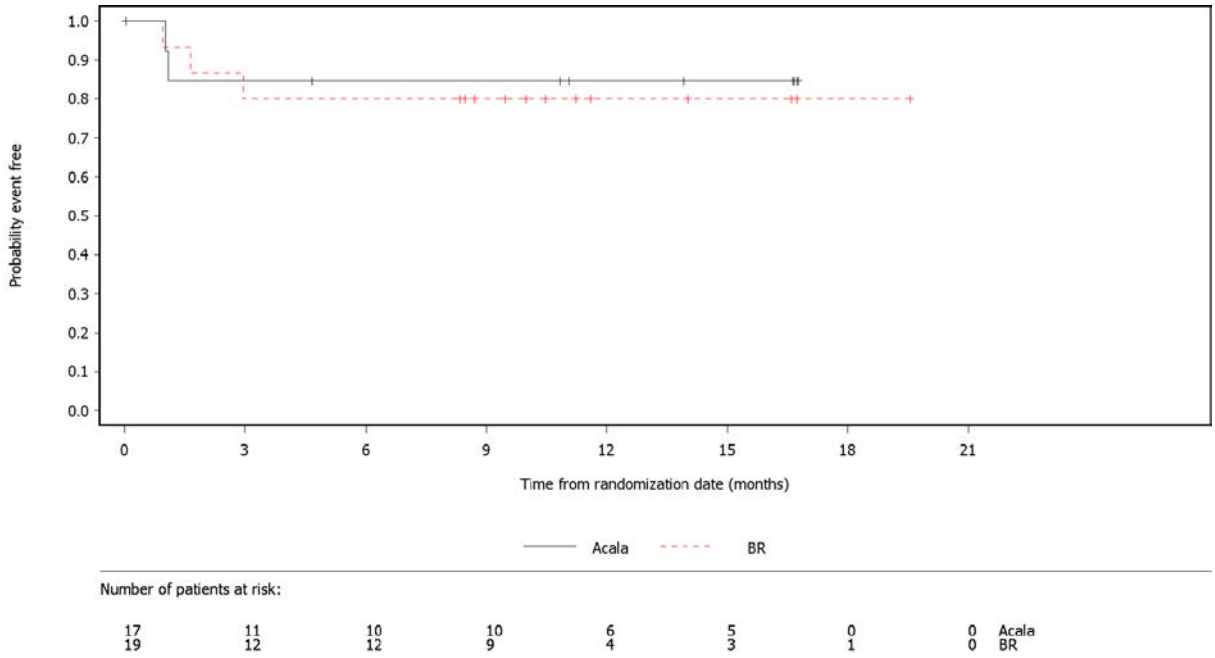

Figure 3: Kaplan-Meier-curves for symptoms, outcome "fatigue" (EORTC QLQ-C30, time to clinically relevant deterioration by ≥ 15 points), ASCEND study, data cut-off from 15 January 2019

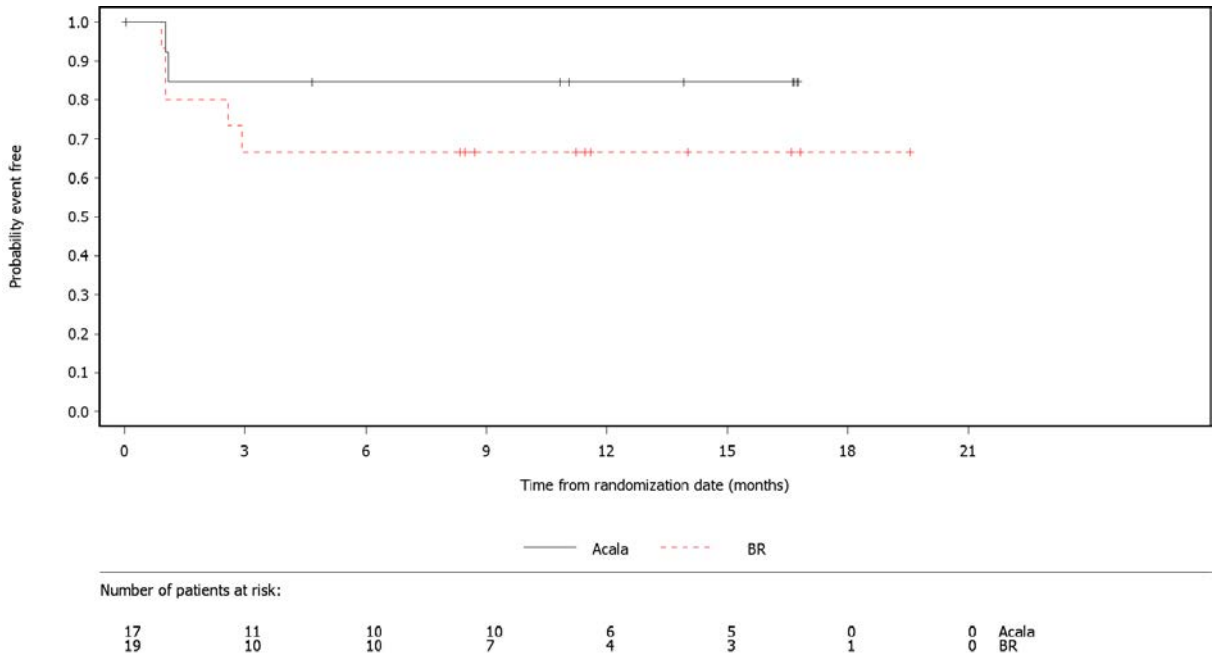

Figure 4: Kaplan-Meier-curves for symptoms, outcome "nausea and vomiting" (EORTC QLQ-C30, time to clinically relevant deterioration by ≥ 15 points), ASCEND study, data cut-off from 15 January 2019

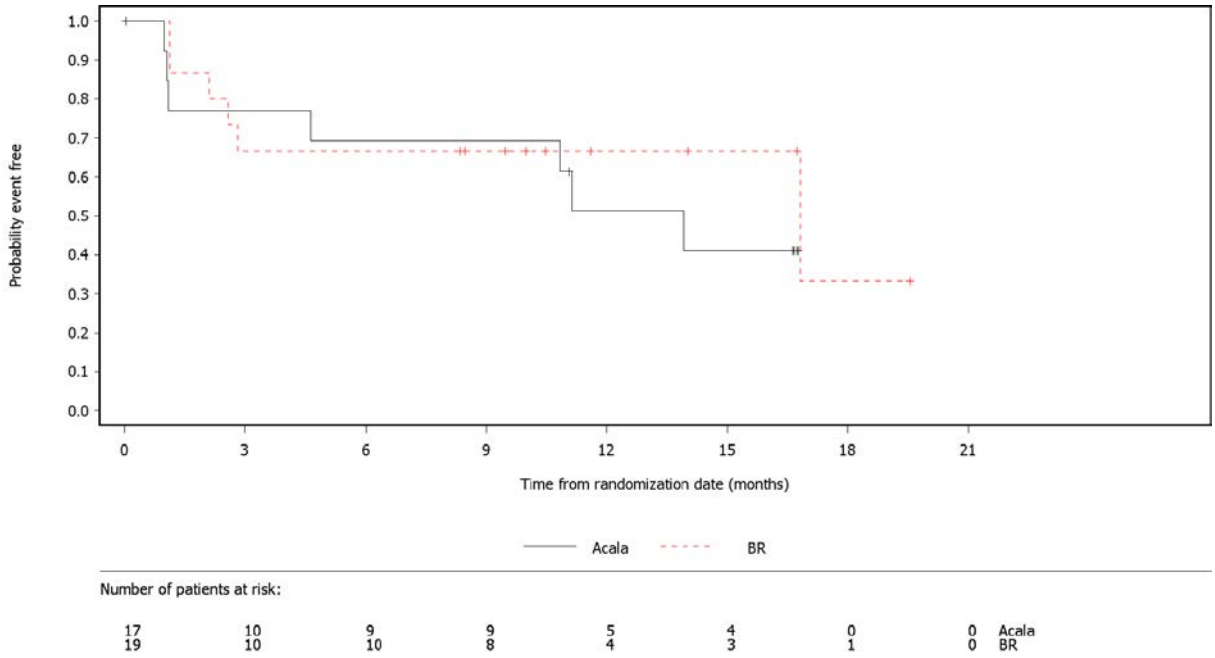

Figure 5: Kaplan-Meier-curves for symptoms, outcome "pain" (EORTC QLQ-C30, time to clinically relevant deterioration by ≥ 15 points), ASCEND study, data cut-off from 15 January 2019

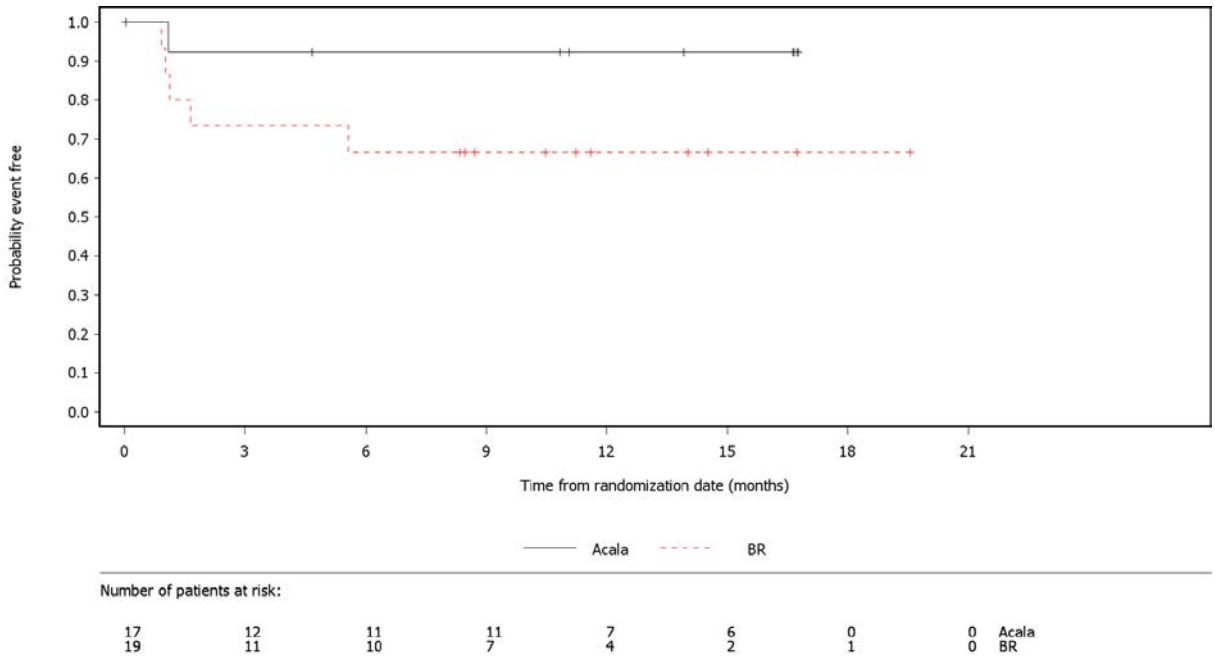

Figure 6: Kaplan-Meier-curves for symptoms, outcome "appetite loss" (EORTC QLQ-C30, time to clinically relevant deterioration by ≥ 15 points), ASCEND study, data cut-off from 15 January 2019

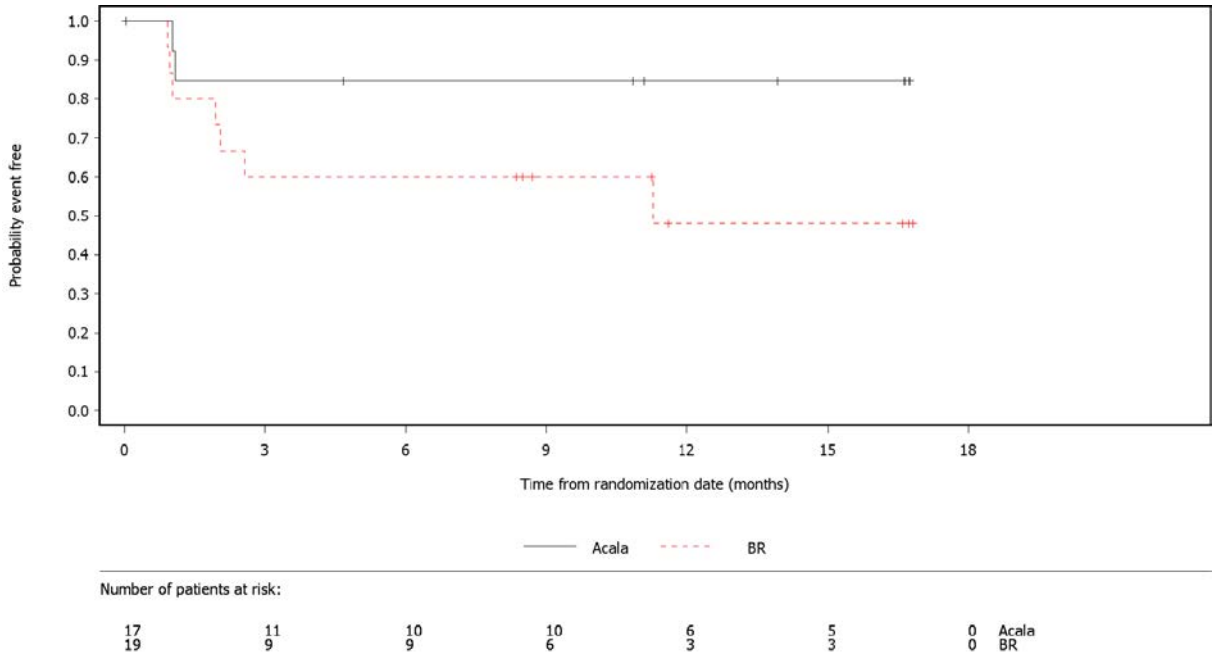

Figure 7: Kaplan-Meier-curves for symptoms, outcome "diarrhoea" (EORTC QLQ-C30, time to clinically relevant deterioration by ≥ 15 points), ASCEND study, data cut-off from 15 January 2019

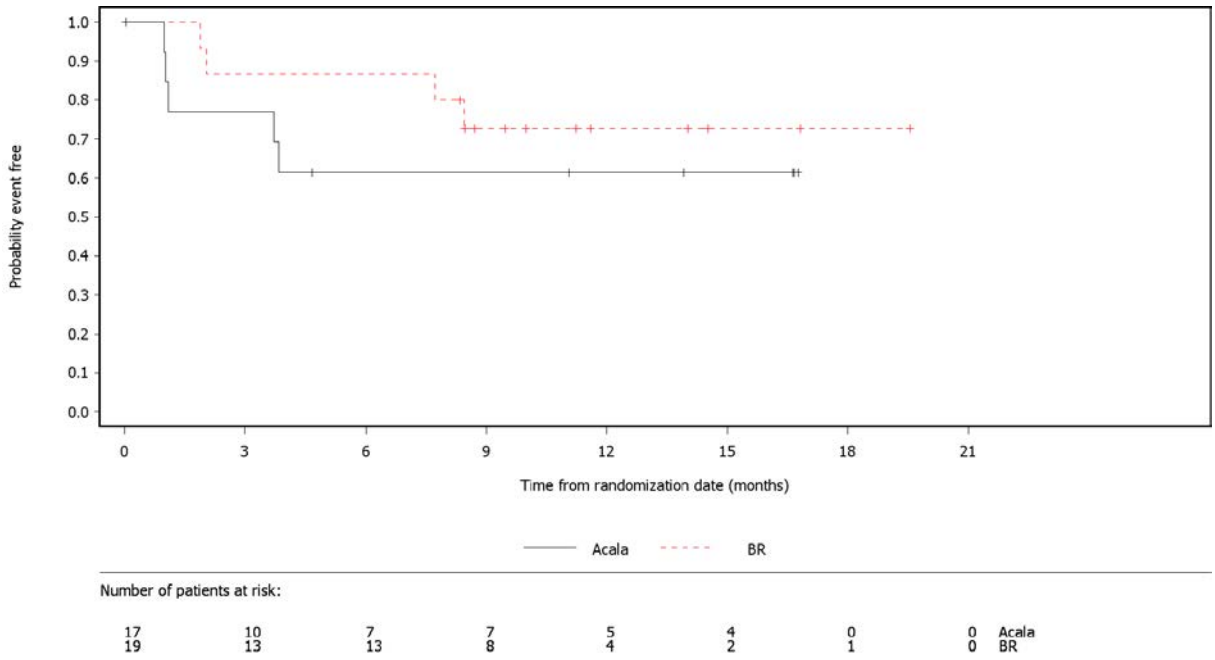

Figure 8: Kaplan-Meier-curves for symptoms, outcome "dyspnoea" (EORTC QLQ-C30, time to clinically relevant deterioration by ≥ 15 points), ASCEND study, data cut-off from 15 January 2019

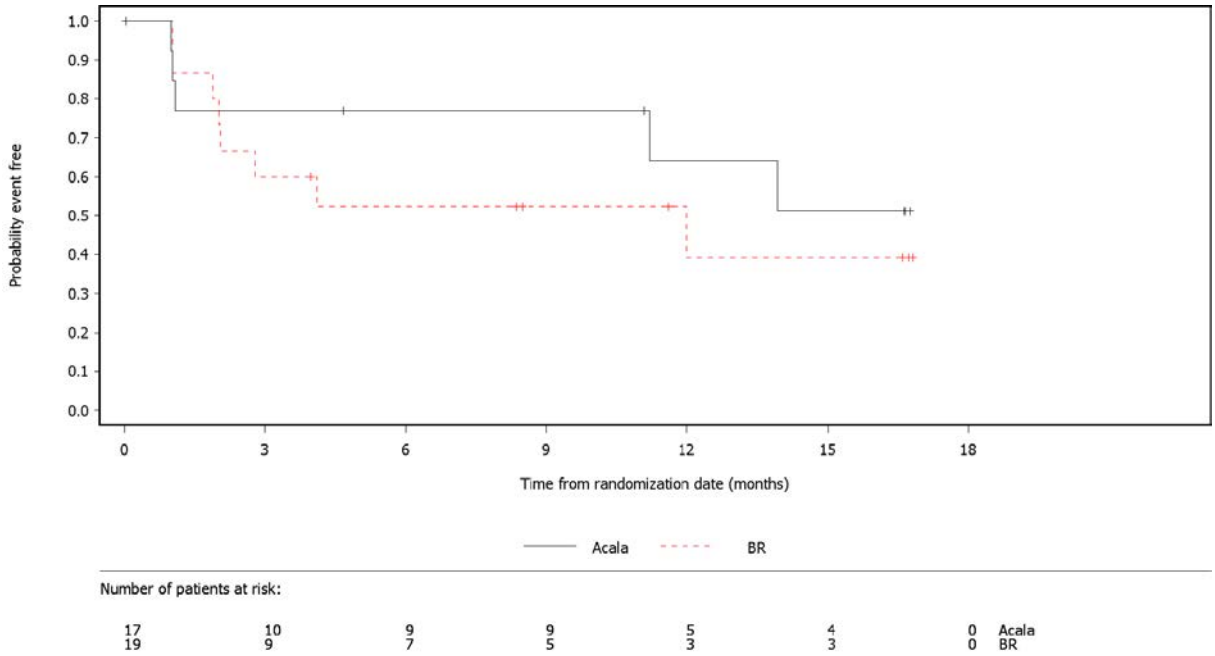

Figure 9: Kaplan-Meier-curves for symptoms, outcome "insomnia" (EORTC QLQ-C30, time to clinically relevant deterioration by ≥ 15 points), ASCEND study, data cut-off from 15 January 2019

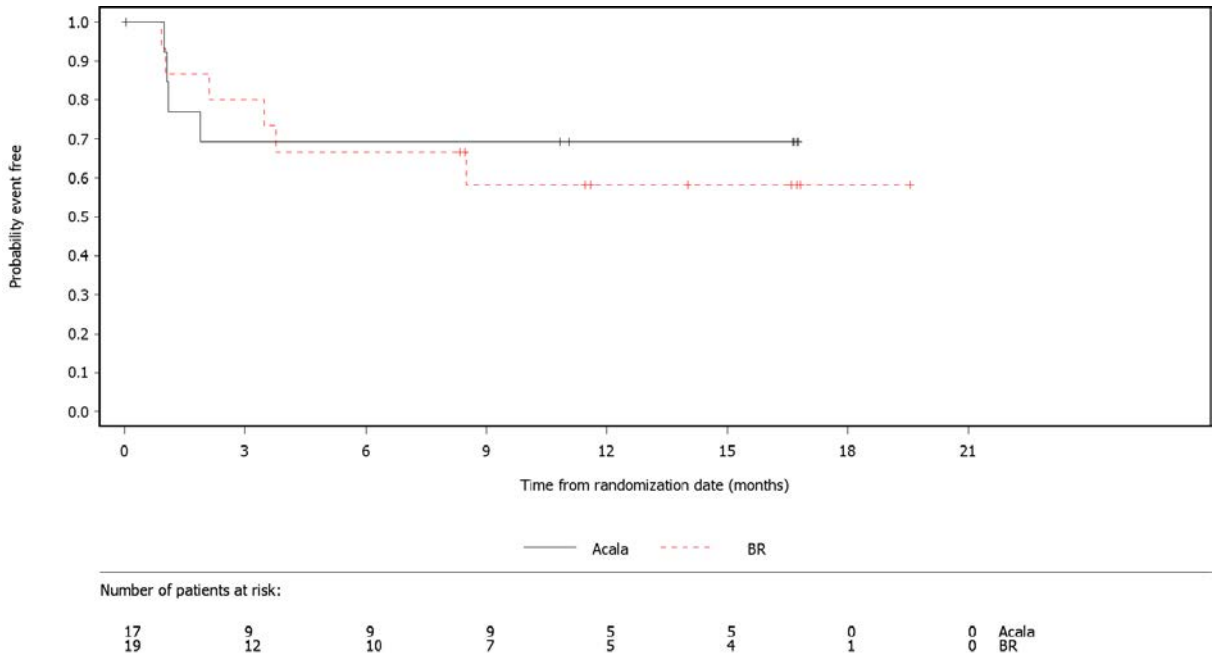

Figure 10: Kaplan-Meier-curves for symptoms, outcome "constipation" (EORTC QLQ-C30, time to clinically relevant deterioration by ≥ 15 points), ASCEND study, data cut-off from 15 January 2019

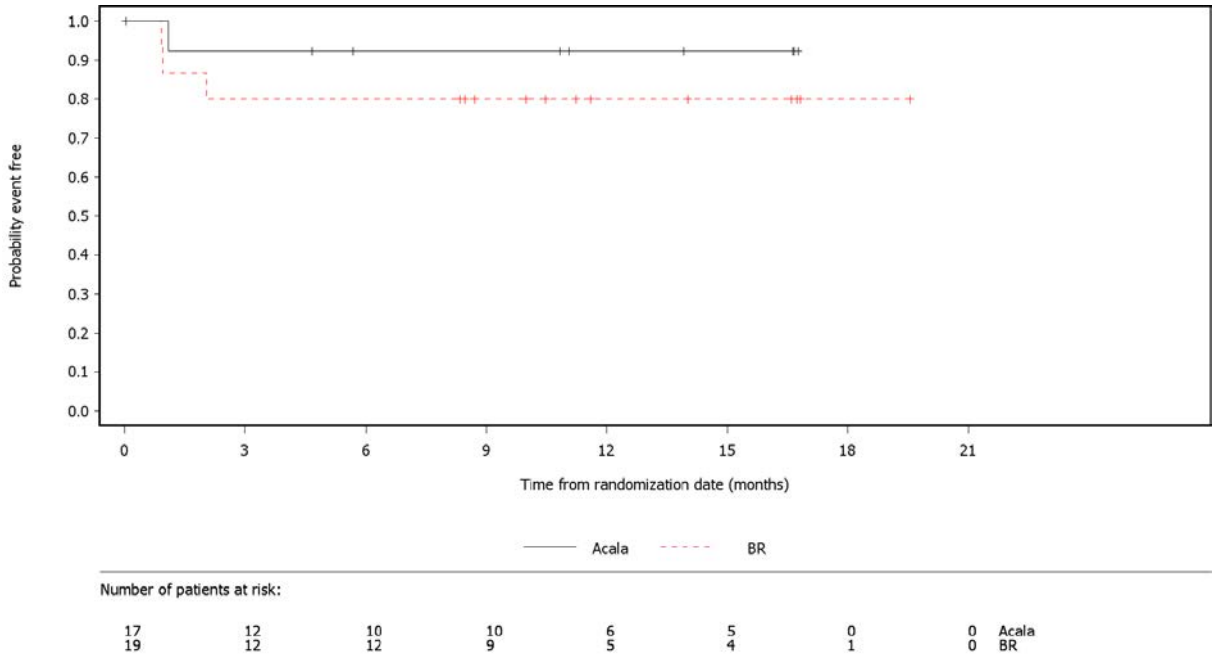

Figure 11: Kaplan-Meier-curves for symptoms, outcome "health status" (EQ-5D VAS, time to clinically relevant deterioration by ≥ 15 points), ASCEND study, data cut-off from 15 January 2019

C.3 – Health-related quality of life

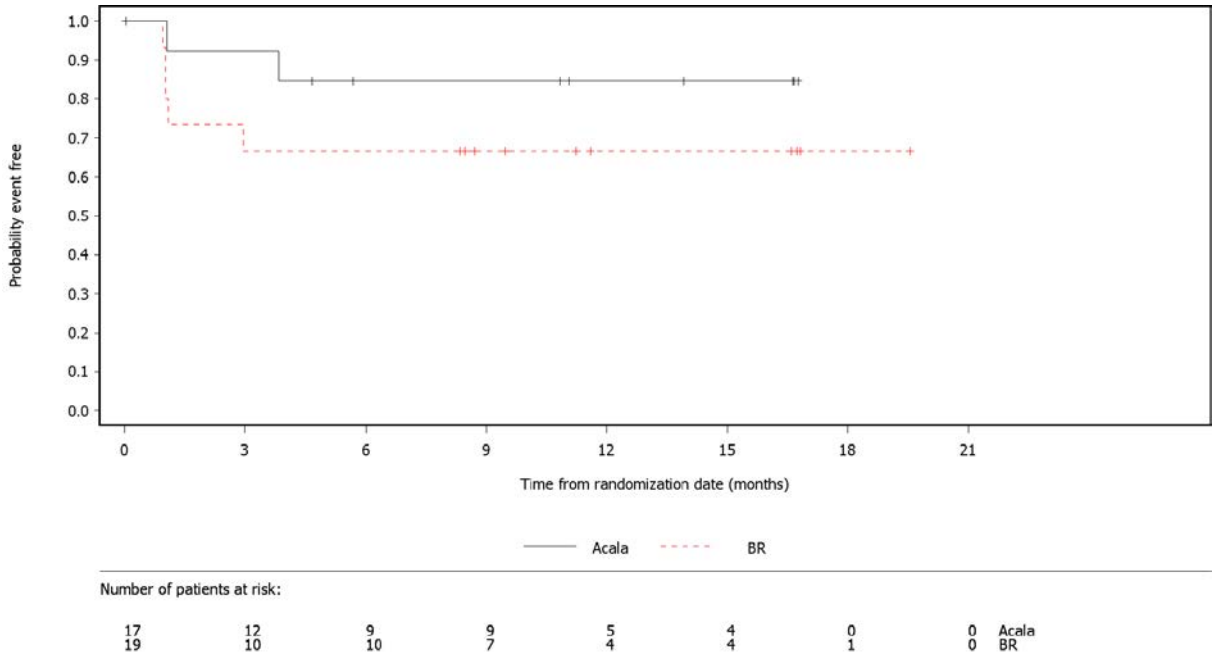

Figure 12: Kaplan-Meier-curves for symptoms, outcome "global health status" (EORTC QLQ-C30, time to clinically relevant deterioration by ≥ 15 points), ASCEND study, data cut-off from 15 January 2019

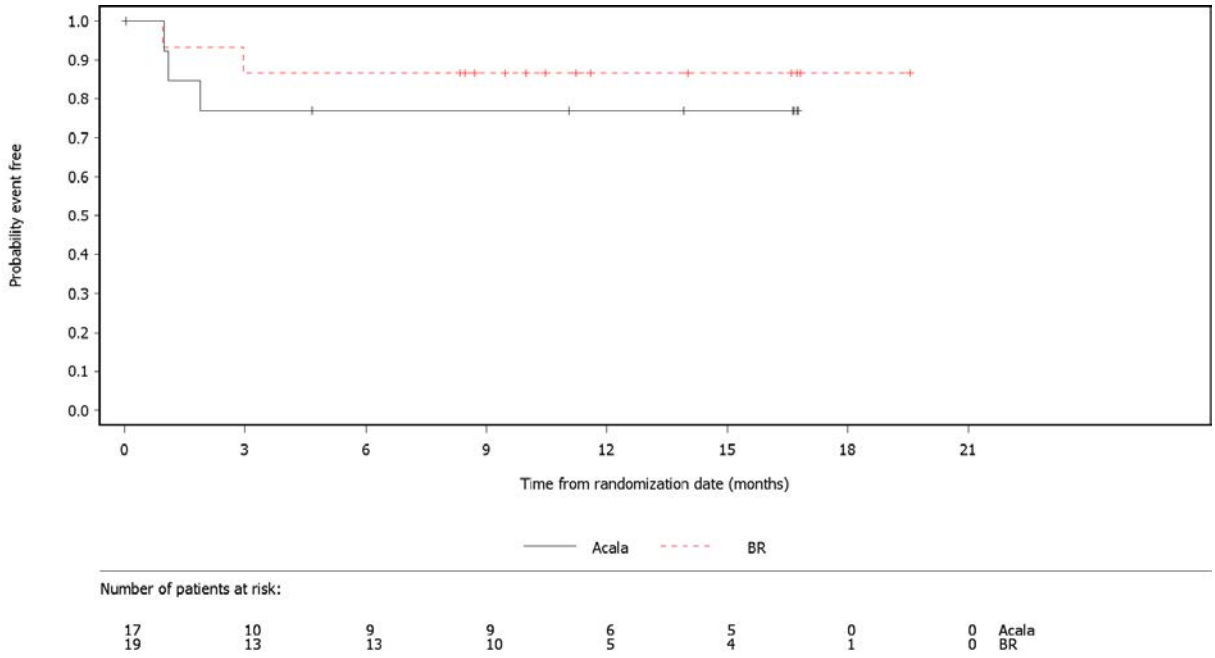

Figure 13: Kaplan-Meier-curves for symptoms, outcome "physical functioning" (EORTC QLQ-C30, time to clinically relevant deterioration by ≥ 15 points), ASCEND study, data cut-off from 15 January 2019

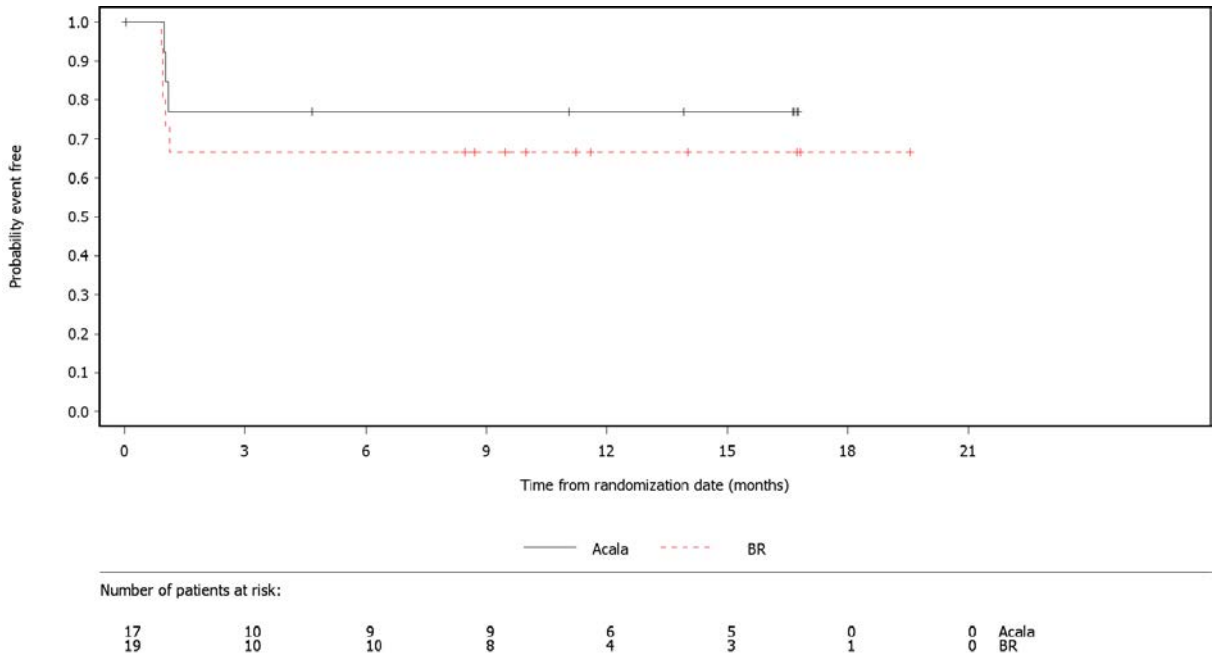

Figure 14: Kaplan-Meier-curves for symptoms, outcome "role functioning" (EORTC QLQ-C30, time to clinically relevant deterioration by ≥ 15 points), ASCEND study, data cut-off from 15 January 2019

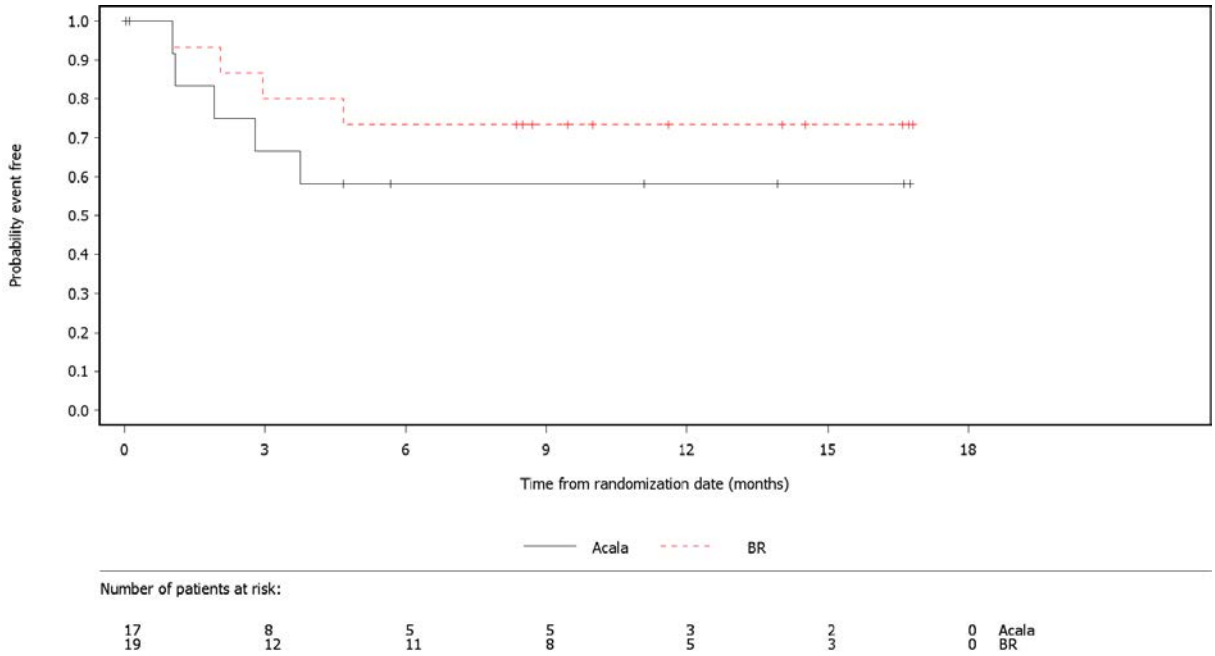

Figure 15: Kaplan-Meier-curves for symptoms, outcome "cognitive functioning" (EORTC QLQ-C30, time to clinically relevant deterioration by ≥ 15 points), ASCEND study, data cut-off from 15 January 2019

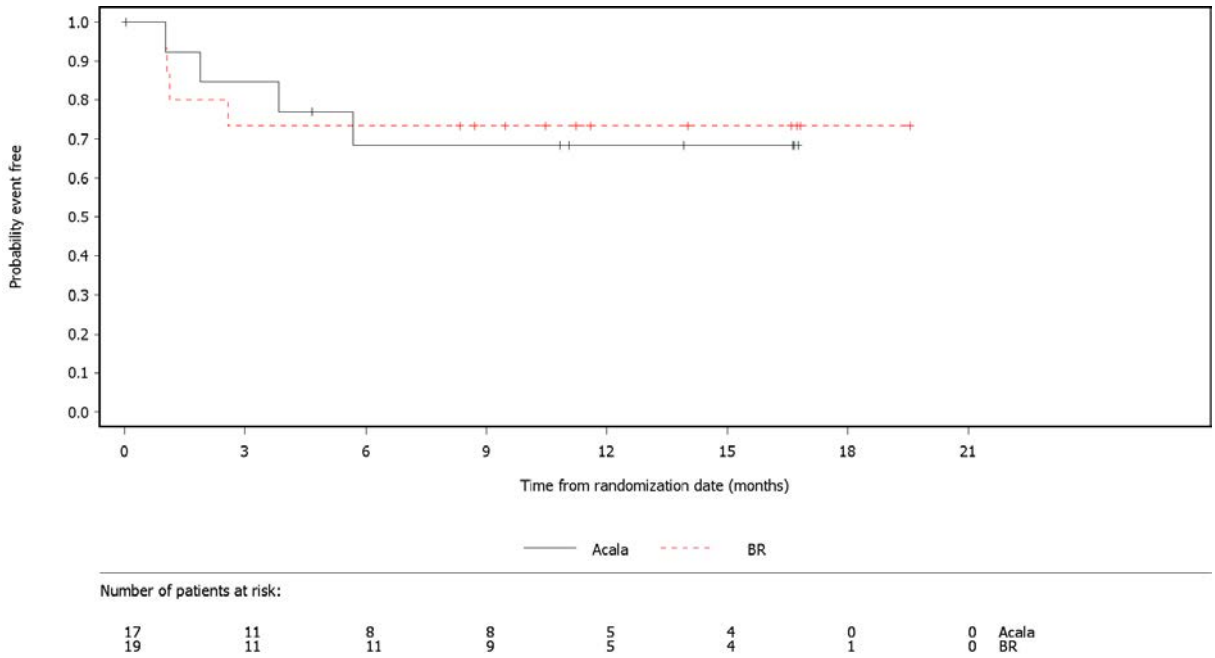

Figure 16: Kaplan-Meier-curves for symptoms, outcome "emotional functioning" (EORTC QLQ-C30, time to clinically relevant deterioration by ≥ 15 points), ASCEND study, data cut-off from 15 January 2019

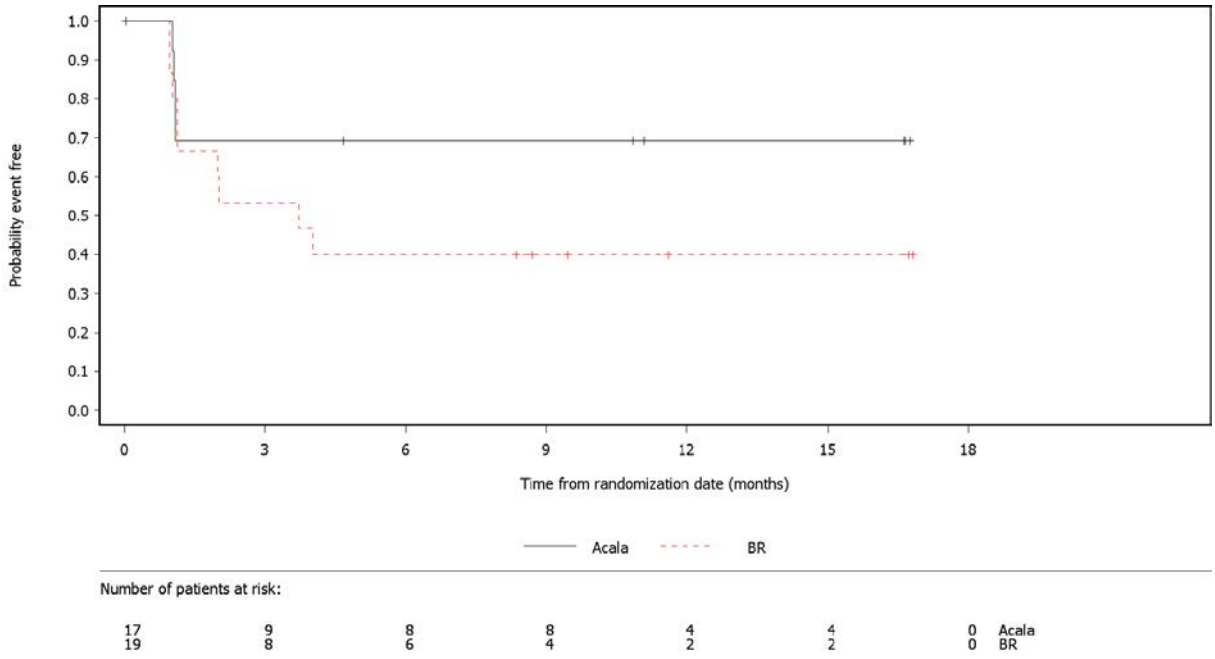

Figure 17: Kaplan-Meier-curves for symptoms, outcome "social functioning" (EORTC QLQ-C30, time to clinically relevant deterioration by ≥ 15 points), ASCEND study, data cut-off from 15 January 2019

C.4 – Side effects

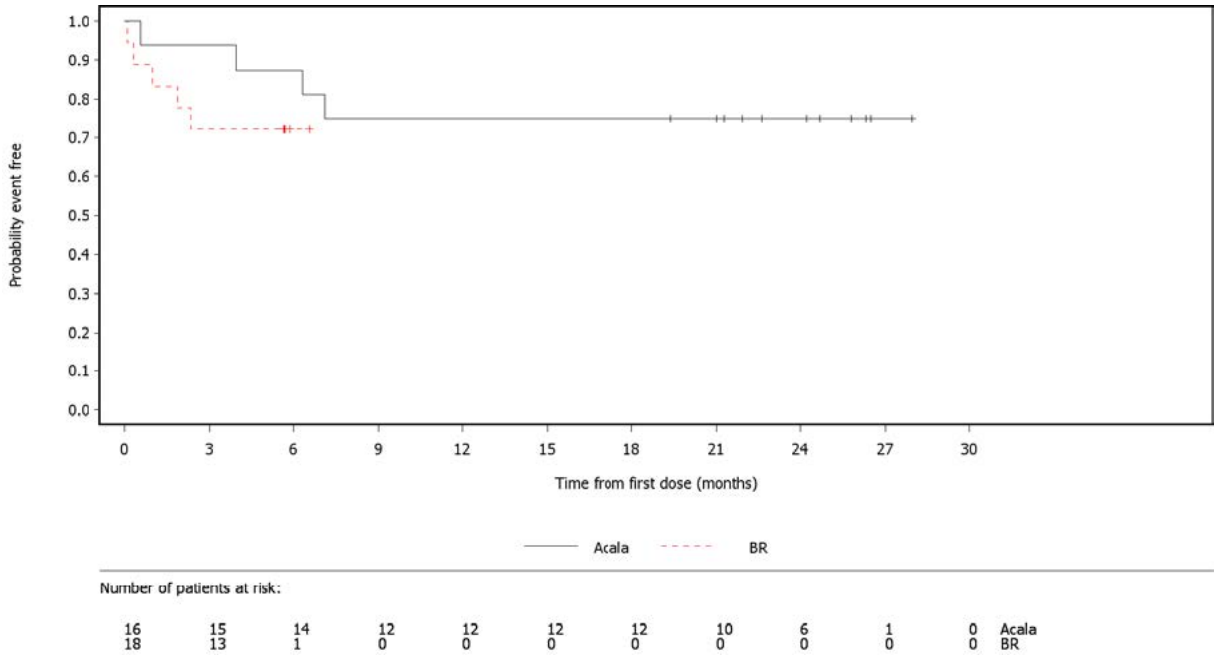

Figure 18: Kaplan-Meier curves, outcome "SAEs", ASCEND study, data cut-off from 1 August 2019

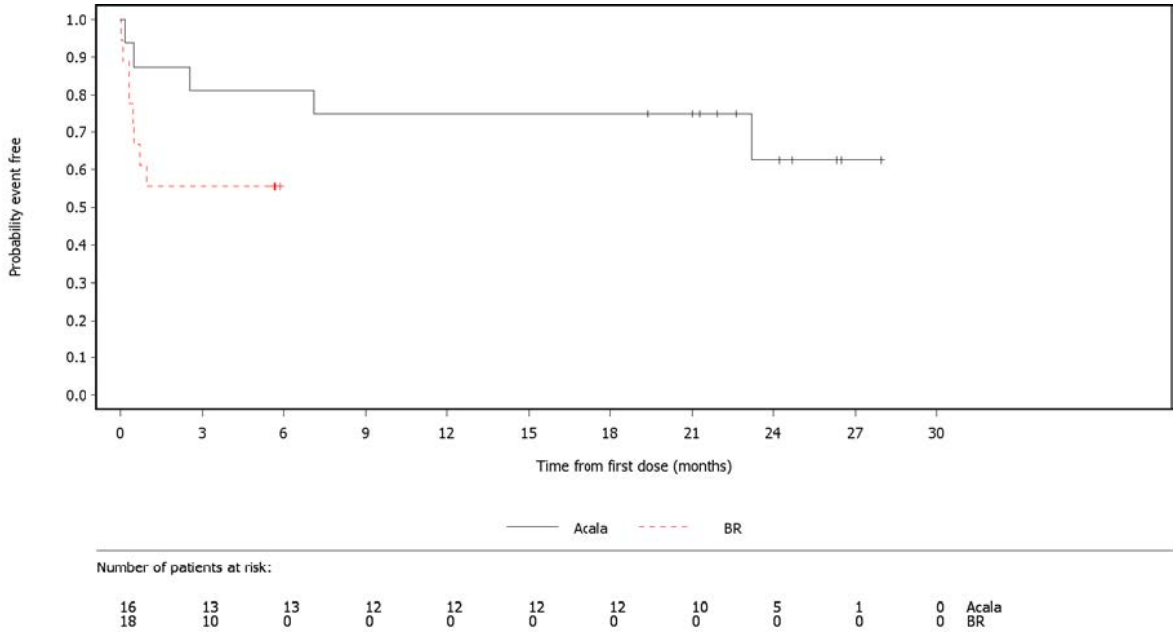

Figure 19: Kaplan-Meier curves, outcome "severe AEs" (CTCAE grade ≥ 3), ASCEND study, data cut-off from 1 August 2019

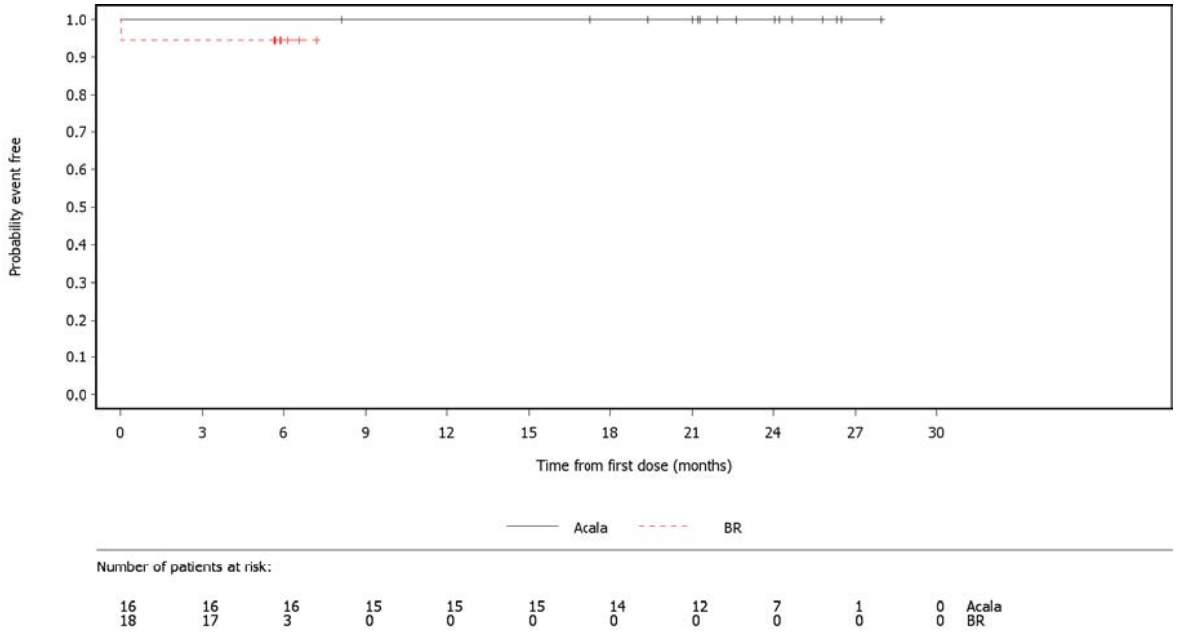

Figure 20: Kaplan-Meier curves, outcome "discontinuation due to AEs", ASCEND study, data cut-off from 1 August 2019

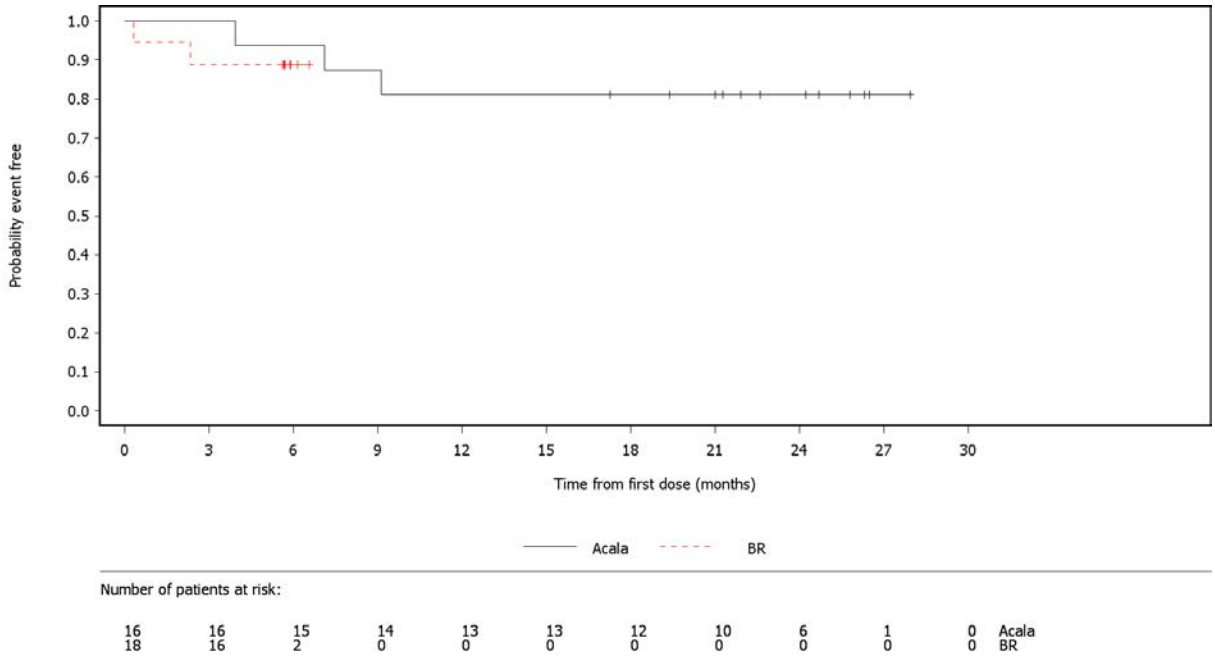

Figure 21: Kaplan-Meier curves, outcome "infections and infestations" (SOC, severe AEs [CTCAE grade ≥ 3]), ASCEND study, data cut-off from 1 August 2019

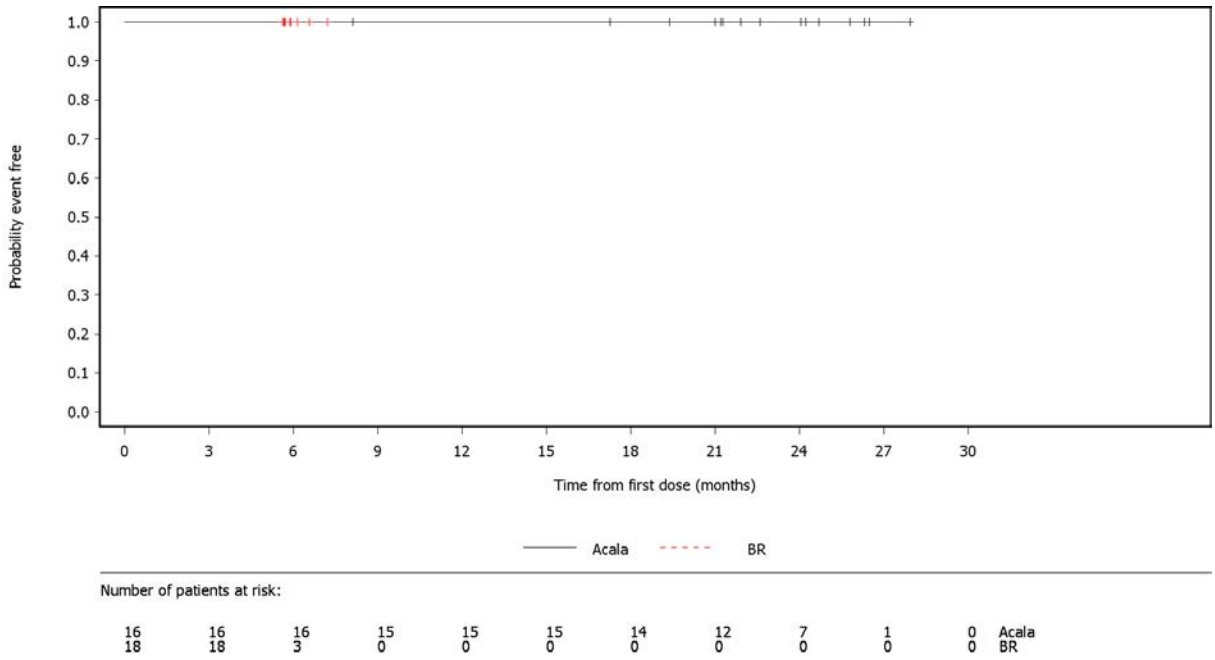

Figure 22: Kaplan-Meier curves, outcome "haemorrhages" (severe AEs [CTCAE grade ≥ 3]), ASCEND study, data cut-off from 1 August 2019

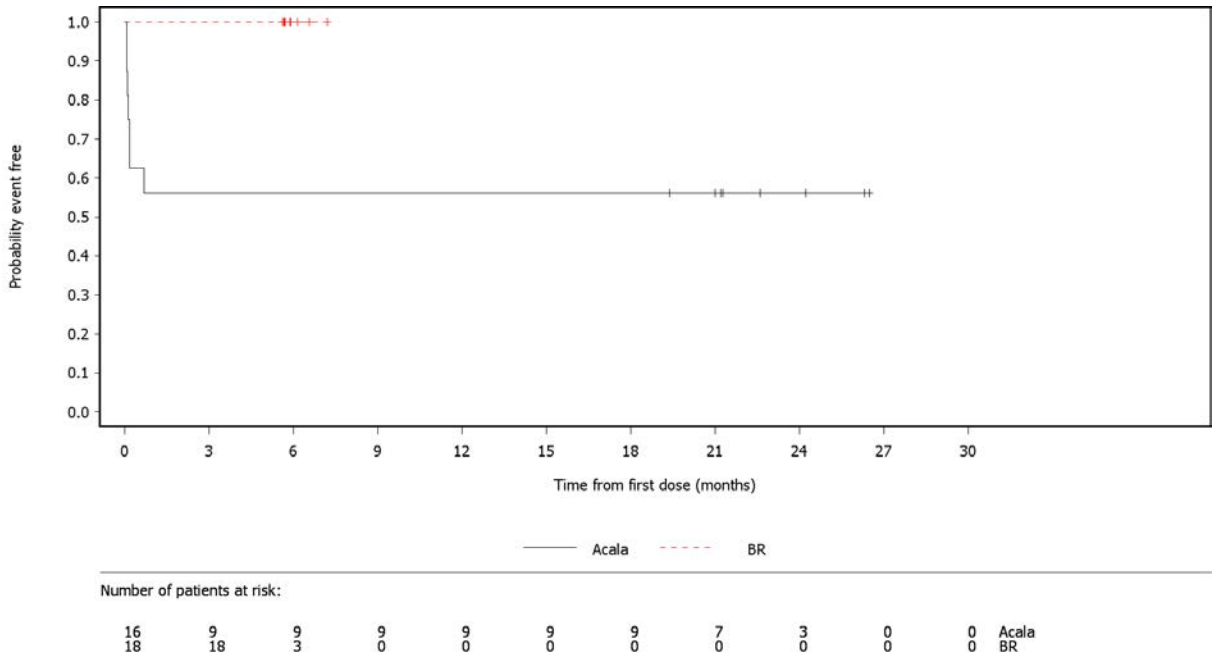

Figure 23: Kaplan-Meier curves, outcome "headache" (PT, AEs), ASCEND study, data cut-off from 1 August 2019

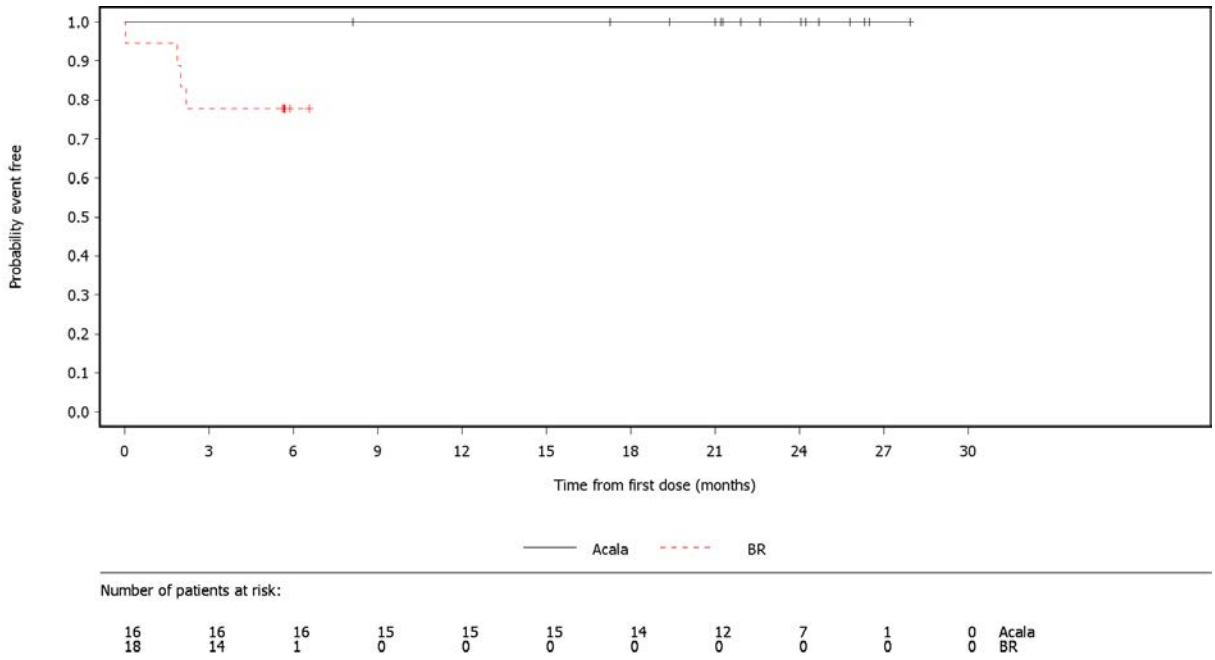

Figure 24: Kaplan-Meier curves, outcome "diarrhoea" (PT, AEs), ASCEND study, data cut-off from 1 August 2019

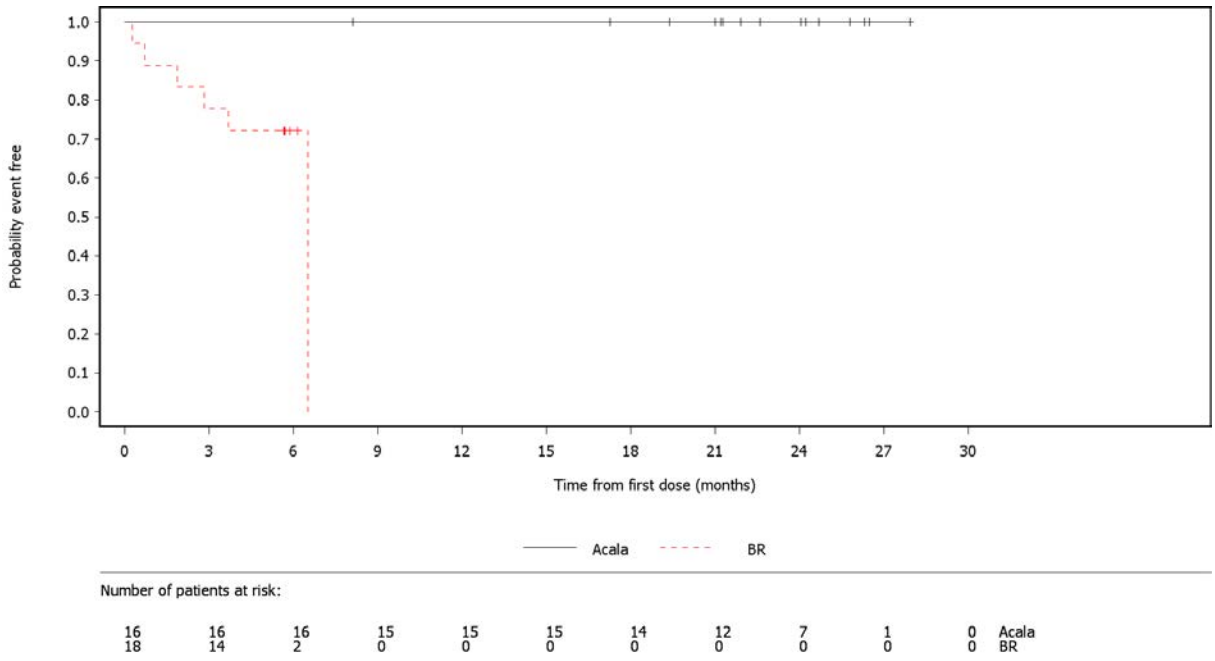

Figure 25: Kaplan-Meier curves, outcome "neutropenia" (PT, severe AEs [CTCAE grade ≥ 3]), ASCEND study, data cut-off from 1 August 2019

Appendix D – Kaplan-Meier curves: adults with CLL; ≥ 2 prior therapies

D.1 – Mortality

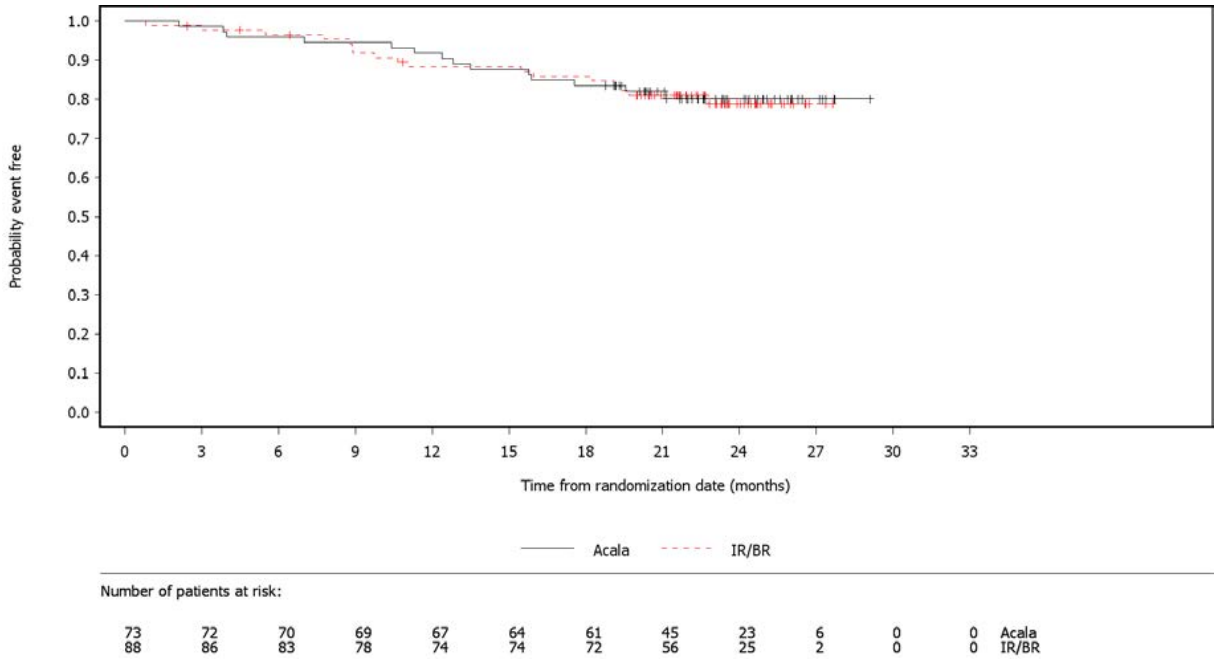

Figure 26: Kaplan-Meier curves, outcome "overall survival", ASCEND study, data cut-off from 1 August 2019

D.2 – Morbidity

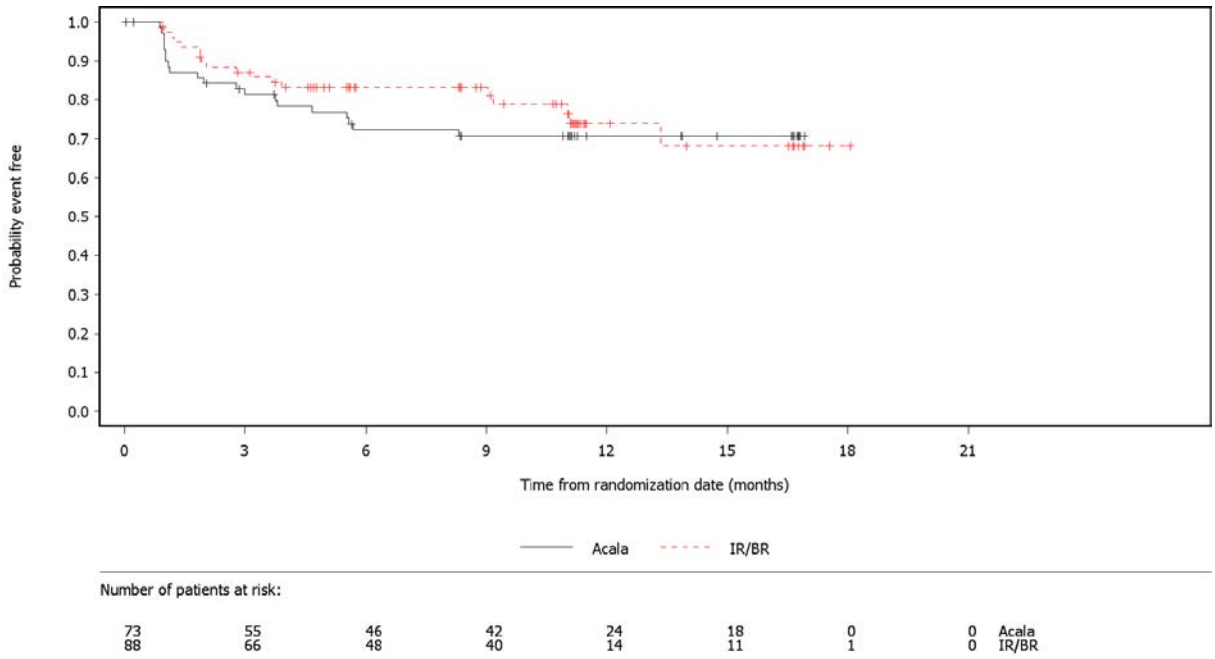

Figure 27: Kaplan-Meier-curves for symptoms, outcome "fatigue" (FACIT-Fatigue, time to clinically relevant deterioration by ≥ 7.8 points), ASCEND study, data cut-off from 15 January 2019

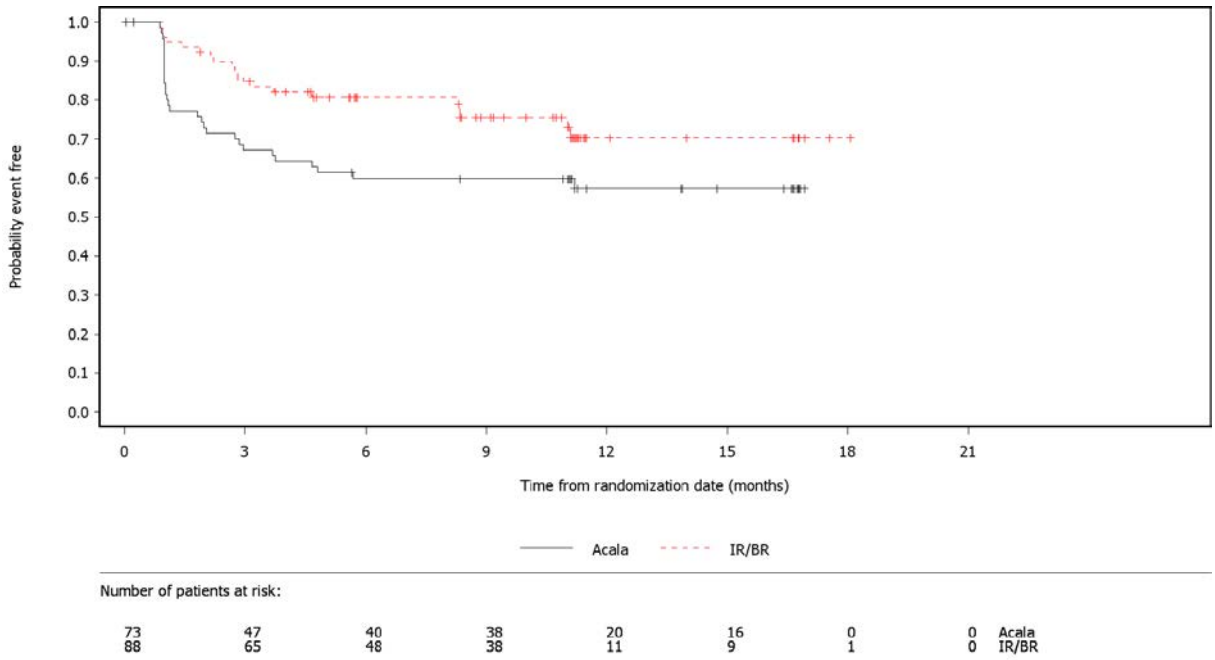

Figure 28: Kaplan-Meier-curves for symptoms, outcome "fatigue" (EORTC QLQ-C30, time to clinically relevant deterioration by ≥ 15 points), ASCEND study, data cut-off from 15 January 2019

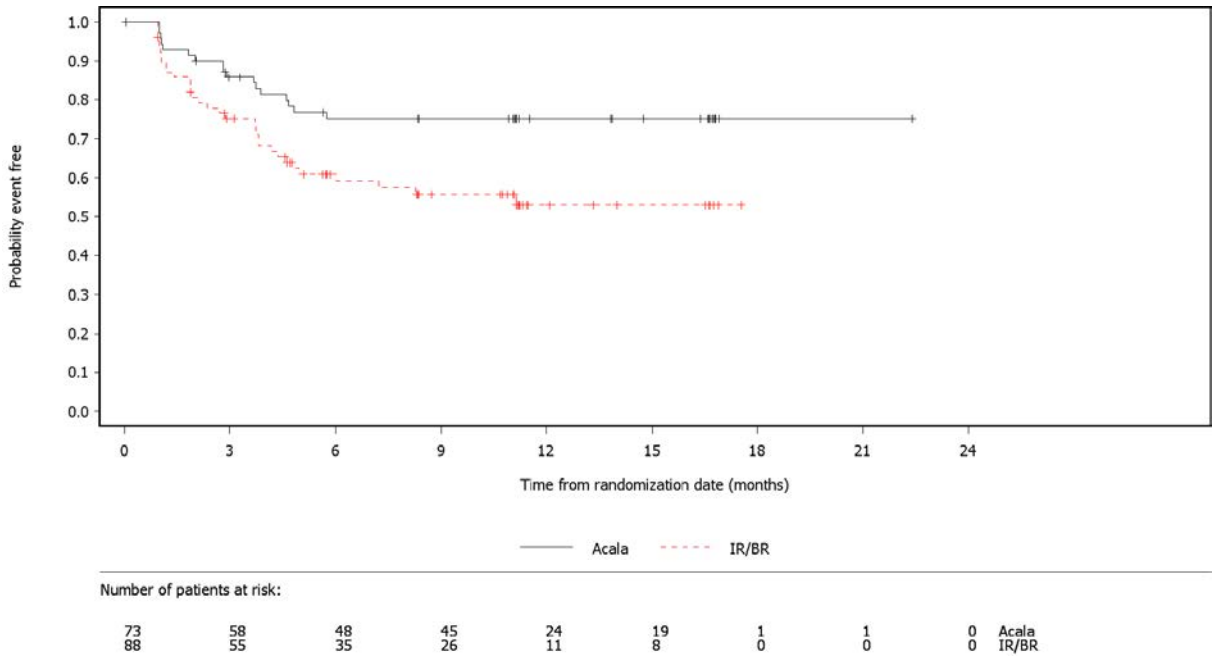

Figure 29: Kaplan-Meier-curves for symptoms, outcome "nausea and vomiting" (EORTC QLQ-C30, time to clinically relevant deterioration by ≥ 15 points), ASCEND study, data cut-off from 15 January 2019

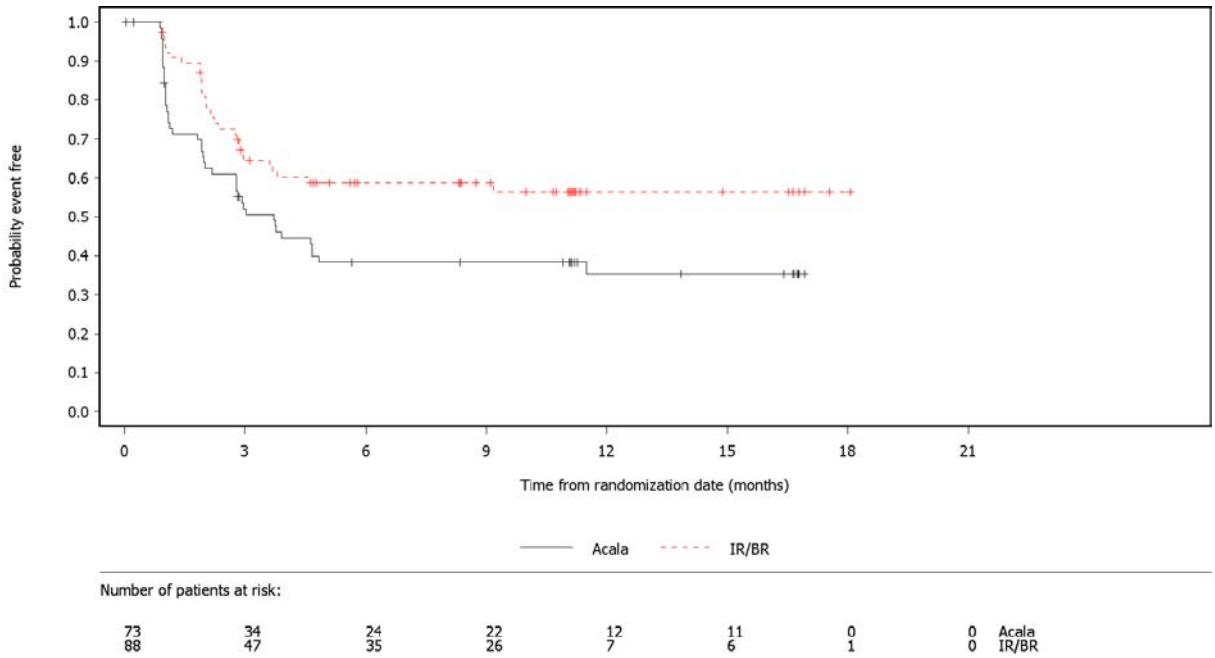

Figure 30: Kaplan-Meier-curves for symptoms, outcome "pain" (EORTC QLQ-C30, time to clinically relevant deterioration by ≥ 15 points), ASCEND study, data cut-off from 15 January 2019

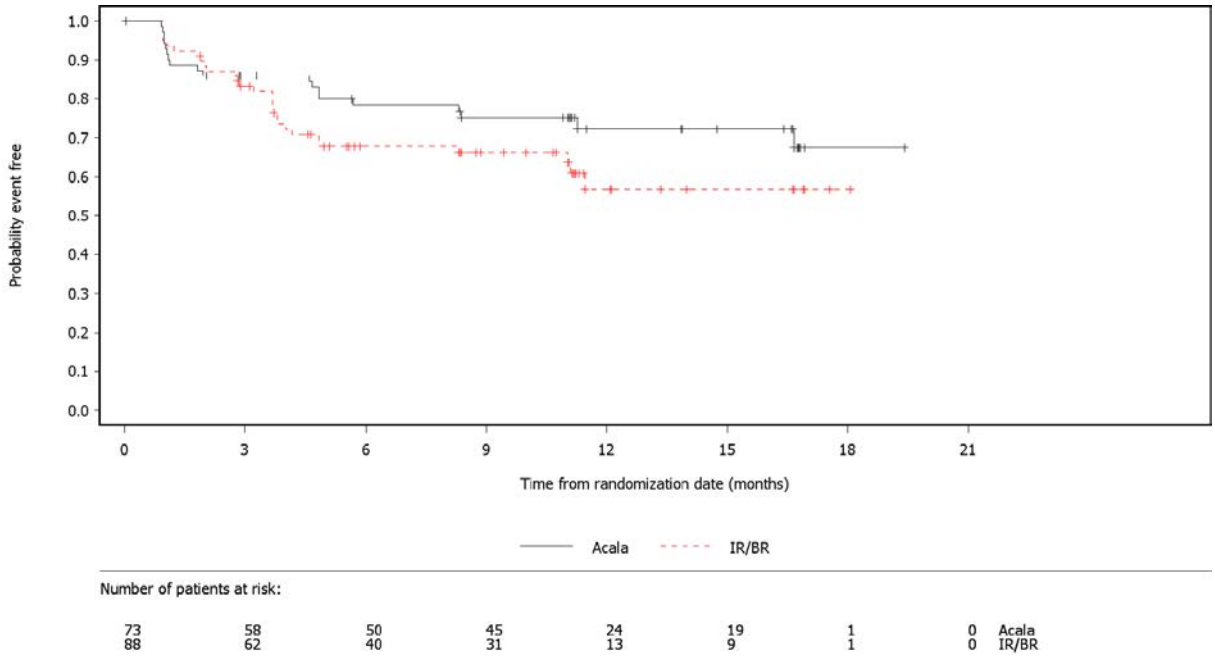

Figure 31: Kaplan-Meier-curves for symptoms, outcome "appetite loss" (EORTC QLQ-C30, time to clinically relevant deterioration by ≥ 15 points), ASCEND study, data cut-off from 15 January 2019

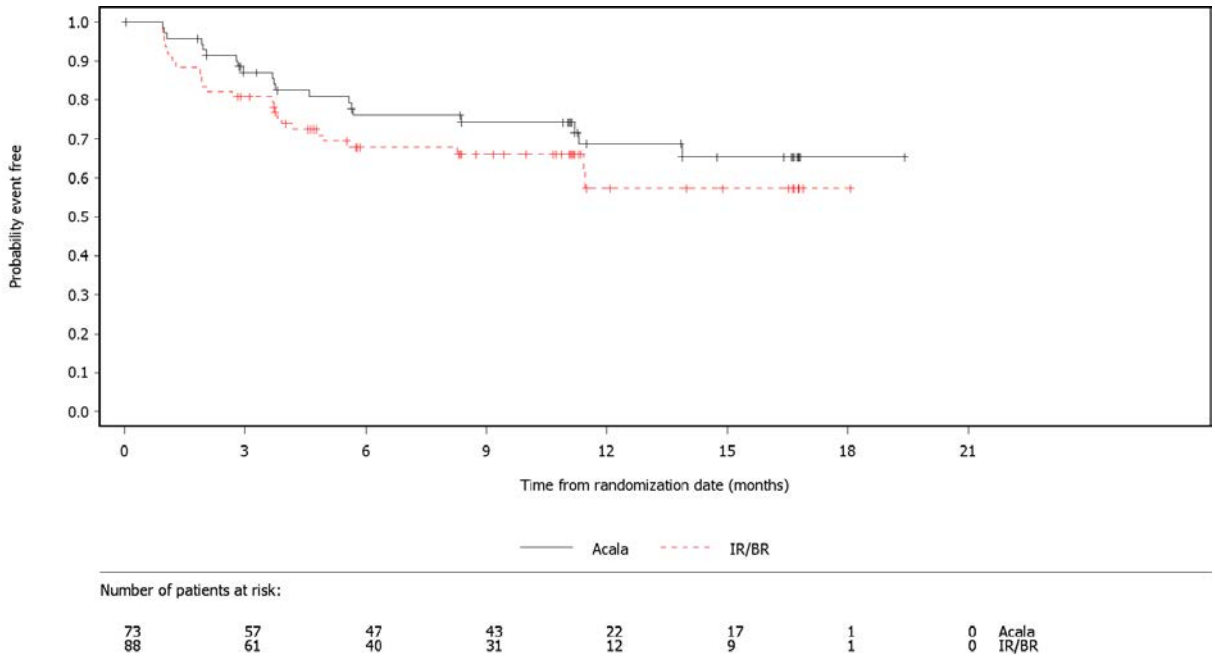

Figure 32: Kaplan-Meier-curves for symptoms, outcome "diarrhoea" (EORTC QLQ-C30, time to clinically relevant deterioration by ≥ 15 points), ASCEND study, data cut-off from 15 January 2019

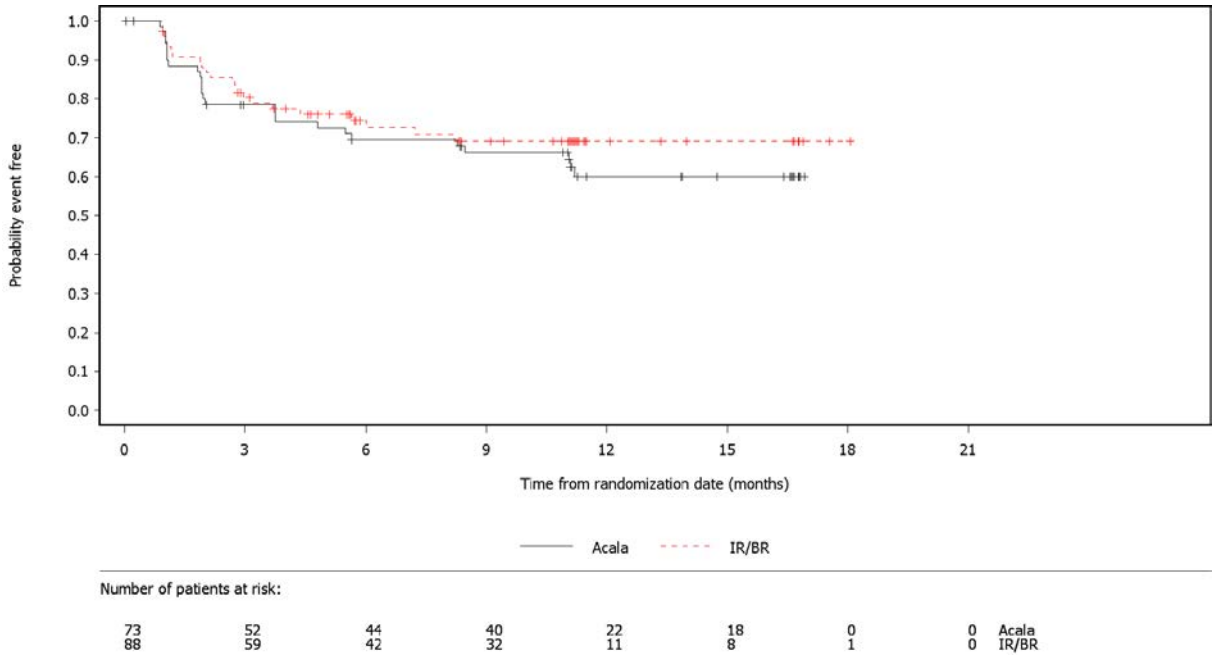

Figure 33: Kaplan-Meier-curves for symptoms, outcome "dyspnoea" (EORTC QLQ-C30, time to clinically relevant deterioration by ≥ 15 points), ASCEND study, data cut-off from 15 January 2019

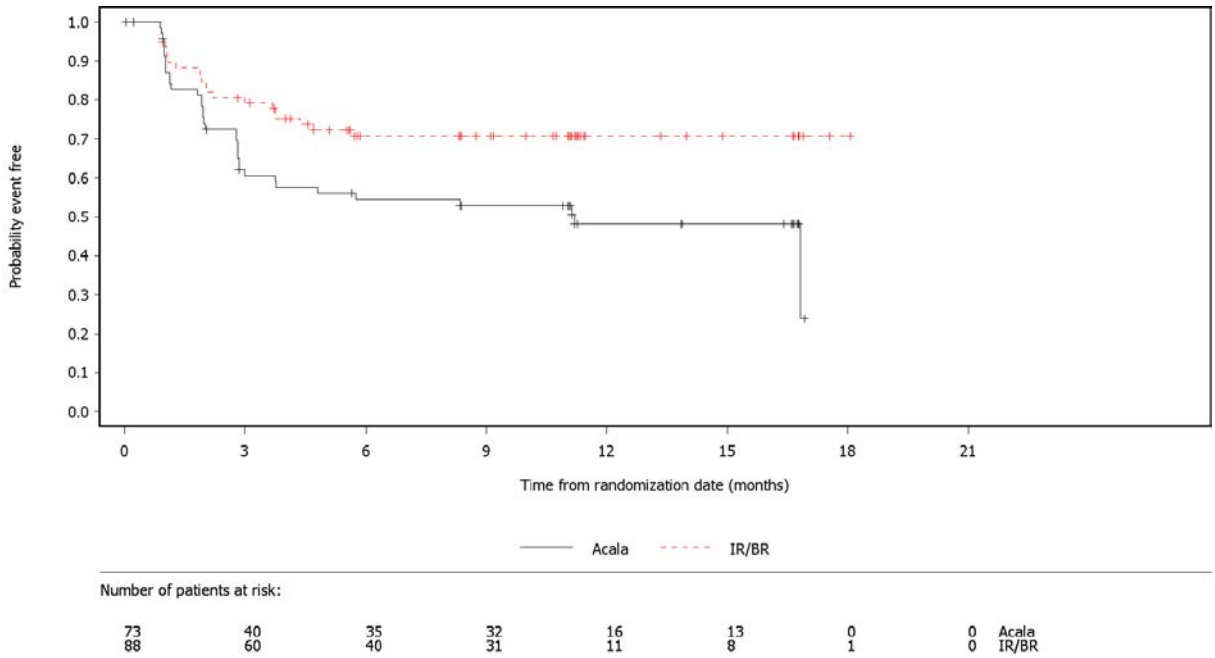

Figure 34: Kaplan-Meier-curves for symptoms, outcome "insomnia" (EORTC QLQ-C30, time to clinically relevant deterioration by ≥ 15 points), ASCEND study, data cut-off from 15 January 2019

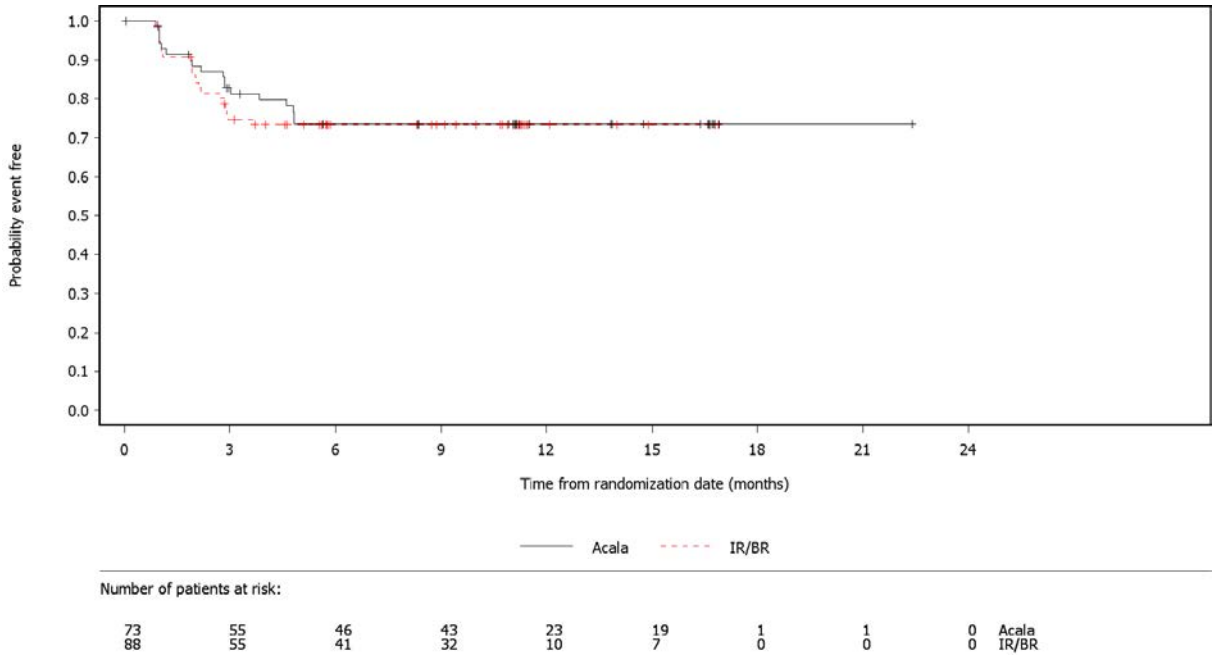

Figure 35: Kaplan-Meier-curves for symptoms, outcome "constipation" (EORTC QLQ-C30, time to clinically relevant deterioration by ≥ 15 points), ASCEND study, data cut-off from 15 January 2019

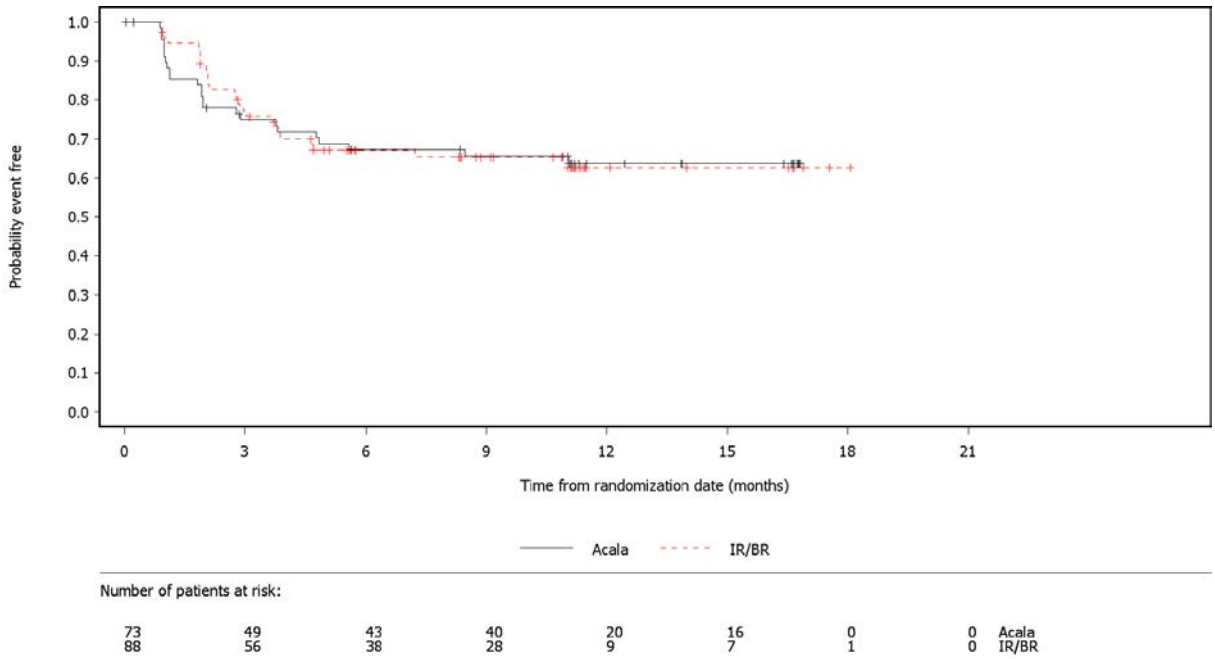

Figure 36: Kaplan-Meier-curves for symptoms, outcome "health status" (EQ-5D VAS, time to clinically relevant deterioration by ≥ 15 points), ASCEND study, data cut-off from 15 January 2019

D.3 – Health-related quality of life

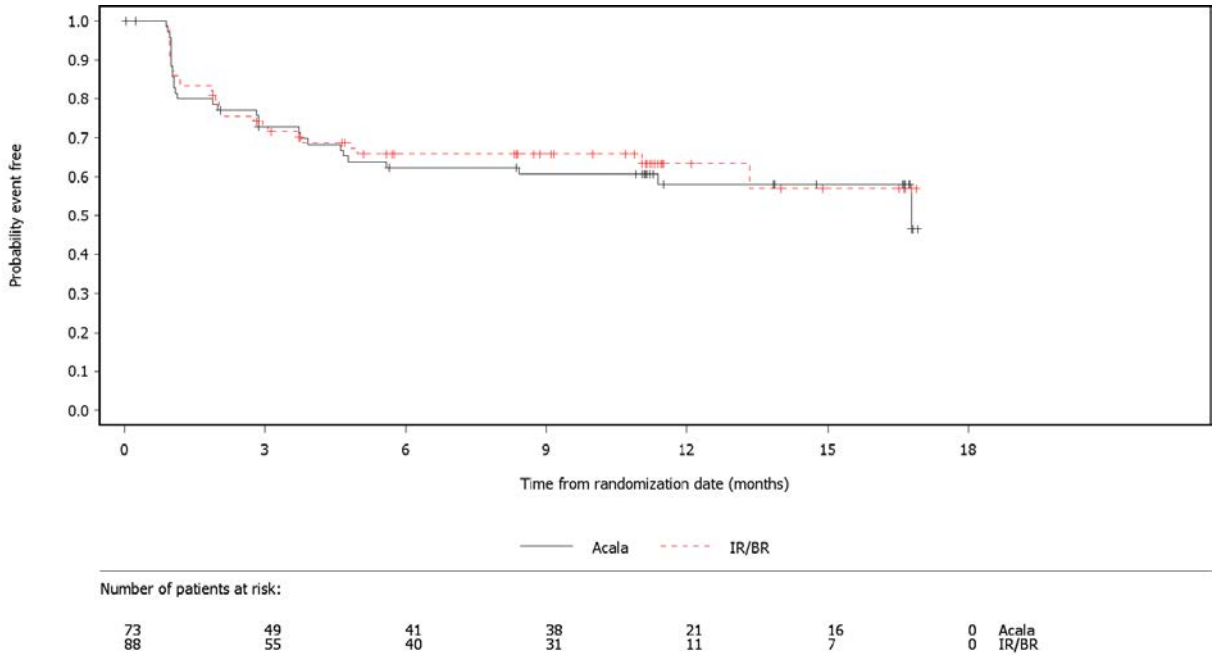

Figure 37: Kaplan-Meier-curves for symptoms, outcome "global health status" (EORTC QLQ-C30, time to clinically relevant deterioration by ≥ 15 points), ASCEND study, data cut-off from 15 January 2019

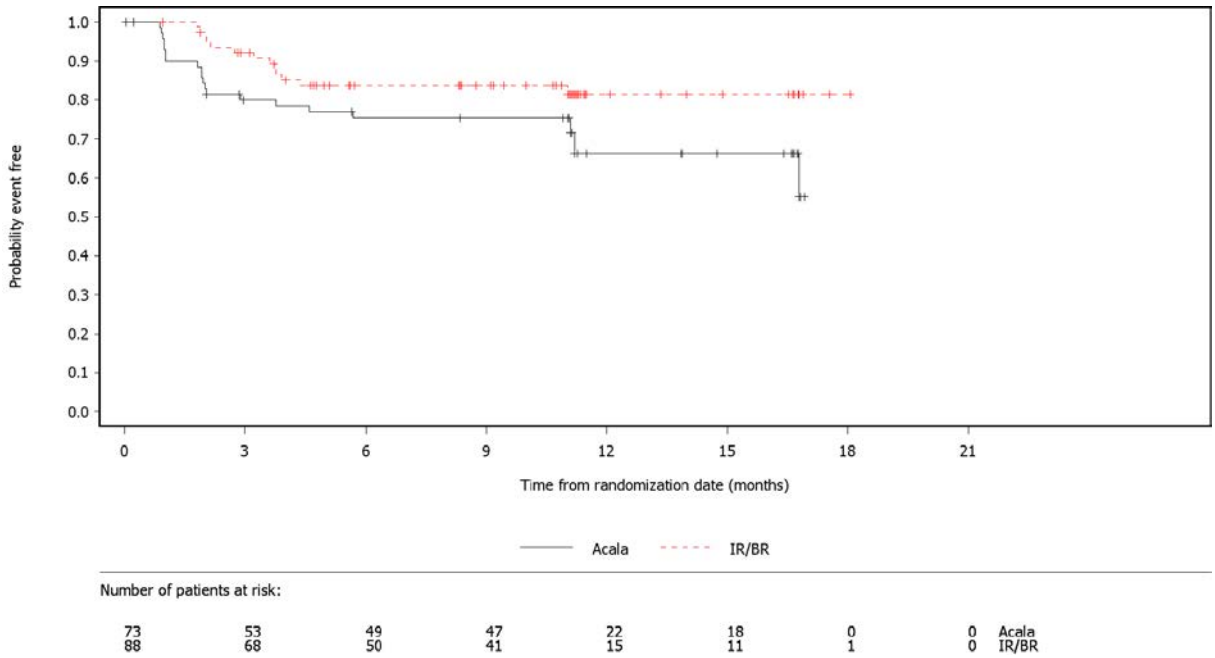

Figure 38: Kaplan-Meier-curves for symptoms, outcome "physical functioning" (EORTC QLQ-C30, time to clinically relevant deterioration by ≥ 15 points), ASCEND study, data cut-off from 15 January 2019

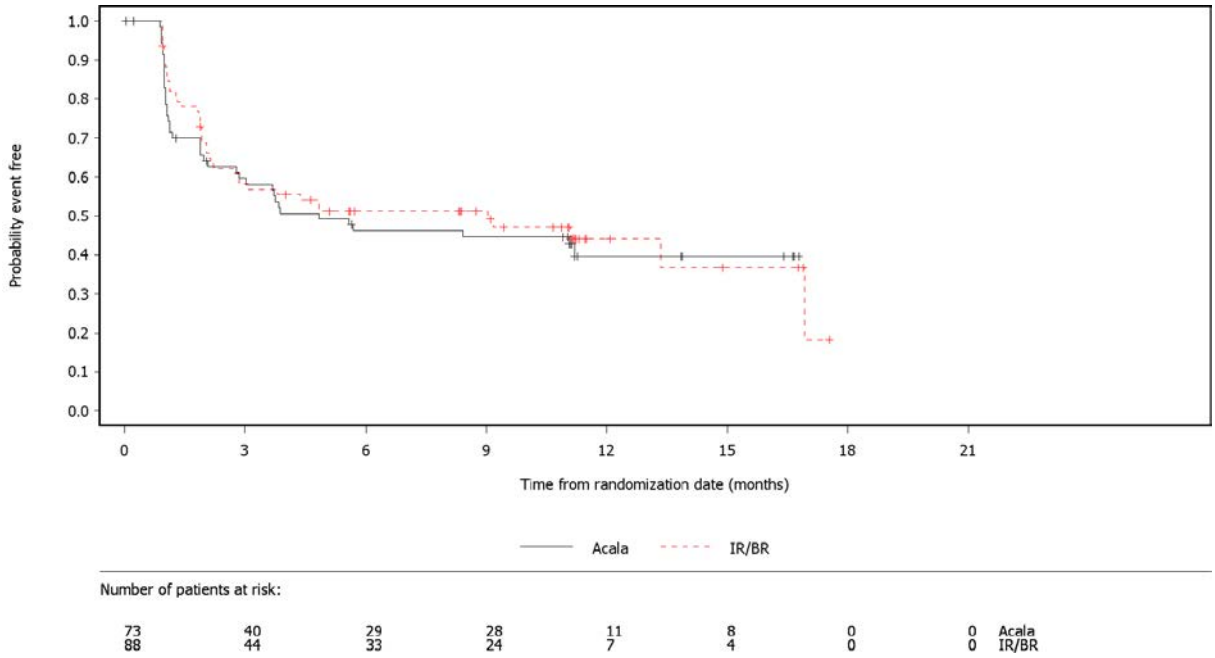

Figure 39: Kaplan-Meier-curves for symptoms, outcome "role functioning" (EORTC QLQ-C30, time to clinically relevant deterioration by ≥ 15 points), ASCEND study, data cut-off from 15 January 2019

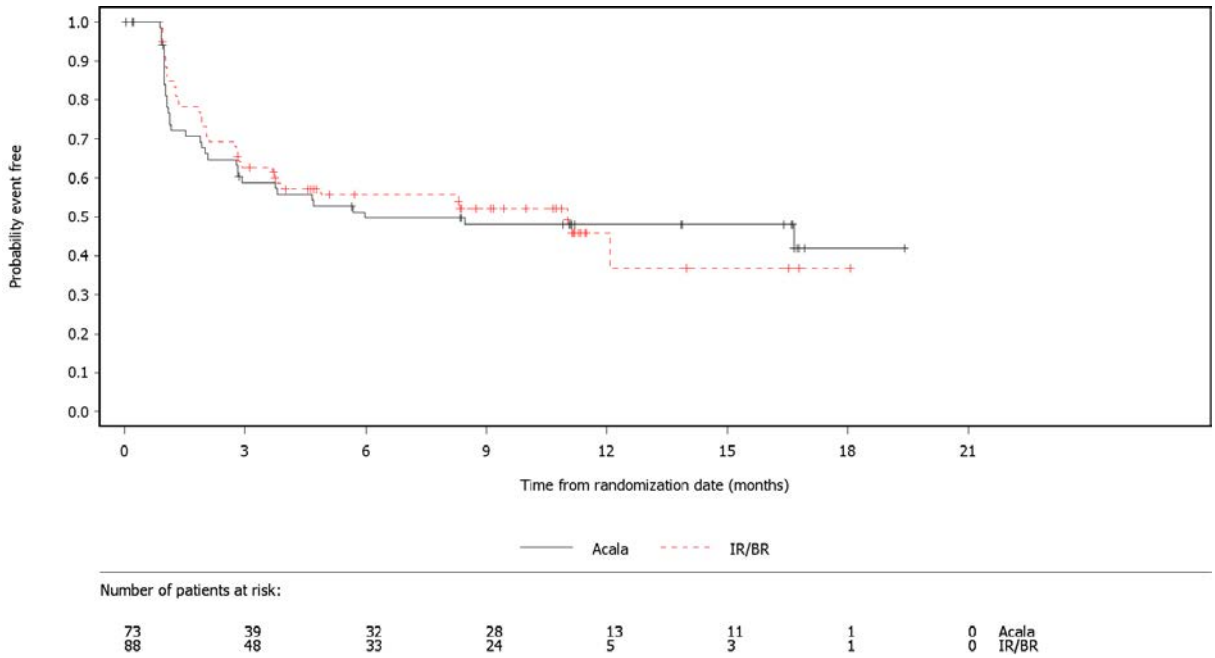

Figure 40: Kaplan-Meier-curves for symptoms, outcome "cognitive functioning" (EORTC QLQ-C30, time to clinically relevant deterioration by ≥ 15 points), ASCEND study, data cut-off from 15 January 2019

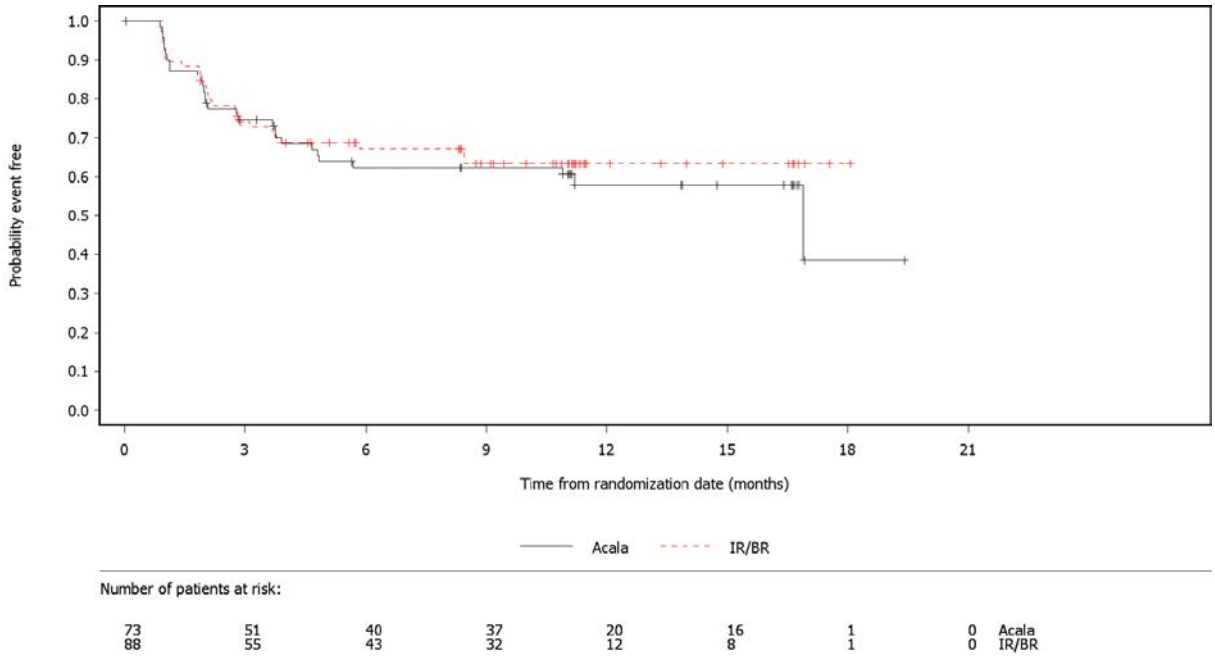

Figure 41: Kaplan-Meier-curves for symptoms, outcome "emotional functioning" (EORTC QLQ-C30, time to clinically relevant deterioration by ≥ 15 points), ASCEND study, data cut-off from 15 January 2019

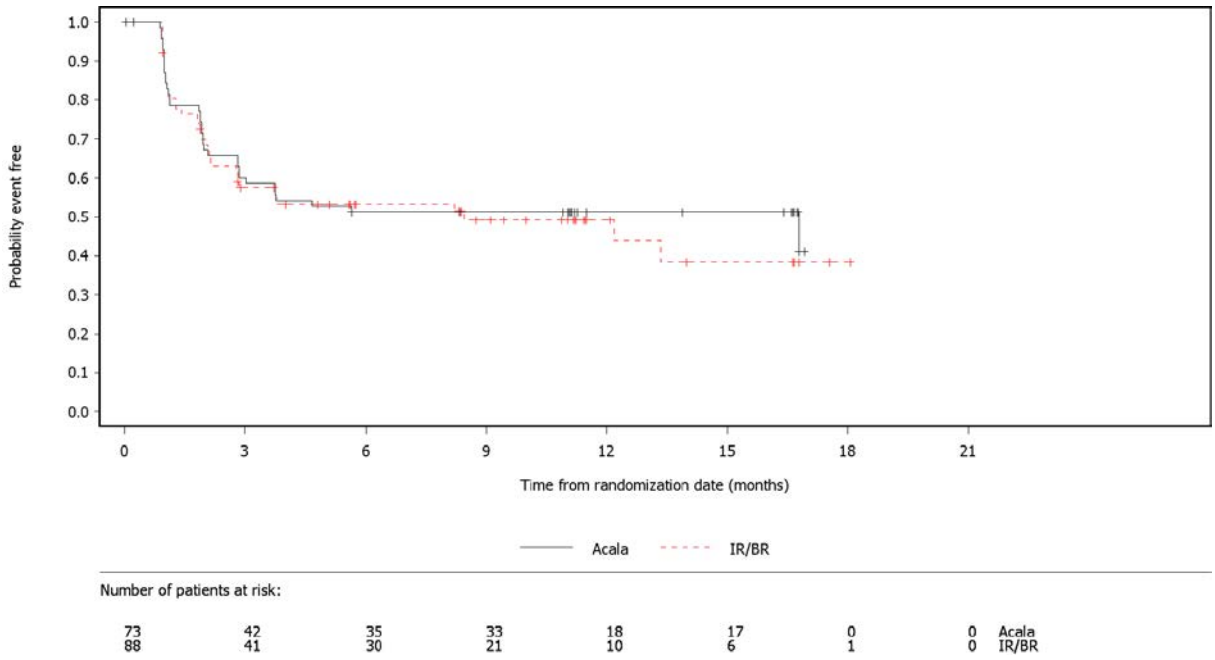

Figure 42: Kaplan-Meier-curves for symptoms, outcome "social functioning" (EORTC QLQ-C30, time to clinically relevant deterioration by ≥ 15 points), ASCEND study, data cut-off from 15 January 2019

D.4 – Side effects

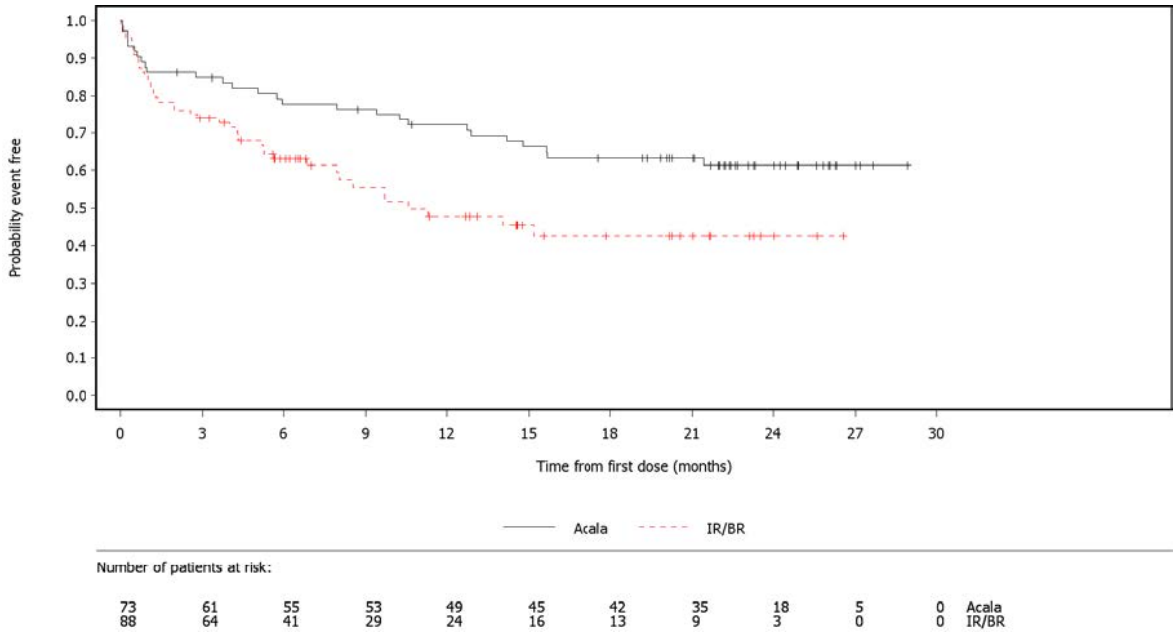

Figure 43: Kaplan-Meier curves, outcome "SAEs", ASCEND study, data cut-off from 1 August 2019

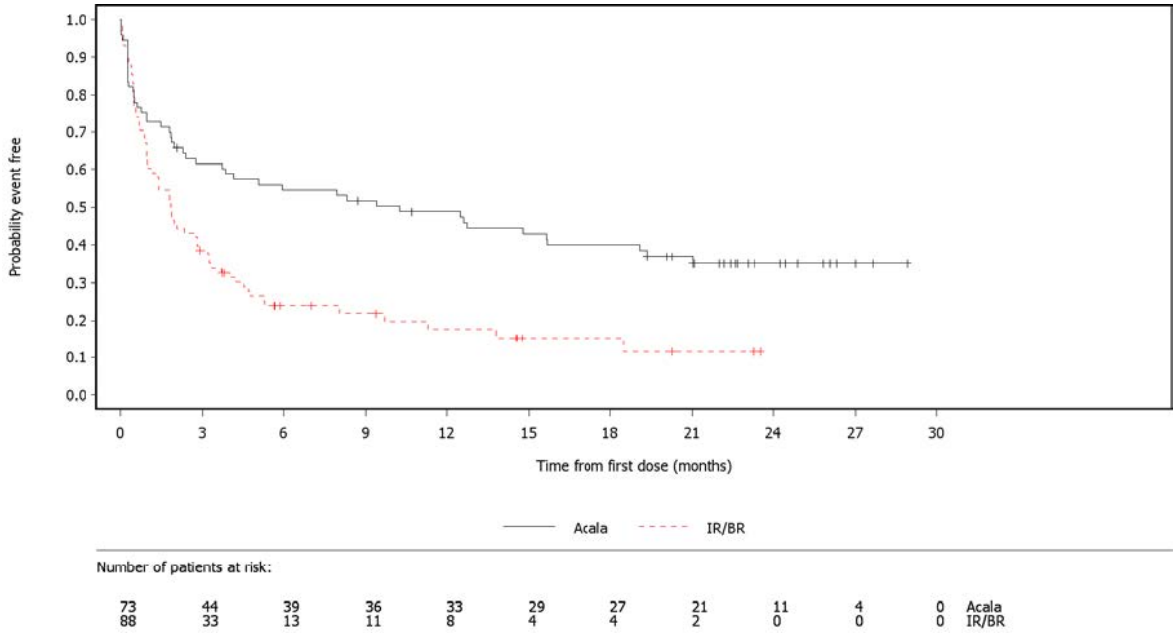

Figure 44: Kaplan-Meier curves, outcome "severe AEs" (CTCAE grade ≥ 3), ASCEND study, data cut-off from 1 August 2019

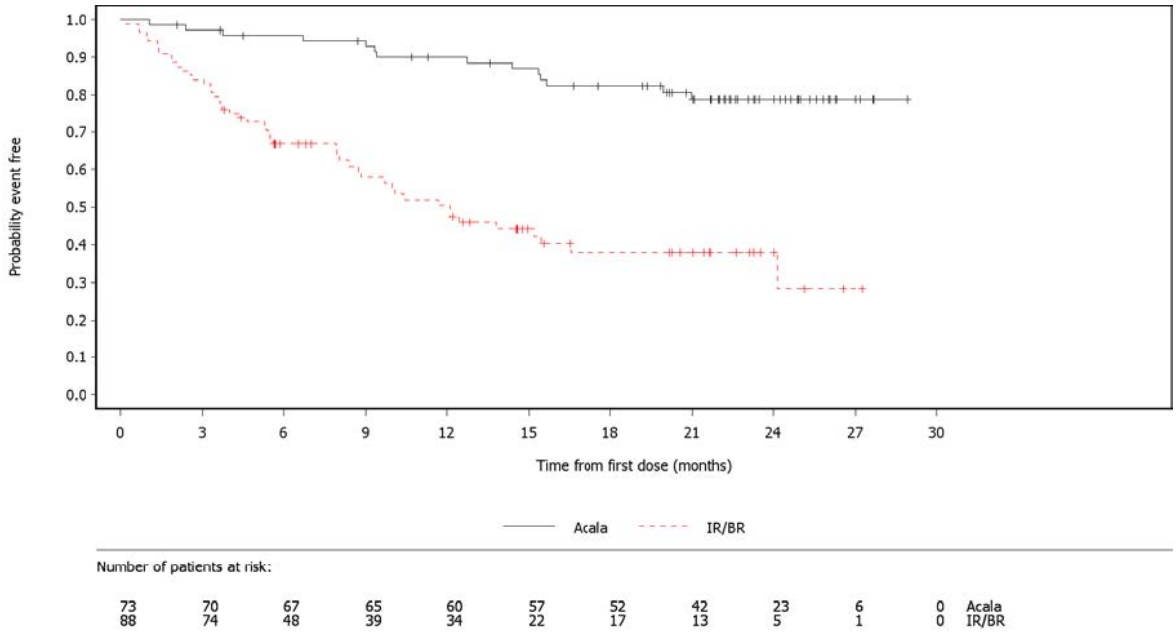

Figure 45: Kaplan-Meier curves, outcome "discontinuation due to AEs", ASCEND study, data cut-off from 1 August 2019

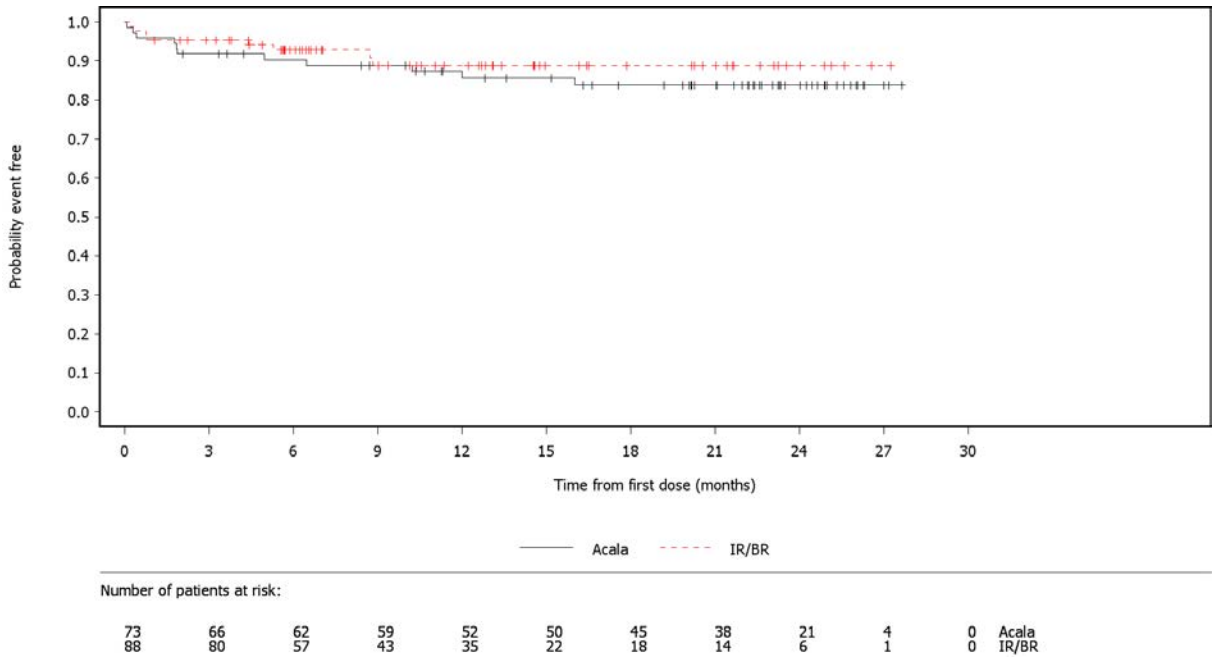

Figure 46: Kaplan-Meier curves, outcome "cardiac disorders" (SOC, AEs), ASCEND study, data cut-off from 1 August 2019

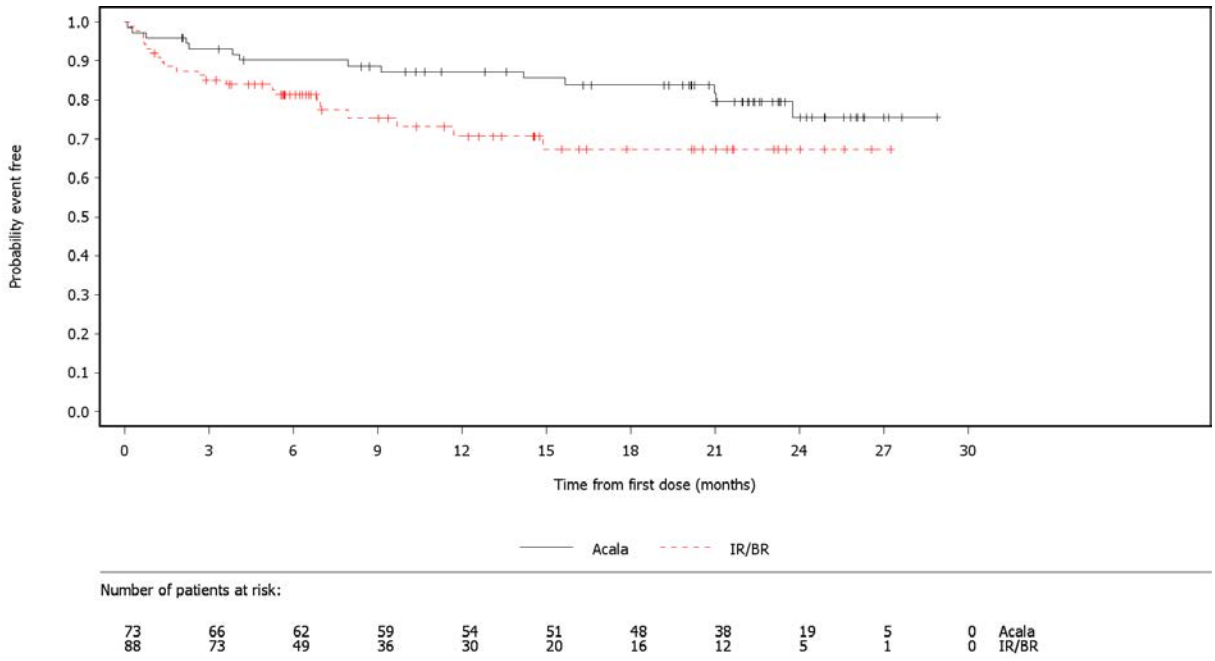

Figure 47: Kaplan-Meier curves, outcome "infections and infestations" (SOC, severe AEs [CTCAE grade ≥ 3]), ASCEND study, data cut-off from 1 August 2019

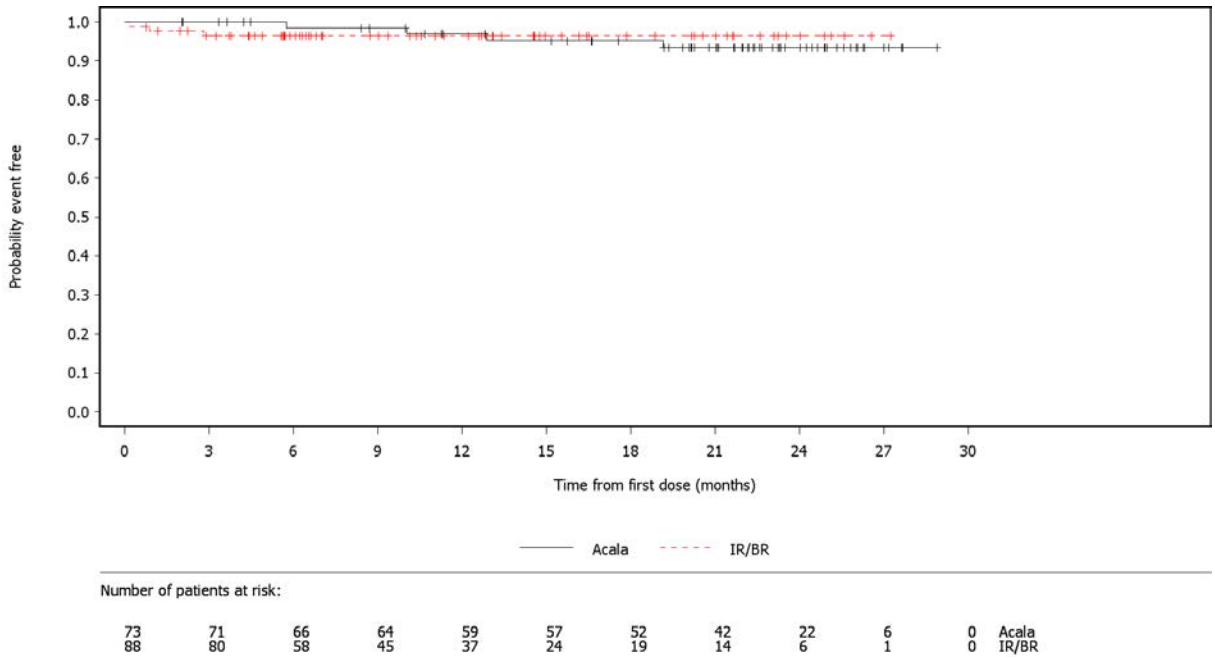

Figure 48: Kaplan-Meier curves, outcome "haemorrhages" (severe AEs [CTCAE grade ≥ 3]), ASCEND study, data cut-off from 1 August 2019

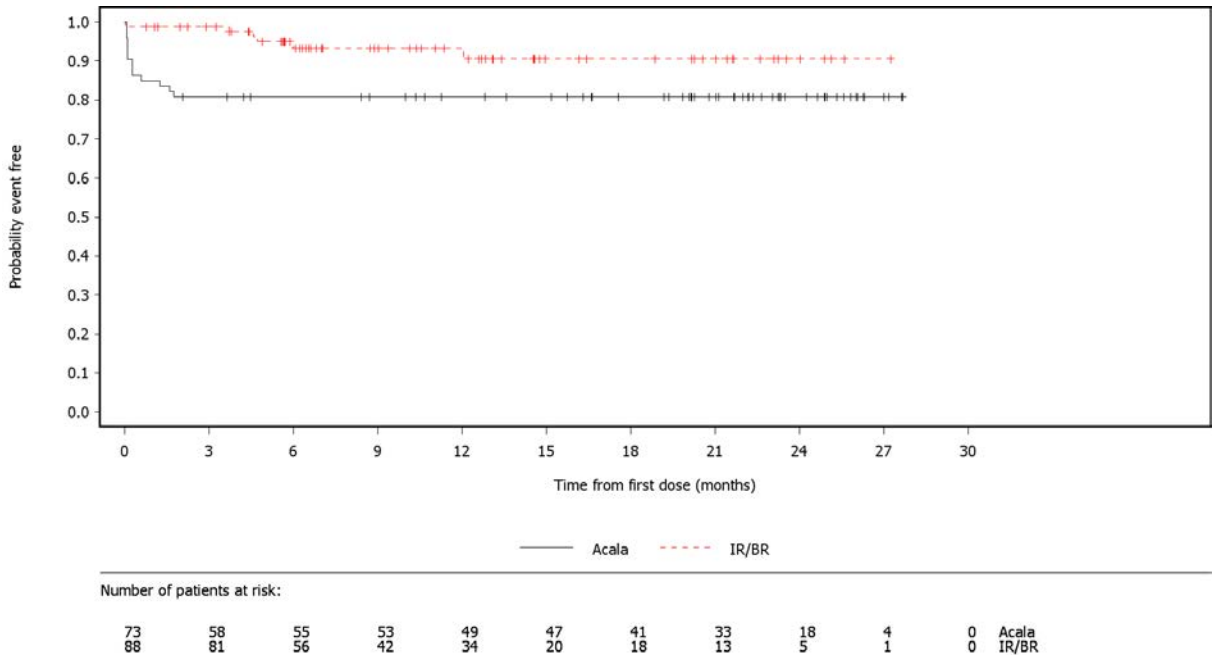

Figure 49: Kaplan-Meier curves, outcome "headache" (PT, AEs), ASCEND study, data cut-off from 1 August 2019

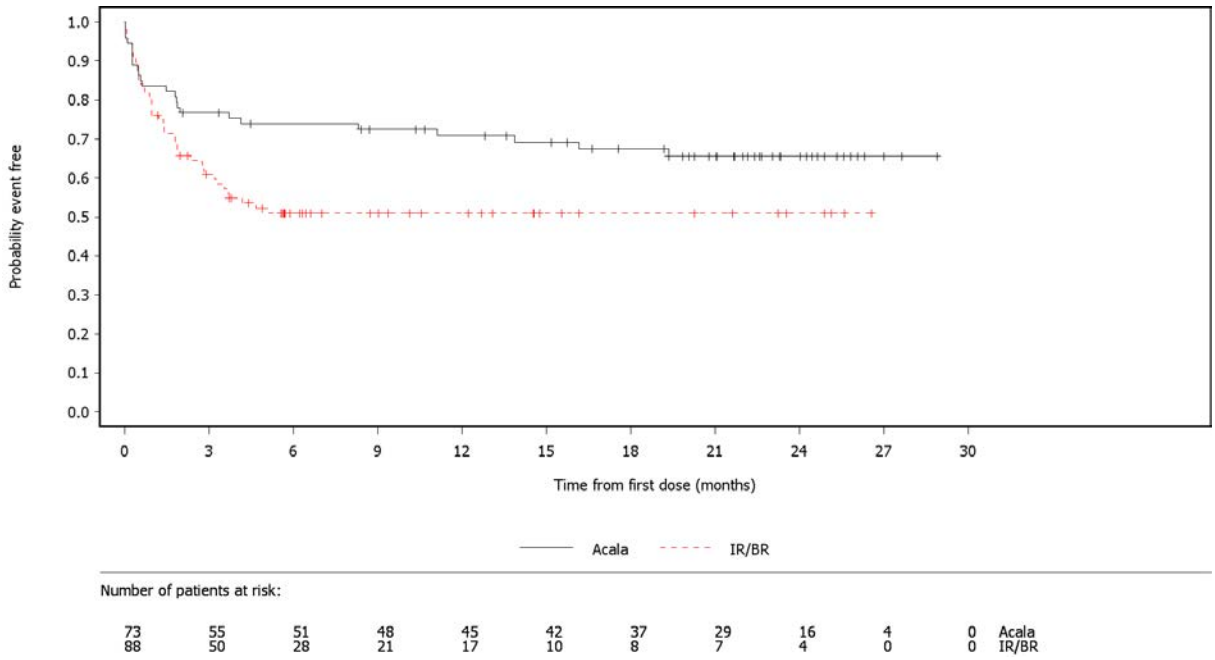

Figure 50: Kaplan-Meier curves, outcome "blood and lymphatic system disorders" (SOC, severe AEs [CTCAE grade ≥ 3]), ASCEND study, data cut-off from 1 August 2019

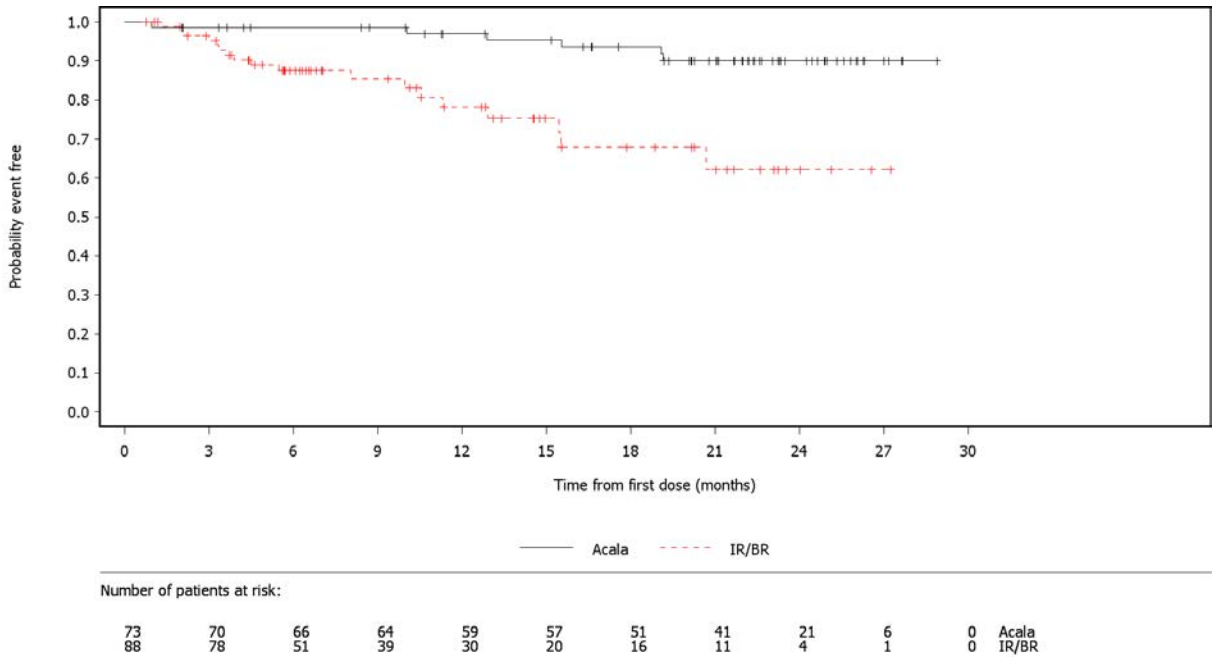

Figure 51: Kaplan-Meier curves, outcome "gastrointestinal disorders" (SOC, severe AEs [CTCAE grade ≥ 3]), ASCEND study, data cut-off from 1 August 2019

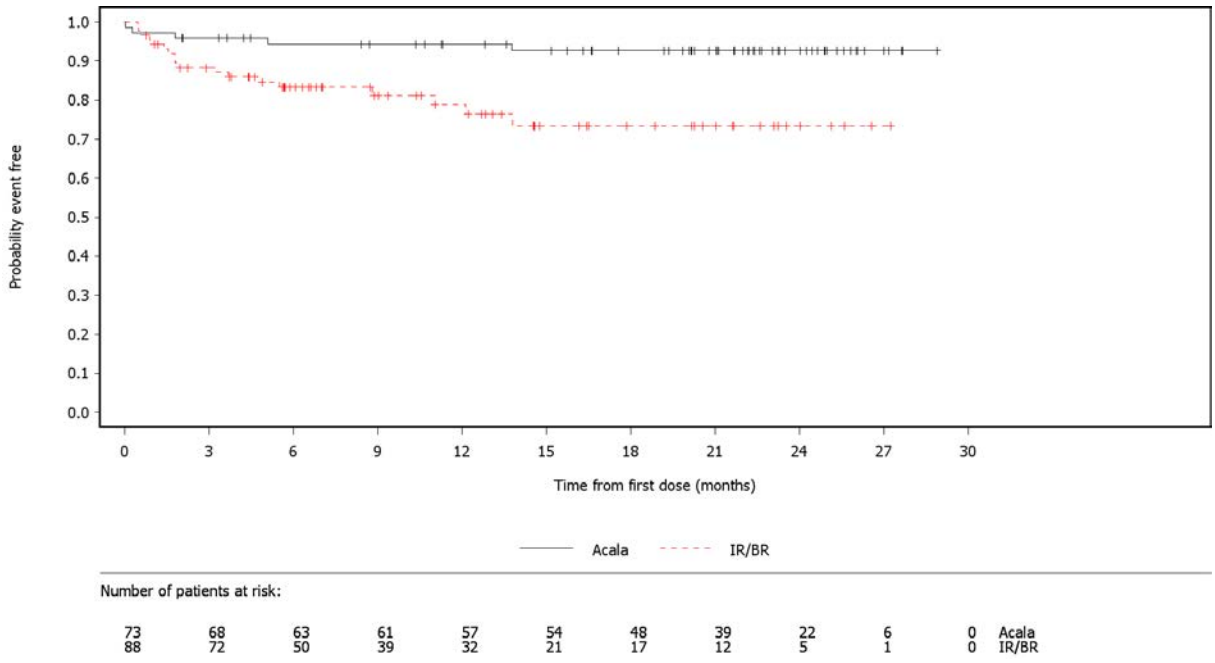

Figure 52: Kaplan-Meier curves, outcome "investigations" (SOC, severe AEs [CTCAE grade ≥ 3]), ASCEND study, data cut-off from 1 August 2019

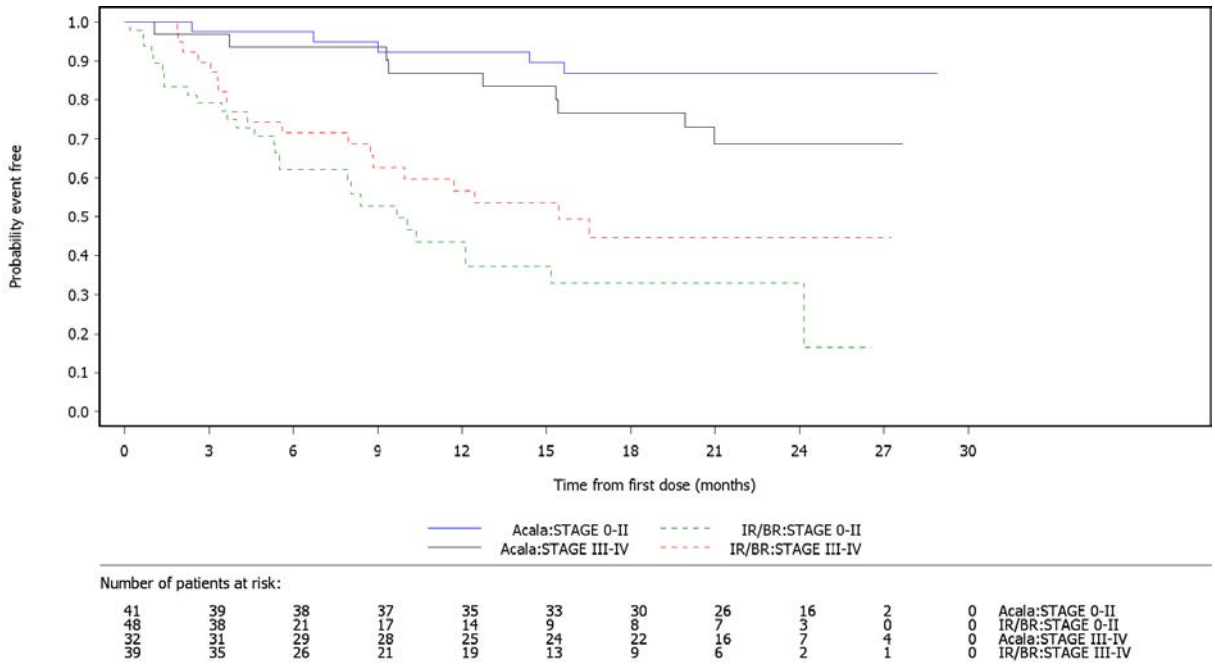

Figure 53: Kaplan-Meier curves, outcome "discontinuation due to AEs", subgroup of Rai stage at baseline (0/I/II vs. III/IV), ASCEND study, data cut-off from 1 August 2019

Appendix E – Results on side effects: adults with CLL; one prior therapy; chemo-immunotherapy suitable

The following tables present events for SOCs and PTs according to the Medical Dictionary for Regulatory Activities (MedDRA) for the overall rates of the outcomes "AEs", "SAEs" and "severe AEs (CTCAE grade ≥ 3), each on the basis of the following criteria:

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

For the outcome "discontinuation due to AEs", a complete presentation of all events (SOCs/PTs) that resulted in discontinuation is provided.

Table 14: Common AEs[a] – RCT, direct comparison: acalabrutinib vs. bendamustine + rituximab (adults with CLL; one prior therapy; chemo-immunotherapy suitable) (multipage table)

Study	**Patients with event n (%)**	
SOC[b] **PT[b]**	**Acalabrutinib** **N = 16**	**Bendamustine + rituximab** **N = 18**
ASCEND		
Overall AE rate	16 (100.0)	15 (83.3)
General disorders and administration site conditions	7 (43.8)	8 (44.4)
Asthenia	2 (12.5)	0 (0)
Fatigue	3 (18.8)	6 (33.3)
Pyrexia	3 (18.8)	4 (22.2)
Influenza like illness	2 (12.5)	1 (5.6)
Oedema peripheral	0 (0)	2 (11.1)
Chills	1 (6.3)	2 (11.1)
Respiratory, thoracic and mediastinal disorders	7 (43.8)	2 (11.1)
Cough	4 (25.0)	2 (11.1)
Skin and subcutaneous tissue disorders	7 (43.8)	3 (16.7)
Rash	2 (12.5)	1 (5.6)
Renal and urinary disorders	2 (12.5)	3 (16.7)
Blood and lymphatic system disorders	5 (31.3)	7 (38.9)
Anaemia	1 (6.3)	3 (16.7)
Neutropenia	0 (0)	6 (33.3)
Thrombocytopenia	1 (6.3)	2 (11.1)
Gastrointestinal disorders	8 (50.0)	8 (44.4)
Diarrhoea	0 (0)	4 (22.2)
Gastrooesophageal reflux disease	2 (12.5)	0 (0)
Constipation	2 (12.5)	4 (22.2)
Nausea	1 (6.3)	4 (22.2)
Immune system disorders	2 (12.5)	1 (5.6)
Nervous system disorders	8 (50.0)	0 (0)
Dysgeusia	2 (12.5)	0 (0)
Headache	7 (43.8)	0 (0)
Vascular disorders	3 (18.8)	5 (27.8)
Hypotension	1 (6.3)	2 (11.1)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	5 (31.3)	1 (5.6)
Squamous cell carcinoma of skin	2 (12.5)	0 (0)

Table 14: Common AEs[a] – RCT, direct comparison: acalabrutinib vs. bendamustine + rituximab (adults with CLL; one prior therapy; chemo-immunotherapy suitable) (multipage table)

Study	**Patients with event n (%)**	
SOC[b] **PT[b]**	**Acalabrutinib** **N = 16**	**Bendamustine + rituximab** **N = 18**
Infections and infestations	12 (75.0)	10 (55.6)
Bronchitis	3 (18.8)	2 (11.1)
Urinary tract infection	2 (12.5)	0 (0)
Upper respiratory tract infection	4 (25.0)	4 (22.2)
Lower respiratory tract infection	2 (12.5)	0 (0)
Nasopharyngitis	2 (12.5)	1 (5.6)
Pharyngitis	2 (12.5)	0 (0)
Rhinitis	2 (12.5)	2 (11.1)
Psychiatric disorders	2 (12.5)	0 (0)
Insomnia	2 (12.5)	0 (0)
Musculoskeletal and connective tissue disorders	7 (43.8)	2 (11.1)
Arthralgia	2 (12.5)	1 (5.6)
Back pain	2 (12.5)	0 (0)
Musculoskeletal pain	2 (12.5)	0 (0)
Metabolism and nutrition disorders	6 (37.5)	2 (11.1)
Hyperglycaemia	2 (12.5)	0 (0)
Investigations	2 (12.5)	6 (33.3)
Alanine aminotransferase increased	0 (0)	2 (11.1)
Aspartate aminotransferase increased	0 (0)	2 (11.1)
Blood creatinine increased	1 (6.3)	2 (11.1)
Injury, poisoning and procedural complications	4 (25.0)	5 (27.8)
Infusion related reactions	0 (0)	5 (27.8)

a. Events that occurred in ≥ 10% of the patients in at least one study arm.
b. MedDRA version 21.1; SOCs and PTs taken from Module 4.

AE: adverse event; CLL: chronic lymphocytic leukaemia; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least one event; N: number of patients who received at least one dose of the study medication, analysed according to the first study medication actually taken; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class

Table 15: Common SAEs[a] – RCT, direct comparison: acalabrutinib vs. bendamustine + rituximab (adults with CLL; one prior therapy; chemo-immunotherapy suitable)

Study	Patients with event n (%)	
SOC[b] PT[b]	Acalabrutinib N = 16	Bendamustine + rituximab N = 18
ASCEND		
Overall SAE rate	4 (25.0)	5 (27.8)
General disorders and administration site conditions	0 (0)	1 (5.6)
Pyrexia	0 (0)	1 (5.6)
Respiratory, thoracic and mediastinal disorders	1 (6.3)	0 (0)
Pulmonary embolism	1 (6.3)	0 (0)
Blood and lymphatic system disorders	0 (0)	2 (11.1)
Anaemia	0 (0)	1 (5.6)
Febrile neutropenia	0 (0)	1 (5.6)
Cardiac disorders	0 (0)	1 (5.6)
Acute myocardial infarction	0 (0)	1 (5.6)
Angina pectoris	0 (0)	1 (5.6)
Myocardial infarction	0 (0)	1 (5.6)
Infections and infestations	3 (18.8)	2 (11.1)
Influenza	0 (0)	1 (5.6)
Urinary tract infection	2 (12.5)	0 (0)
Upper respiratory tract infection	0 (0)	1 (5.6)
Infection in connection with a medical device	1 (6.3)	0 (0)
Postoperative wound infection	1 (6.3)	0 (0)
Gastroenteritis viral	0 (0)	1 (5.6)
Injury, poisoning and procedural complications	1 (6.3)	0 (0)
Spinal compression fracture	1 (6.3)	0 (0)

a. Events that occurred in ≥ 5% of the patients in at least one study arm.
b. MedDRA version 21.1; SOCs and PTs taken from Module 4.

CLL: chronic lymphocytic leukaemia; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least one event; N: number of patients who received at least one dose of the study medication, analysed according to the first study medication actually taken; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class

Table 16: Common severe AEs[a] (CTCAE grade ≥ 3) – RCT, direct comparison: acalabrutinib vs. bendamustine + rituximab (adults with CLL; one prior therapy; chemo-immunotherapy suitable) (multipage table)

Study	**Patients with event n (%)**	
SOC[b] **PT[b]**	**Acalabrutinib** **N = 16**	**Bendamustine + rituximab** **N = 18**
ASCEND		
Overall rate of severe AEs (CTCAE grade ≥ 3)	5 (31.3)	8 (44.4)
General disorders and administration site conditions	0 (0)	2 (11.1)
Fatigue	0 (0)	1 (5.6)
Pyrexia	0 (0)	1 (5.6)
Respiratory, thoracic and mediastinal disorders	2 (12.5)	0 (0)
Pulmonary embolism	1 (6.3)	0 (0)
Nasal polyps	1 (6.3)	0 (0)
Skin and subcutaneous tissue disorders	0 (0)	1 (5.6)
Urticaria	0 (0)	1 (5.6)
Blood and lymphatic system disorders	1 (6.3)	7 (38.9)
Anaemia	1 (6.3)	3 (16.7)
Febrile neutropenia	0 (0)	1 (5.6)
Neutropenia	0 (0)	6 (33.3)
Gastrointestinal disorders	1 (6.3)	2 (11.1)
Dental caries	1 (6.3)	0 (0)
Constipation	0 (0)	2 (11.1)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0 (0)	1 (5.6)
Squamous cell carcinoma of skin	0 (0)	1 (5.6)
Cardiac disorders	0 (0)	1 (5.6)
Acute myocardial infarction	0 (0)	1 (5.6)
Angina pectoris	0 (0)	1 (5.6)
Myocardial infarction	0 (0)	1 (5.6)
Infections and infestations	3 (18.8)	2 (11.1)
Influenza	0 (0)	1 (5.6)
Urinary tract infection	2 (12.5)	0 (0)
Upper respiratory tract infection	0 (0)	1 (5.6)
Infection in connection with a medical device	1 (6.3)	0 (0)
Postoperative wound infection	1 (6.3)	0 (0)
Sinusitis	1 (6.3)	0 (0)
Gastroenteritis viral	0 (0)	1 (5.6)

Table 16: Common severe AEs[a] (CTCAE grade ≥ 3) – RCT, direct comparison: acalabrutinib vs. bendamustine + rituximab (adults with CLL; one prior therapy; chemo-immunotherapy suitable) (multipage table)

Study	**Patients with event n (%)**	
SOC[b] **PT[b]**	**Acalabrutinib** **N = 16**	**Bendamustine + rituximab** **N = 18**
Musculoskeletal and connective tissue disorders	1 (6.3)	0 (0)
Osteoarthritis	1 (6.3)	0 (0)
Metabolism and nutrition disorders	3 (18.8)	0 (0)
Hyperglycaemia	1 (6.3)	0 (0)
Hyperuricaemia	1 (6.3)	0 (0)
Hyponatraemia	1 (6.3)	0 (0)
Investigations	0 (0)	3 (16.7)
Alanine aminotransferase increased	0 (0)	1 (5.6)
Aspartate aminotransferase increased	0 (0)	1 (5.6)
Neutrophil count decreased	0 (0)	1 (5.6)
Injury, poisoning and procedural complications	1 (6.3)	0 (0)
Spinal compression fracture	1 (6.3)	0 (0)

a. Events that occurred in ≥ 5% of the patients in at least one study arm.
b. MedDRA version 21.1; SOCs and PTs taken from Module 4.

AE: adverse event; CLL: chronic lymphocytic leukaemia; CTCAE: Common Terminology Criteria for Adverse Events; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least one event; N: number of patients who received at least one dose of the study medication, analysed according to the first study medication actually taken; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class

Table 17: Discontinuation due to AEs – RCT, direct comparison: acalabrutinib vs. bendamustine + rituximab (adults with CLL; one prior therapy; chemo-immunotherapy suitable)

Study	**Patients with event n (%)**	
SOC[a] **PT[a]**	**Acalabrutinib** **N = 16**	**Bendamustine + rituximab** **N = 18**
ASCEND		
Overall rate of discontinuations due to AEs[b]	0 (0)	1 (5.6)
Skin and subcutaneous tissue disorders	0 (0)	1 (5.6)
Urticaria	0 (0)	1 (5.6)

a. MedDRA version 21.1; SOCs and PTs taken from Module 4.
b. If one of the components was discontinued prematurely in a combination therapy, the entire therapy was considered discontinued.

AE: adverse event; CLL: chronic lymphocytic leukaemia; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least one event; N: number of patients who received at least one dose of the study medication, analysed according to the first study medication actually taken; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class

Appendix F – Results on side effects: adults with CLL; ≥ 2 prior therapies

The following tables present events for SOCs and PTs according to the Medical Dictionary for Regulatory Activities (MedDRA) for the overall rates of the outcomes "AEs", "SAEs" and "severe AEs (CTCAE grade ≥ 3), each on the basis of the following criteria:

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

For the outcome "discontinuation due to AEs", a complete presentation of all events (SOCs/PTs) that resulted in discontinuation is provided.

Table 18: Common AEs[a] – RCT, direct comparison: acalabrutinib vs. bendamustine + rituximab/idelalisib + rituximab (adults with CLL; ≥ 2 prior therapies) (multipage table)

Study	**Patients with event n (%)**	
SOC[b] **PT[b]**	**Acalabrutinib** **N = 73**	**Bendamustine + rituximab/idelalisib + rituximab** **N = 88**
ASCEND		
Overall AE rate	70 (95.9)	83 (94.3)
General disorders and administration site conditions	30 (41.1)	38 (43.2)
Fatigue	10 (13.7)	11 (12.5)
Pyrexia	13 (17.8)	16 (18.2)
Respiratory, thoracic and mediastinal disorders	27 (37.0)	24 (27.3)
Cough	12 (16.4)	12 (13.6)
Skin and subcutaneous tissue disorders	18 (24.7)	20 (22.7)
Blood and lymphatic system disorders	32 (43.8)	50 (56.8)
Anaemia	14 (19.2)	8 (9.1)
Neutropenia	16 (21.9)	40 (45.5)
Thrombocytopenia	8 (11.0)	14 (15.9)

Table 18: Common AEs[a] – RCT, direct comparison: acalabrutinib vs. bendamustine + rituximab/idelalisib + rituximab (adults with CLL; ≥ 2 prior therapies) (multipage table)

Study	**Patients with event n (%)**	
SOC[b] **PT[b]**	**Acalabrutinib** **N = 73**	**Bendamustine + rituximab/idelalisib + rituximab** **N = 88**
Gastrointestinal disorders	30 (41.1)	55 (62.5)
Diarrhoea	14 (19.2)	34 (38.6)
Nausea	7 (9.6)	17 (19.3)
Nervous system disorders	21 (28.8)	16 (18.2)
Headache	14 (19.2)	6 (6.8)
Vascular disorders	13 (17.8)	12 (13.6)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	15 (20.5)	6 (6.8)
Cardiac disorders	11 (15.1)	8 (9.1)
Infections and infestations	47 (64.4)	58 (65.9)
Respiratory tract infections	9 (12.3)	6 (6.8)
Bronchitis	9 (12.3)	5 (5.7)
Upper respiratory tract infection	15 (20.5)	10 (11.4)
Pneumonia	13 (17.8)	12 (13.6)
Psychiatric disorders	9 (12.3)	9 (10.2)
Musculoskeletal and connective tissue disorders	25 (34.2)	15 (17.0)
Arthralgia	9 (12.3)	2 (2.3)
Metabolism and nutrition disorders	13 (17.8)	21 (23.9)
Investigations	14 (19.2)	29 (33.0)
Neutrophil count decreased	2 (2.7)	9 (10.2)
Injury, poisoning and procedural complications	16 (21.9)	18 (20.5)
Contusion	8 (11.0)	3 (3.4)
Infusion related reaction	0 (0)	11 (12.5)

a. Events that occurred in ≥ 10% of the patients in at least one study arm.
b. MedDRA version 21.1; SOCs and PTs taken from Module 4.

AE: adverse event; CLL: chronic lymphocytic leukaemia; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least one event; N: number of patients who received at least one dose of the study medication, analysed according to the first study medication actually taken; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class

Table 19: Common SAEs[a] – RCT, direct comparison: acalabrutinib vs. bendamustine + rituximab/idelalisib + rituximab (adults with CLL; ≥ 2 prior therapies)

Study	**Patients with event n (%)**	
SOC[b] **PT[b]**	**Acalabrutinib** **N = 73**	**Bendamustine + rituximab/idelalisib + rituximab** **N = 88**
ASCEND		
Overall SAE rate	27 (37.0)	42 (47.7)
General disorders and administration site conditions	3 (4.1)	10 (11.4)
Pyrexia	1 (1.4)	6 (6.8)
Respiratory, thoracic and mediastinal disorders	7 (9.6)	5 (5.7)
Blood and lymphatic system disorders	3 (4.1)	7 (8.0)
Gastrointestinal disorders	3 (4.1)	11 (12.5)
Diarrhoea	0 (0)	8 (9.1)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	7 (9.6)	1 (1.1)
Cardiac disorders	4 (5.5)	6 (6.8)
Infections and infestations	11 (15.1)	19 (21.6)
Pneumonia	6 (8.2)	9 (10.2)

a. Events that occurred in ≥ 5% of the patients in at least one study arm.
b. MedDRA version 21.1; SOCs and PTs taken from Module 4.

CLL: chronic lymphocytic leukaemia; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least one event; N: number of patients who received at least one dose of the study medication, analysed according to the first study medication actually taken; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class

Table 20: Common severe AEs[a] (CTCAE grade ≥ 3) – RCT, direct comparison: acalabrutinib vs. bendamustine + rituximab/idelalisib + rituximab (adults with CLL; ≥ 2 prior therapies)

Study	**Patients with event n (%)**	
SOC[b] **PT[b]**	**Acalabrutinib** **N = 73**	**Bendamustine + rituximab/idelalisib + rituximab** **N = 88**
ASCEND		
Overall rate of severe AEs (CTCAE grade ≥ 3)	46 (63.0)	71 (80.7)
General disorders and administration site conditions	6 (8.2)	8 (9.1)
Pyrexia	1 (1.4)	6 (6.8)
Respiratory, thoracic and mediastinal disorders	8 (11.0)	5 (5.7)
Blood and lymphatic system disorders	24 (32.9)	42 (47.7)
Anaemia	12 (16.4)	6 (6.8)
Neutropenia	13 (17.8)	33 (37.5)
Thrombocytopenia	3 (4.1)	7 (8.0)
Gastrointestinal disorders	6 (8.2)	18 (20.5)
Diarrhoea	2 (2.7)	16 (18.2)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	6 (8.2)	1 (1.1)
Cardiac disorders	5 (6.8)	6 (6.8)
Infections and infestations	14 (19.2)	22 (25.0)
Pneumonia	6 (8.2)	8 (9.1)
Musculoskeletal and connective tissue disorders	4 (5.5)	3 (3.4)
Investigations	5 (6.8)	18 (20.5)
Alanine aminotransferase increased	1 (1.4)	6 (6.8)
Neutrophil count decreased	1 (1.4)	9 (10.2)
Injury, poisoning and procedural complications	3 (4.1)	5 (5.7)

a. Events that occurred in ≥ 5% of the patients in at least one study arm.
b. MedDRA version 21.1; SOCs and PTs taken from Module 4.

AE: adverse event; CLL: chronic lymphocytic leukaemia; CTCAE: Common Terminology Criteria for Adverse Events; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least one event; N: number of patients who received at least one dose of the study medication, analysed according to the first study medication actually taken; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class

Table 21: Discontinuation due to AEs – RCT, direct comparison: acalabrutinib vs. bendamustine + rituximab/idelalisib + rituximab (adults with CLL; ≥ 2 prior therapies) (multipage table)

Study	Patients with event n (%)	
SOC[a] PT[a]	Acalabrutinib N = 73	Bendamustine + rituximab/idelalisib + rituximab N = 88
ASCEND		
Overall rate of discontinuations due to AEs[b]	14 (19.2)	48 (54.5)
Respiratory, thoracic and mediastinal disorders	0 (0)	4 (4.5)
Organizing pneumonia	0 (0)	1 (1.1)
Pneumonitis	0 (0)	3 (3.4)
Skin and subcutaneous tissue disorders	0 (0)	1 (1.1)
Rash maculo-papular	0 (0)	1 (1.1)
Blood and lymphatic system disorders	1 (1.4)	3 (3.4)
Haemolytic anaemia	0 (0)	1 (1.1)
Immune thrombocytopenic purpura	1 (1.4)	0 (0)
Neutropenia	0 (0)	1 (1.1)
Thrombocytopenia	0 (0)	1 (1.1)
Gastrointestinal disorders	1 (1.4)	11 (12.5)
Abdominal pain	1 (1.4)	0 (0)
Diarrhoea	0 (0)	8 (9.1)
Dyspepsia	0 (0)	1 (1.1)
Colitis	0 (0)	2 (2.3)
Nervous system disorders	3 (4.1)	0 (0)
Hemiparesis	1 (1.4)	0 (0)
Headache	1 (1.4)	0 (0)
Cerebral ischaemia	1 (1.4)	0 (0)
Vascular disorders	1 (1.4)	0 (0)
Aortic aneurysm	1 (1.4)	0 (0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	6 (8.2)	1 (1.1)
Adenocarcinoma gastric	0 (0)	1 (1.1)
Brain neoplasm malignant	1 (1.4)	0 (0)
Metastatic squamous cell carcinoma	1 (1.4)	0 (0)
Brain neoplasm	1 (1.4)	0 (0)
Squamous cell carcinoma of skin	2 (2.7)	0 (0)
Prostate cancer	1 (1.4)	0 (0)

Table 21: Discontinuation due to AEs – RCT, direct comparison: acalabrutinib vs. bendamustine + rituximab/idelalisib + rituximab (adults with CLL; ≥ 2 prior therapies) (multipage table)

Study	**Patients with event n (%)**	
SOC[a] **PT[a]**	**Acalabrutinib** **N = 73**	**Bendamustine + rituximab/idelalisib + rituximab** **N = 88**
Cardiac disorders	1 (1.4)	4 (4.5)
Cardiac failure acute	0 (0)	1 (1.1)
Cardiac failure chronic	0 (0)	1 (1.1)
Cardiopulmonary failure	0 (0)	1 (1.1)
Myocardial infarction	0 (0)	1 (1.1)
Cardiac failure congestive	1 (1.4)	0 (0)
Infections and infestations	1 (1.4)	13 (14.8)
Bronchitis	1 (1.4)	1 (1.1)
Gastroenteritis	0 (0)	1 (1.1)
Hepatitis E	0 (0)	1 (1.1)
Pneumocystis jirovecii pneumonia	0 (0)	1 (1.1)
Pneumonia	0 (0)	5 (5.7)
Pneumococcal pneumonia	0 (0)	1 (1.1)
Hepatitis B reactivation	0 (0)	1 (1.1)
Urosepsis	0 (0)	1 (1.1)
Cytomegalovirus infection	0 (0)	1 (1.1)
Hepatobiliary disorders	0 (0)	3 (3.4)
Hepatotoxicity	0 (0)	2 (2.3)
Liver injury	0 (0)	1 (1.1)
Musculoskeletal and connective tissue disorders	0 (0)	1 (1.1)
Pain in extremity	0 (0)	1 (1.1)
Investigations	1 (1.4)	7 (8.0)
Alanine aminotransferase increased	1 (1.4)	3 (3.4)
Aspartate aminotransferase increased	0 (0)	3 (3.4)
Hepatic enzyme increased	0 (0)	1 (1.1)
Neutrophil count decreased	0 (0)	2 (2.3)
Transaminases increased	0 (0)	1 (1.1)
Injury, poisoning and procedural complications	0 (0)	2 (2.3)
Infusion related reaction	0 (0)	2 (2.3)

a. MedDRA version 21.1; SOCs and PTs taken from Module 4.
b. If one of the components was discontinued prematurely in a combination therapy, the entire therapy was considered discontinued.

Table 21: Discontinuation due to AEs – RCT, direct comparison: acalabrutinib vs. bendamustine + rituximab/idelalisib + rituximab (adults with CLL; ≥ 2 prior therapies) (multipage table)

Study	**Patients with event n (%)**	
SOC[a] **PT[a]**	**Acalabrutinib** **N = 73**	**Bendamustine + rituximab/idelalisib + rituximab** **N = 88**
AE: adverse event; CLL: chronic lymphocytic leukaemia; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least one event; N: number of patients who received at least one dose of the study medication, analysed according to the first study medication actually taken; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class		