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Acalabrutinib (pretreated chronic lymphocytic leukaemia) –

Addendum to Commission A20-105[1]

Addendum

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Table of contents

List of tables

Page

List of figures

Page

List of abbreviations

Abbreviation	Meaning
17p deletion	deletion of the short arm of chromosome 17
ACT	appropriate comparator therapy
AE	adverse event
CLL	chronic lymphocytic leukaemia
CTCAE	Common Terminology Criteria for Adverse Events
DGHO	Deutsche Gesellschaft für Hämatologie und Onkologie (German Society for Haematology and Medical Oncology)
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EMA	European Medicines Agency
EORTC	European Organisation for Research and Treatment of Cancer
EQ-5D	European Quality of Life-5 Dimensions
FACIT-Fatigue	Functional Assessment of Chronic Illness Therapy-Fatigue
FIS	fatigue impact score
FSS	fatigue symptom score
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
GFS	global fatigue score
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
iwCLL	International Workshop on Chronic Lymphocytic Leukemia
MMRM	mixed-effects model with repeated measures
PFS	progression-free survival
QLQ-C30	Quality of Life Questionnaire-Core 30
RCT	randomized controlled trial
SOC	System Organ Class
SPC	Summary of Product Characteristics
TP53 mutation	mutation of the tumour protein p53
VAS	visual analogue scale

1 Background

On 27 April 2021, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Commission A21-105 (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. Therefore, the analyses presented by the company could not be used for the dossier assessment. 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]. The company also included aspects from the simultaneous dossier assessments of acalabrutinib as monotherapy or in combination with obinutuzumab in previously untreated CLL (A20-103 [4] and A20-104 [5]) and submitted corresponding data and analyses.

To be able to decide on the added benefit, the G-BA needs further analyses in this procedure. The G-BA therefore 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, taking into account the information provided in the dossier.

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 Assessment

In accordance with the G-BA's specification of the ACT, 3 research questions resulted for the benefit assessment of acalabrutinib in adult patients with CLL who have received at least one prior therapy. These are presented in Table 1:

Table 1: Research questions of the benefit assessment of acalabrutinib

Research question	Subindication[a]	ACT[b]
1	Adult patients with CLL after one prior therapy who have no 17p deletion or TP53 mutation and for whom chemo-immunotherapy[c] is indicated	Patient-specific therapy[d] choosing from FCR, BR, venetoclax in combination with rituximab and ClbR
2	Adult patients with CLL after one prior therapy who have 17p deletion or TP53 mutation or for whom chemo-immunotherapy[c] is not indicated for other reasons	Ibrutinib or **idelalisib + rituximab** or best supportive care[e, f]
3	Adult patients with CLL after at least 2 prior therapies	Patient-specific therapy[d] choosing from ibrutinib, idelalisib in combination with rituximab, venetoclax in combination with rituximab, FCR, BR, ClbR, ibrutinib in combination with BR, and best supportive care[f]

a. It is assumed that the patients require treatment and that allogeneic stem cell transplantation is not indicated at the time point of treatment.
b. Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in **bold**.
c. Or therapy with rituximab in combination with venetoclax.
d. Taking into account the molecular-cytogenetic characteristics of the disease, the general condition and the success and tolerability of the prior therapy. For the implementation of patient-specific therapy, it is expected that a choice of several treatment options is available, allowing a patient-specific therapy decision (multi-comparator study). The choice and, if necessary, limitation of treatment options must be justified.
e. Only for patients with failure of a previous therapy with ibrutinib as monotherapy or idelalisib + rituximab.
f. Best supportive care refers to the therapy that provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life.

17p deletion: deletion of the short arm of chromosome 17; ACT: appropriate comparator therapy;
BR: rituximab in combination with bendamustine; ClbR: rituximab in combination with chlorambucil;
CLL: chronic lymphocytic leukaemia; FCR: rituximab in combination with fludarabine and cyclophosphamide;
G-BA: Federal Joint Committee; TP53 mutation: mutation of the tumour protein p53

The company's study pool comprised the ASCEND study. With its comments [3], the company presented results for 3 subpopulations of the RCT ASCEND to address the 3 research questions arising from the ACT of the G-BA.

The ASCEND study is a 2-arm, randomized, open-label, multicentre study comparing acalabrutinib with bendamustine + rituximab or idelalisib + rituximab, depending on the investigator's choice. It included adult patients with relapsed or refractory CLL requiring treatment according to the International Workshop on Chronic Lymphocytic Leukemia

(iwCLL) criteria (2008) who had received at least one prior therapy. Patients pretreated with a B-cell lymphoma 2 protein inhibitor, a Bruton tyrosine kinase inhibitor, or a phosphatidylinositol 3-kinase inhibitor were excluded from the study. Information on the study design can be found in benefit assessment A20-105 [1].

The following Sections 2.1 to 2.3 contain the assessment of the subpopulations presented by the company.

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

2.1.1 Results on added benefit

The company presented analyses of a subpopulation of the ASCEND study for research question 1 (adults with CLL, one prior therapy, chemo-immunotherapy suitable). In this subpopulation, it included those patients with one prior therapy who, at the discretion of the investigators, were to receive bendamustine + rituximab if randomized to the comparator arm (17 patients in the intervention arm, 19 in the comparator arm).

The data presented by the company are unsuitable for the assessment of the added benefit of acalabrutinib in comparison with the ACT. The company did not provide any information on the criteria used by the investigators to assign patients to treatment with bendamustine + rituximab. All patients in the ASCEND study were already pretreated with chemo-immunotherapy. For such patients, repeated chemo-immunotherapy is rather a secondary therapy option [6] (see also explanations in Section 2.2.1 on research question 2). In addition, in deviation from the ACT specified by the G-BA, the decision for the therapy in the comparator arm was not made on an individual patient basis. Instead, all patients in the subpopulation operationalized by the company in research question 1 received chemo-immunotherapy with bendamustine + rituximab (for explanation, see also dossier assessment A20-105 [1]).

2.1.2 Probability and extent of added benefit

The company did not subsequently submit any relevant data for the assessment of the added benefit of acalabrutinib in comparison with the ACT in adult patients with CLL after one prior therapy who have no deletion of the short arm of chromosome 17 (17p deletion) or mutation of the tumour protein p53 (TP53 mutation) and for whom chemo-immunotherapy is indicated. This resulted in no change in comparison with dossier assessment A20-105 [1]; an added benefit is not proven.

2.2 Research question 2: adults with CLL; one prior therapy; chemo-immunotherapy unsuitable

2.2.1 Study characteristics

Table 2 describes the intervention of the ASCEND study.

Table 2: Characteristics of the intervention – RCT, direct comparison: acalabrutinib vs. idelalisib + rituximab (adults with CLL; one prior therapy; chemo-immunotherapy unsuitable)

Study	Intervention	Comparison
ASCEND	Acalabrutinib 200 mg (100 mg 2 x daily) orally until disease progression or unacceptable toxicity	Idelalisib 300 mg (150 mg 2 x 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) [7]. Treatment with idelalisib in combination with rituximab followed an established dosing regimen [8].

Planned duration of follow-up observation

Table 3 shows the planned duration of follow-up observation of the patients for the individual outcomes.

Table 3: Planned duration of follow-up observation – RCT, direct comparison: acalabrutinib vs. idelalisib + rituximab (adults with CLL; one prior therapy; chemo-immunotherapy unsuitable)

Study **Outcome category** **Outcome**	**Planned follow-up observation**
ASCEND	
Mortality	
Overall survival	▪ Until death or lost to follow-up
Morbidity	
Symptoms (FACIT-Fatigue, EORTC QLQ-C30), health status (EQ-5D VAS), health-related symptoms[a]	▪ Until disease progression
Health-related quality of life (EORTC QLQ-C30)	▪ Until disease progression
Side effects	
All outcomes in the category of side effects	▪ Up to at most 30 days after the last dose of the study medication or until disease progression (whichever is first)
a. Weight loss, fatigue, fever, night sweats.	
EORTC: European Organisation for Research and Treatment of Cancer; EQ-5D: European Quality of Life-5 Dimensions; FACIT: Functional Assessment of Chronic Illness Therapy; ND: no data; QLQ-C30: Quality of Life Questionnaire-Core-30; RCT: randomized controlled trial; VAS: visual analogue scale	

The observation periods for the outcomes "morbidity", "health-related quality of life" and "side effects" were systematically shortened because they were only recorded for the time period of treatment with the study medication (plus 30 days) or until disease progression. To be able to draw a reliable conclusion on the total study period or the time until death of the patients, it would be necessary, however, to record these outcomes over the total period of time, as was the case for survival.

Data cut-offs and analyses

For the ASCEND study, 2 data cut-offs were available in the company's dossier:

- first data cut-off from 15 January 2019 (planned interim analysis on achieving a total of 79 progression-free survival [PFS] events)
- second data cut-off from 1 August 2019 (not prespecified) The company stated in the dossier that a safety update had been submitted to the European Medicines Agency (EMA) on this date.

The company presented analyses only for the first data cut-off for the outcome categories of morbidity and health-related quality of life, and only for the second data cut-off for the outcome categories of mortality and side effects. The data cut-offs considered by the company were used for the present benefit assessment.

Subpopulations relevant for research question 2

For research question 2 (adults with CLL; one prior therapy who have 17p deletion or TP53 mutation or for whom chemo-immunotherapy is not indicated for other reasons), the company presented analyses of a subpopulation of those patients with one prior therapy who, at the discretion of the investigators, were to receive idelalisib + rituximab if randomized to the comparator arm (65 patients in the intervention arm, 48 in the comparator arm).

Based on the information on cytogenetics (see Table 4), 27% of the patients assigned by the company to research question 2 had 17p deletion or TP53 mutation. Furthermore, 27% had a complex karyotype. According to guidelines, chemo-immunotherapy is no longer an option for these patients [6,9,10]. It is not clear from the data provided by the company why chemo-immunotherapy was not indicated for the other patients included in the subpopulation by the company.

The ASCEND study only included patients who had received chemo-immunotherapy as first-line therapy. In the second-line setting, chemo-immunotherapy is listed as a treatment option in the CLL guidelines only in the case of late relapse [6,9,10]. In the case of good response and a remission duration of at least 2 to 3 years, the German Society for Haematology and Medical Oncology (DGHO) considers repeated chemo-immunotherapy only as a secondary therapy option [6]. For patients with refractory CLL, who were also included in the ASCEND study, treatment with chemo-immunotherapy is not a regular treatment option according to the guidelines [6,9,10]. In the commenting procedure, the company did not provide information on the pretreatment and remission duration of the patients in the subpopulation. Therefore, it remains unclear whether chemo-immunotherapy would have been an option for a relevant proportion of patients.

The data of the subpopulation presented by the company were used for research question 2. However, the certainty of conclusions of the results is limited due to the remaining uncertainty.

Characteristics of the relevant subpopulation

Table 4 shows the characteristics of the patients in the study included.

Table 4: Patient characteristics – RCT, direct comparison: acalabrutinib vs. idelalisib + rituximab (adults with CLL; one prior therapy; chemo-immunotherapy unsuitable) (multipage table)

Study **Characteristic** **Category**	**Acalabrutinib** **N[a] = 65**	**Idelalisib + rituximab** **N[a] = 48**
ASCEND		
Age [years], mean (SD)	66 (10)	66 (11)
Sex [F/M], %	34/66	35/65
Region, n (%)		
North America	3 (5)	3 (6)
Western Europe	16 (25)	10 (21)
Central/Eastern Europe	41 (63)	33 (69)
Australia/New Zealand	1 (2)	1 (2)
Asia	4 (6)	1 (2)
Family origin, n (%)		
White	59 (91)	45 (94)
Other[b]	6 (9)[c]	3 (6)[c]
ECOG PS, n (%)		
0	29 (45)	20 (42)
1	31 (48)	23 (48)
2	5 (8)	5 (10)
Disease duration: time between first diagnosis and randomization [months], median [min; max]	62.3 [3.1; 229.6]	60.2 [5.0; 158.9]
Bulky disease[d], n (%)		
< 5 cm	34 (52)	21 (44)
≥ 5 cm	31 (48)	27 (56)
Rai stage, n (%)		
0/I/II	38 (58)[c]	33 (69)[c]
III/IV	27 (42)[c]	15 (31)[c]
Binet stage, n (%)		
A	6 (9)	9 (19)
B	29 (45)	22 (46)
C	27 (42)	12 (25)
Missing	3 (5)	5 (10)
Beta 2 microglobulin, n (%)		
> 3.5 mg/L	52 (80)	38 (79)
≤ 3.5 mg/L	12 (19)	9 (19)
Missing	1 (2)	1 (2)
Cytopenia[e], n (%)	32 (49)	20 (42)
Disease-related symptoms[f], n (%)	35 (54)	31 (65)

Table 4: Patient characteristics – RCT, direct comparison: acalabrutinib vs. idelalisib + rituximab (adults with CLL; one prior therapy; chemo-immunotherapy unsuitable) (multipage table)

Study **Characteristic** **Category**	**Acalabrutinib** **N[a] = 65**	**Idelalisib + rituximab** **N[a] = 48**
Chromosome anomaly, n (%)		
17p deletion[g]	11 (17)	6 (13)
11q deletion[g]	18 (28)	14 (29)
TP53 mutation[h]	14 (22)	10 (21)
17p deletion and TP53 mutation	7 (11)	3 (6)
IGHV status, n (%)		
Mutated	11 (17)	8 (17)
Unmutated	53 (82)	36 (75)
Not determined/missing	1 (2)	4 (8)[c]
Complex karyotype[i]		
Yes	15 (23)	15 (31)
No	45 (69)	27 (56)
Not determinable/missing	5 (8)[c]	6 (13)[c]
Treatment discontinuation, n (%)	14 (22)	33 (69)
Study discontinuation, n (%)	8 (12)	12 (25)

a. Number of randomized patients.
b. Composed of Asian family origin or not reported.
c. Institute's calculation.
d. The assessment was made by the investigator.
e. Neutrophil count ≤ 1.5 x 10^9/L, haemoglobin ≤ 110 g/L or platelet count ≤ 100 x 10^9/L.
f. At least one of the following symptoms: weight loss, fever, night sweats, fatigue.
g. Not usable in one patient in the comparator arm.
h. The mutation status is missing in 3 patients in the intervention arm and 2 patients in the comparator arm.
i. 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 similar between the treatment arms. The mean age of the patients was 66 years, and most of them were male. Almost all patients were of white family origin and had an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 or 1. The majority of patients had a prognostically unfavourable unmutated immunoglobulin heavy-chain variable region (IGHV). 14 (22%) patients discontinued therapy in the intervention arm, 33 (69%) in the comparator arm.

Information on the course of the study

Table 5 shows the mean/median treatment duration of the patients and the mean/median observation period for individual outcomes.

Table 5: Information on the course of the study – RCT, direct comparison: acalabrutinib vs. idelalisib + rituximab (adults with CLL; one prior therapy; chemo-immunotherapy unsuitable)

Study **Duration of the study phase** **Outcome category**	**Acalabrutinib** **N = 65**	**Idelalisib + rituximab** **N = 48**
ASCEND		
Treatment duration [months]		
Median [min; max]	21.9 [3.1; 27.6]	11.4 [0.1; 25.1][a]
Mean (SD)	20.48 (5.56)	13.51 (7.55)[a]
Observation period[b] [months]		
Overall survival		
Median [min; max]	22.21 [ND]	21.63 [ND]
Mean (SD)	ND	ND
Morbidity		
Health status (EQ-5D VAS), fatigue (FACIT-Fatigue), symptoms (EORTC QLQ-C30)		
Median [min; max]	ND[c]	ND[c]
Mean (SD)	ND	ND
Disease-specific symptoms[d]	No usable data available[e]	
Health-related quality of life (EORTC QLQ-C30)		
Median [min; max]	ND[c]	ND[c]
Mean (SD)	ND	ND
Side effects		
Median [min; max]	21.9 [ND]	12.4 [ND]
Mean (SD)	ND	ND

a. Data on 47 patients and idelalisib; the median treatment duration with rituximab was 5.5 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. The data provided by the company are not plausible (median in the acalabrutinib arm 11.24 months vs. 11.10 months in the idelalisib + rituximab arm), with great differences in the time to disease progression between the study arms (median: NA vs. 16.9 months).
d. Weight loss, fatigue, fever, night sweats.
e. The analysed population contains only a maximum of 65% of the relevant subpopulation.

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 analysed 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 twice as long as in the comparator arm.

The median observation period for the outcome "mortality" was comparable between the 2 study arms. There are no usable data for the outcome categories of morbidity and health-related quality of life. Observation of side effects was about twice as long in the intervention arm as 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 6 shows which subsequent therapies patients received after discontinuing the study medication.

Table 6: Data on subsequent antineoplastic therapies – RCT, direct comparison: acalabrutinib vs. idelalisib + rituximab (adults with CLL; one prior therapy; chemo-immunotherapy unsuitable)

Study **Drug**	**Patients with subsequent therapy n (%)**	
	Acalabrutinib **N = 65**	**Idelalisib + rituximab** **N = 48**
ASCEND		
Total	8 (12.3)	17 (35.4)
Acalabrutinib	0 (0)	14 (29.2)
Purine analogues	0 (0)	0 (0)
Alkylating agents other than bendamustine	3 (4.6)	1 (2.1)
Bendamustine	0 (0)	1 (2.1)
Anti-CD20 monoclonal antibodies	3 (4.6)	1 (2.1)
Ibrutinib	1 (1.5)	2 (4.2)
Venetoclax	2 (3.1)	1 (2.1)
Cytarabine + methotrexate	0 (0)	1 (2.1)
CD: cluster of differentiation; CLL: chronic lymphocytic leukaemia; n: number of patients with subsequent therapy; N: number of analysed patients; RCT: randomized 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 8 patients in the relevant intervention arm and 17 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 prior therapy.

Transferability to the German health care context

The company stated that the patients included in the ASCEND study were almost exclusively Caucasian and came from Europe and North America. The median age of the patients was only

slightly below the average age of CLL patients at disease onset in Germany. According to the company, the study results were basically transferable to the German health care context.

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

Risk of bias across outcomes (study level)

Table 7 shows the risk of bias across outcomes (risk of bias at study level).

Table 7: Risk of bias across outcomes (study level) – RCT, direct comparison: acalabrutinib vs. idelalisib + rituximab (adults with CLL, one prior therapy; chemo-immunotherapy unsuitable)

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of the results	No additional aspects	Risk of bias at study level
			Patients	Treating staff			
ASCEND	Yes	Yes	No	No	Yes	Yes	Low
CLL: chronic lymphocytic leukaemia; RCT: randomized controlled trial							

The risk of bias across outcomes was rated as low for the study.

Limitations resulting from the open-label study design are described in Section 2.2.2 with the outcome-specific risk of bias.

2.2.2 Results on added benefit

2.2.2.1 Outcomes included

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

- Mortality
  - overall survival
- Morbidity
  - fatigue (Functional Assessment of Chronic Illness Therapy-Fatigue [FACIT-Fatigue])
  - disease-related symptoms
  - symptoms measured with the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Core 30 (QLQ-C30) symptom scales
  - health status (European Quality of Life-5 Dimensions [EQ-5D] visual analogue scale [VAS])

- Health-related quality of life
  - health-related quality of life measured with the EORTC QLQ-C30 functional scales
- Side effects
  - serious adverse events (SAEs)
  - severe adverse events (AEs) (Common Terminology Criteria for Adverse Events [CTCAE] grade ≥ 3)
  - discontinuation due to AEs
  - infections and infestations (System Organ Class [SOC], severe AE)
  - cardiac disorders (SOC, AE)
  - haemorrhages (severe AE)
  - further specific AEs, if any

Table 8 shows for which outcomes data were available in the study included.

Table 8: Matrix of outcomes – RCT, direct comparison: acalabrutinib vs. idelalisib + rituximab (adults with CLL; one prior therapy; chemo-immunotherapy unsuitable)

Study	Outcomes												
	Overall survival	Fatigue (FACIT-Fatigue)	Disease-related symptoms	Symptoms (EORTC QLQ-C30)	Health status (EQ-5D VAS)	Health-related quality of life (EORTC QLQ-C30)	SAEs	Severe AEs[a]	Discontinuation due to AEs	Infections and infestations (SOC, severe AEs[a])	Cardiac disorders (SOC, AEs)	Haemorrhages[b] (severe AEs[a])	Further specific AEs[a, c]
ASCEND	Yes	Yes	No[d]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

a. Operationalized as CTCAE grade ≥ 3.
b. No information on which bleeding episodes are included in the AE of special clinical interest.
c. The following events are considered (MedDRA coding): headache (PT, AEs), general disorders and administration site conditions (SOC, severe AEs), respiratory, thoracic and mediastinal disorders (SOC, severe AEs), skin and subcutaneous tissue disorders (SOC, severe AEs), renal failure (PT, severe AEs), blood and lymphatic system disorders (SOC, severe AEs), gastrointestinal disorders (SOC, severe AEs), hepatobiliary disorders (SOC, severe AEs), metabolism and nutrition disorders (SOC, severe AEs) and investigations (SOC, severe AEs).
d. No usable data available; the analysed population only contains a maximum of 65% of the relevant subpopulation.

AE: adverse event; 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; MedDRA: Medical Dictionary for Regulatory Activities; PT: Preferred Term; QLQ-C30: Quality of Life Questionnaire-Core-30; RCT: randomized controlled trial; SAE: serious adverse event; SMQ: Standardized MedDRA Query; SOC: System Organ Class; VAS: visual analogue scale

Analyses of the company on the patient-reported outcomes of fatigue (FACIT-Fatigue), symptoms (EORTC QLQ-C30), health status (EQ-5D VAS) and health-related quality of life (EORTC QLQ-C30)

The company presented both responder analyses and analyses of the mean changes for the patient-reported outcomes.

Responder analyses on the instruments FACIT-Fatigue, EQ-5D VAS, EORTC QLQ-C30

The company presented usable responder analyses with its comments. The analyses cover all documentation times regardless of the response rates. Patients were censored at the time point of the last recording before 2 or more missed visits if symptoms had progressed thereafter. Overall, this censoring affected a maximum of 2 patients in the respective treatment arm according to the information in the comments, and therefore had no further consequence for the present benefit assessment.

The company presented the following responder analyses:

- FACIT-Fatigue
  - time to first improvement by ≥ 15% of the scale range compared with baseline (global fatigue score [GFS]: ≥ 7.8 points [scale range: 0–52])
  - time to first deterioration by ≥ 15% of the scale range compared with baseline (GFS: ≥ 7.8 points [scale range: 0–52])

In addition, the company presented analyses of the FACIT-Fatigue subscales created by the company (fatigue symptom score [FSS] and fatigue impact score [FIS]). These are not considered for the present assessment, as the scoring guidelines on the FACIT-Fatigue and the FACIT-F do not contain information on the analysis of FACIT-Fatigue subscales [11,12].

- EORTC QLQ-C30 and EQ-5D VAS (scale range of each: 0–100)
  - time to first improvement by ≥ 15 points
  - time to first deterioration by ≥ 15 points

The results of the analyses with a response threshold of 15% were used for the instruments FACIT-Fatigue, EQ-5D VAS and EORTC QLQ-C30. The time to first deterioration was considered as operationalization in each case.

Mixed-effects model with repeated measures (MMRM) analyses on the instruments FACIT-Fatigue, EQ-5D VAS, EORTC QLQ-C30

The methodologically adequate analyses of mean changes for the instruments FACIT-Fatigue, EQ-5D VAS and EORTC QLQ-C30, which were subsequently submitted in the commenting procedure, are not considered for the present assessment, as the respective responder analyses are used [13].

The analyses of the mean change for the EORTC QLQ-C30 are presented in Table 14 in Appendix A.

Disease-related symptoms

With its comments, the company subsequently submitted analyses on the patient-relevant outcome "disease-related symptoms". This outcome included the following symptoms recorded in the ASCEND study:

- 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

According to information provided by the company, all patients were asked about these symptoms. However, for this outcome, the company only presented analyses of patients who had at least one disease-related symptom at baseline. For these patients, it calculated the time to first absence of any disease-related symptoms. Only 35 patients in the intervention arm (54%) and 31 patients in the comparator arm (65%) of the subpopulation presented by the company were included in the analyses. Considering only patients with at least one disease-related symptom at baseline therefore does not allow drawing a conclusion for all patients of the subpopulation presented by the company. The analyses presented by the company are therefore not usable for the present benefit assessment. The results for patients with disease-related symptoms at baseline are presented as supplementary information in Table 15 in Appendix A.

2.2.2.2 Risk of bias

Table 9 describes the risk of bias for the results of the relevant outcomes.

Table 9: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: acalabrutinib vs. idelalisib + rituximab (adults with CLL; one prior therapy; chemo-immunotherapy unsuitable)

Study		Outcomes												
	Study level	Overall survival	Fatigue (FACIT-Fatigue)	Disease-related symptoms	Symptoms (EORTC QLQ-C30)	Health status (EQ-5D VAS)	Health-related quality of life (EORTC QLQ-C30)	SAEs	Severe AEs[a]	Discontinuation due to AEs	Infections and infestations (SOC, severe AEs[a])	Cardiac disorders (SOC, AEs)	Haemorrhages[b] (severe AEs[a])	Further specific AEs[a, c]
ASCEND	L	L	H[d, e]	–[f]	H[d, e]	H[d, e]	H[d, e]	H[g]	L	H[d]	H[g]	H[d, g]	H[g]	H[d, g]

a. Operationalized as CTCAE grade ≥ 3.
b. No information on which bleeding episodes are included in the AE of special clinical interest.
c. The following events are considered (MedDRA coding): headache (PT, AEs), general disorders and administration site conditions (SOC, severe AEs), respiratory, thoracic and mediastinal disorders (SOC, severe AEs), skin and subcutaneous tissue disorders (SOC, severe AEs), renal failure (PT, severe AEs), blood and lymphatic system disorders (SOC, severe AEs), gastrointestinal disorders (SOC, severe AEs), hepatobiliary disorders (SOC, severe AEs), metabolism and nutrition disorders (SOC, severe AEs) and investigations (SOC, severe AEs).
d. Lack of blinding (patient) in subjective recording of outcomes. In the case of specific AEs, this concerns the non-severe or non-serious AEs.
e. Marked decrease in the response rate of questionnaires over the course of the study, which cannot be explained by death alone.
f. No usable data available; the analysed population only contains a maximum of 65% of the relevant subpopulation.
g. Incomplete observations for potentially informative reasons.

AE: adverse event; 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; H: high; L: low; MedDRA: Medical Dictionary for Regulatory Activities; PT: Preferred Term; QLQ-C30: Quality of Life Questionnaire-Core-30; RCT: randomized controlled trial; SAE: serious adverse event; SMQ: Standardized MedDRA Query; SOC: System Organ Class; VAS: visual analogue scale

There was a low risk of bias for the results of the outcome "overall survival". The progression-related switch of almost 29% of the patients in the subpopulation from the comparator arm to therapy with acalabrutinib had no influence on the risk of bias. This use of acalabrutinib is in compliance with the approval. This differs from the assessment of the company, which considered the results for this outcome to have a high risk of bias due to the switch to acalabrutinib therapy.

The risk of bias was rated as high for the results of the outcomes "fatigue" (FACIT-Fatigue) and "health status" (EQ-5D VAS), and of symptoms and health-related quality of life (EORTC QLQ-C30). Reasons for this are in each case incomplete observations for potentially informative reasons as well as the marked decrease in the response rate of questionnaires over

the course of the study, which cannot be explained by deaths alone. This concurs with the company's assessment.

With the exception of severe AEs, there was a high risk of bias for the results on side effects. For the outcomes "SAEs", "infections and infestations" and "haemorrhages", this was due to incomplete observations for potentially informative reasons. For the outcomes "discontinuation due to AEs", the high risk of bias was due to the lack of blinding (patient) in subjective recording of outcomes. For the outcome "cardiac disorders" as well as the other specific AEs, if they were not severe side effects of CTCAE grade ≥ 3, the risk of bias was rated as high both due to incomplete observations for potentially informative reasons and due to lack of blinding (patient) in subjective recording of outcomes. The company rated the risk of bias as high for the results of the outcomes on side effects.

2.2.2.3 Results

Table 10 summarizes the results of the comparison of acalabrutinib with idelalisib + rituximab in adult patients with CLL after one prior therapy who have 17p deletion or TP53 mutation or for whom chemo-immunotherapy is not indicated for other reasons.

Kaplan-Meier curves on the event time analyses are presented in Appendix B. The results on the common AEs, SAEs, severe AEs, as well as all AEs that led to treatment discontinuation are presented in Appendix C.

Table 10: Results (mortality, morbidity; health-related quality of life and side effects) – RCT, direct comparison: acalabrutinib vs. idelalisib + rituximab (adults with CLL; one prior therapy; chemo-immunotherapy unsuitable) (multipage table)

Study Outcome category	Acalabrutinib		Idelalisib + rituximab		Acalabrutinib vs. idelalisib + rituximab
Outcome	**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	65	NA 6 (9.2)	48	NA 7 (14.6)	0.58 [0.19; 1.75]; 0.322
Morbidity (data cut-off: 15 January 2019)					
Fatigue (FACIT-Fatigue, deterioration[b])	65	NA 18 (27.7)	48	NA 10 (20.8)	0.99 [0.47; 2.23]; 0.981
Disease-related symptoms				No usable data available[c]	
EORTC QLQ-C30 (symptom scales, deterioration[d])					
Fatigue	65	NA 17 (26.2)	48	NA 9 (18.8)	1.07 [0.49; 2.52]; 0.865
Nausea and vomiting	65	NA 21 (32.3)	48	15.7 [5.5; NC] 16 (33.3)	0.77 [0.40; 1.50]; 0.429
Pain	65	4.7 [2.8; NC] 33 (50.8)	48	11.1 [3.0; NC] 17 (35.4)	1.19 [0.67; 2.18]; 0.569
Appetite loss	65	16.6 [16.6; NC] 20 (30.8)	48	NA 13 (27.1)	0.83 [0.41; 1.71]; 0.581
Diarrhoea	65	16.6 [8.7; NC] 25 (38.5)	48	NA 16 (33.3)	0.84 [0.45; 1.60]; 0.578
Dyspnoea	65	NA 18 (27.7)	48	NA 12 (25.0)	0.86 [0.42; 1.83]; 0.677
Insomnia	65	NA 28 (43.1)	48	NA 17 (35.4)	0.95 [0.53; 1.78]; 0.873
Constipation	65	NA 14 (21.5)	48	NA 10 (20.8)	0.80 [0.36; 1.86]; 0.589
Health status (EQ-5D VAS, deterioration[e])	65	NA 12 (18.5)	48	NA 11 (22.9)	0.62 [0.27; 1.43]; 0.246

Table 10: Results (mortality, morbidity; health-related quality of life and side effects) – RCT, direct comparison: acalabrutinib vs. idelalisib + rituximab (adults with CLL; one prior therapy; chemo-immunotherapy unsuitable) (multipage table)

Study Outcome category	Acalabrutinib		Idelalisib + rituximab		Acalabrutinib vs. idelalisib + rituximab
Outcome	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 (functional scales, deterioration[e])					
Global health status	65	16.7 [5.6; NC] 25 (38.5)	48	NA 16 (33.3)	0.94 [0.51; 1.80]; 0.852
Physical functioning	65	NA 12 (18.5)	48	NA 7 (14.6)	0.99 [0.40; 2.66]; 0.980
Role functioning	65	5.6 [3.0; NC] 35 (53.8)	48	4.7 [2.8; NC] 19 (39.6)	1.04 [0.60; 1.86]; 0.887
Cognitive functioning	65	NA 24 (36.9)	48	4.8 [3.0; NC] 20 (41.7)	0.59 [0.32; 1.09]; 0.084
Emotional functioning	65	NA 18 (27.7)	48	NA 13 (27.1)	0.84 [0.42; 1.76]; 0.633
Social functioning	65	11.2 [4.7; NC] 29 (44.6)	48	16.6 [2.8; NC] 17 (35.4)	0.98 [0.54; 1.82]; 0.952
Side effects (data cut-off: 1 August 2019)					
AEs (supplementary information)	65	0.7 [0.3; 1.9] 62 (95.4)	47	1.0 [0.5; 1.8] 47 (100.0)	–
SAEs	65	NA 19 (29.2)	47	10.9 [6.1; 17.3] 28 (59.6)	0.29 [0.16; 0.53]; < 0.001
Severe AEs[f]	65	19.6 [8.3; NC] 34 (52.3)	47	3.8 [2.3; 5.1] 44 (93.6)	0.27 [0.16; 0.43]; < 0.001
Discontinuation due to AEs (≥ 1 component)	65	NA 8 (12.3)	47	13.8 [9.2; NC] 27 (57.4)	0.15 [0.06; 0.31]; < 0.001
Cardiac disorders (SOC, AE)	65	NA 9 (13.8)	47	NA 4 (8.5)	1.24 [0.40; 4.60]; 0.723
Infections and infestations (SOC, severe AE[f])	65	NA 13 (20.0)	47	NA 14 (29.8)	0.44 [0.20; 0.95]; 0.031
Haemorrhages[g] (severe AE[f])	65	NA 0 (0)	47	NA 1 (2.1)	NC; 0.232
Headache (PT, AE)	65	NA 13 (20.0)	47	NA 1 (2.1)	10.02 [1.99; 182.05]; 0.006

Table 10: Results (mortality, morbidity; health-related quality of life and side effects) – RCT, direct comparison: acalabrutinib vs. idelalisib + rituximab (adults with CLL; one prior therapy; chemo-immunotherapy unsuitable) (multipage table)

Study Outcome category	Acalabrutinib		Idelalisib + rituximab		Acalabrutinib vs. idelalisib + rituximab
Outcome	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]
General disorders and administration site conditions (SOC, severe AE[f])	65	NA 0 (0)	47	NA 3 (6.4)	NC; 0.026
Respiratory, thoracic and mediastinal disorders (SOC, severe AE[f])	65	NA 0 (0)	47	NA 5 (10.6)	NC; 0.002
Skin and subcutaneous tissue disorders (SOC, severe AE[f])	65	NA 2 (3.1)	47	NA 6 (12.8)	0.20 [0.03; 0.87]; 0.029
Renal failure (PT, severe AE[f])	65	NA 0 (0)	47	NA 3 (6.4)	NC; 0.008
Blood and lymphatic system disorders (SOC, severe AE[f])	65	NA 17 (26.2)	47	8.3 [4.2; NC] 23 (48.9)	0.40 [0.21; 0.75]; 0.004
Gastrointestinal disorders (SOC, severe AE[f])	65	NA 2 (3.1)	47	NA 18 (38.3)	0.05 [0.01; 0.16]; < 0.001
Hepatobiliary disorders (SOC, severe AE[f])	65	NA 0 (0)	47	NA 5 (10.6)	NC; 0.002
Metabolism and nutrition disorders (SOC, severe AE[f])	65	NA 2 (3.1)	47	NA 6 (12.8)	0.18 [0.03; 0.78]; 0.018
Investigations (SOC, severe AE[f])	65	NA 3 (4.6)	47	NA 9 (19.1)	0.19 [0.04; 0.66]; 0.007

a. HR (incl. 95% CI) calculated using Cox proportional hazards model; p-value based on log-rank test. According to the company, adjustment or stratification according to 17p deletion status (yes vs. no).
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; MedDRA: Medical Dictionary for Regulatory Activities; 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; SMQ: Standardized MedDRA Query; SOC: System Organ Class; VAS: visual analogue scale

On the basis of the available information, no more than hints, e.g. of an added benefit, can be determined for all outcomes. This is because it is unclear whether chemo-immunotherapy was not an option for all patients assigned to research question 2 by the company (see Section 2.2.1). In addition, the risk of bias of the results of the included outcomes (excluding overall survival and severe AEs) was rated as high.

Mortality

Overall survival

No statistically significant difference between the treatment groups was shown for the outcome "overall survival". This resulted in no hint of an added benefit of acalabrutinib in comparison with idelalisib + rituximab; an added benefit is therefore not proven.

This concurs with the company's assessment.

Morbidity

Fatigue (FACIT-Fatigue)

For the outcome "fatigue (FACIT-Fatigue)", there was no statistically significant difference between the treatment groups. This resulted in no hint of an added benefit of acalabrutinib in comparison with idelalisib + rituximab; an added benefit is therefore not proven.

This concurs with the company's assessment.

Symptoms (EORTC QLQ-C30)

Symptom outcomes were recorded using the EORTC QLQ-C30 symptom scales.

No statistically significant difference between the treatment groups was shown for any of the outcomes "fatigue", "nausea and vomiting", "pain", "appetite loss", "diarrhoea", "dyspnoea", "insomnia", and "constipation". In each case, this resulted in no hint of an added benefit of acalabrutinib in comparison with idelalisib + rituximab; an added benefit is therefore not proven.

This concurs with the company's assessment.

Health status (EQ-5D VAS)

There was no statistically significant difference between the treatment groups for the outcome "health status" (EQ-5D VAS). This resulted in no hint of an added benefit of acalabrutinib in comparison with idelalisib + rituximab; an added benefit is therefore not proven.

This concurs with the company's assessment.

Disease-related symptoms

There are no usable data for the outcome "disease-related symptoms". This resulted in no hint of an added benefit of acalabrutinib in comparison with idelalisib + rituximab; an added benefit is therefore not proven.

The company did not use the outcome "disease-related symptoms" for its assessment.

Health-related quality of life

EORTC QLQ-C30

Health-related quality of life was recorded using the EORTC QLQ-C30 functional scales.

No statistically significant difference between the treatment groups was shown for the outcomes "global health status", "physical functioning", "role functioning", "emotional functioning", "cognitive functioning" and "social functioning". This resulted in no hint of an added benefit of acalabrutinib in comparison with idelalisib + rituximab; an added benefit is therefore not proven.

This concurs with the company's assessment.

Side effects

For the outcomes in the category of side effects, the company derived a hint of an added benefit across all outcomes. Hence, the company's outcome-specific assessment is not described below.

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

A statistically significant difference in favour of acalabrutinib was shown for each of the outcomes "SAEs", "severe AEs" (CTCAE grade ≥ 3) and "discontinuation due to AEs". In each case, this resulted in a hint of lesser harm from acalabrutinib in comparison with idelalisib + rituximab.

Infections and infestations

A statistically significant difference in favour of acalabrutinib was shown for the outcome "infections and infestations". This resulted in a hint of lesser harm from acalabrutinib in comparison with idelalisib + rituximab.

Cardiac disorders and haemorrhages

There was no statistically significant difference between the treatment groups for the outcomes "cardiac disorders" and "haemorrhages". In each case, this resulted in no hint of an added benefit of acalabrutinib in comparison with idelalisib + rituximab; an added benefit is therefore not proven.

Headache

A statistically significant difference to the disadvantage of acalabrutinib was shown for the outcome "headache". This resulted in a hint of greater harm of acalabrutinib in comparison with idelalisib + rituximab.

Further specific AEs in favour of acalabrutinib

General disorders and administration site conditions, respiratory, thoracic and mediastinal disorders, skin and subcutaneous tissue disorders, renal failure, blood and lymphatic system disorders, gastrointestinal disorders, hepatobiliary disorders, metabolism and nutrition disorders, and investigations

There was a statistically significant difference in favour of acalabrutinib for each of the following outcomes: general disorders and administration site conditions, respiratory, thoracic and mediastinal disorders, skin and subcutaneous tissue disorders, renal failure, blood and lymphatic system disorders, gastrointestinal disorders, hepatobiliary disorders, metabolism and nutrition disorders, and investigations. In each case, this resulted in a hint of lesser harm from acalabrutinib in comparison with idelalisib + rituximab.

2.2.2.4 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.

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

2.2.3 Probability and extent of added benefit

Probability and extent of the added benefit at outcome level are derived below, taking into account the different outcome categories and effect sizes. The methods used for this purpose are explained in the *General Methods* of IQWiG [13].

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

2.2.3.1 Assessment of the added benefit at outcome level

The extent of the respective added benefit at outcome level was estimated from the results presented in Section 2.2.2.3 (see Table 11).

Determination of the outcome category for side effects

The outcome "discontinuation due to AEs" was assigned to the outcome category of serious/severe side effects, as a large proportion of these AEs (intervention arm: 88%; comparator arm: 63%) were severe AEs (CTCAE grade ≥ 3).

Table 11: Extent of added benefit at outcome level: acalabrutinib vs. idelalisib + rituximab (adults with CLL; one prior therapy; chemo-immunotherapy unsuitable) (multipage table)

Outcome category **Outcome**	**Acalabrutinib vs. idelalisib + rituximab** **Median time to event (months)** **Hazard ratio [95% CI]; p-value** **Probability**[a]	**Derivation of extent**[b]
Mortality		
	Median: NA vs. NA HR: 0.58 [0.19; 1.75]; p = 0.322	Lesser benefit/added benefit not proven
Morbidity		
Fatigue (FACIT-Fatigue)	Median: NA vs. NA HR: 0.99 [0.47; 2.23]; p = 0.981	Lesser benefit/added benefit not proven
Disease-related symptoms	No usable data available	Lesser benefit/added benefit not proven
EORTC QLQ-C30 – symptom scales		
Fatigue	Median: NA vs. NA HR: 1.07 [0.49; 2.52]; p = 0.865	Lesser benefit/added benefit not proven
Nausea and vomiting	Median: NA vs. 15.7 HR: 0.77 [0.40; 1.50]; p = 0.429	Lesser benefit/added benefit not proven
Pain	Median: 4.7 vs. 11.1 HR: 1.19 [0.67; 2.18]; p = 0.569	Lesser benefit/added benefit not proven
Appetite loss	Median: 16.6 vs. NA HR: 0.83 [0.41; 1.71]; p = 0.581	Lesser benefit/added benefit not proven
Diarrhoea	Median: 16.6 vs. NA HR: 0.84 [0.45; 1.60]; p = 0.578	Lesser benefit/added benefit not proven
Dyspnoea	Median: NA vs. NA HR: 0.86 [0.42; 1.83]; p = 0.677	Lesser benefit/added benefit not proven
Insomnia	Median: NA vs. NA HR: 0.95 [0.53; 1.78]; p = 0.873	Lesser benefit/added benefit not proven
Constipation	Median: NA vs. NA HR: 0.80 [0.36; 1.86]; p = 0.589	Lesser benefit/added benefit not proven
Health status (EQ-5D VAS)	Median: NA vs. NA HR: 0.62 [0.27; 1.43]; p = 0.246	Lesser benefit/added benefit not proven
Health-related quality of life		
EORTC QLQ-C30 – global health status and functional scales		
Global health status	Median: 16.7 vs. NA HR: 0.94 [0.51; 1.80]; p = 0.852	Lesser benefit/added benefit not proven
Physical functioning	Median: NA vs. NA HR: 0.99 [0.40; 2.66]; p = 0.980	Lesser benefit/added benefit not proven
Role functioning	Median: 5.6 vs. 4.7 HR: 1.04 [0.60; 1.86]; p = 0.887	Lesser benefit/added benefit not proven
Cognitive functioning	Median: NA vs. 4.8 HR: 0.59 [0.32; 1.09]; p = 0.084	Lesser benefit/added benefit not proven

Table 11: Extent of added benefit at outcome level: acalabrutinib vs. idelalisib + rituximab (adults with CLL; one prior therapy; chemo-immunotherapy unsuitable) (multipage table)

Outcome category **Outcome**	**Acalabrutinib vs. idelalisib + rituximab** **Median time to event (months)** **Hazard ratio [95% CI]; p-value** **Probability**[a]	**Derivation of extent**[b]
Emotional functioning	Median: NA vs. NA HR: 0.84 [0.42; 1.76]; p = 0.633	Lesser benefit/added benefit not proven
Social functioning	Median: 11.2 vs. 16.6 HR: 0.98 [0.54; 1.82]; p = 0.952	Lesser benefit/added benefit not proven
Side effects		
SAEs	Median: NA vs. 10.9 HR: 0.29 [0.16; 0.53]; p < 0.001 probability: "hint"	Outcome category: serious/severe side effects $CI_u < 0.75$, risk ≥ 5% lesser harm, extent: "major"
Severe AEs	Median: 19.6 vs. 3.8 HR: 0.27 [0.16; 0.43]; p < 0.001 probability: "hint"	Outcome category: serious/severe side effects $CI_u < 0.75$, risk ≥ 5% lesser harm, extent: "major"
Discontinuation due to AEs (≥ 1 component)	Median: NA vs. 13.8 HR: 0.15 [0.06; 0.31]; p < 0.001 probability: "hint"	Outcome category: serious/severe side effects $CI_u < 0.75$, risk ≥ 5% lesser harm, extent: "major"
Cardiac disorders (AE)	Median: NA vs. NA HR: 1.24 [0.40; 4.60]; p = 0.723	Greater/lesser harm not proven
Infections and infestations (severe AE)	Median: NA vs. NA HR: 0.44 [0.20; 0.95]; p = 0.031 probability: "hint"	Outcome category: serious/severe side effects $0.90 \leq CI_u < 1.00$ lesser harm, extent: "minor"
Haemorrhages (severe AE)	Median: NA vs. NA HR: NC; p = 0.232	Greater/lesser harm not proven
Headache (AE)	Median: NA vs. NA HR: 10.02 [1.99; 182.05]; p = 0.006 HR: 0.10 [0.01; 0.50][c]; probability: "hint"	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ greater harm, extent: "considerable"
General disorders and administration site conditions (severe AE)	Median: NA vs. NA HR: NC; p = 0.026 probability: "hint"	Outcome category: serious/severe side effects lesser harm, extent: "non-quantifiable"
Respiratory, thoracic and mediastinal disorders (severe AE)	Median: NA vs. NA HR: NC; p = 0.002 probability: "hint"	Outcome category: serious/severe side effects lesser harm, extent: "non-quantifiable"
Skin and subcutaneous tissue disorders (severe AE)	Median: NA vs. NA HR: 0.20 [0.03; 0.87]; p = 0.029 probability: "hint"	Outcome category: serious/severe side effects $0.75 \leq CI_u < 0.90$ lesser harm, extent: "considerable"

Table 11: Extent of added benefit at outcome level: acalabrutinib vs. idelalisib + rituximab (adults with CLL; one prior therapy; chemo-immunotherapy unsuitable) (multipage table)

Outcome category **Outcome**	**Acalabrutinib vs. idelalisib + rituximab** **Median time to event (months)** **Hazard ratio [95% CI]; p-value** **Probability**[a]	**Derivation of extent**[b]
Renal failure (severe AE)	Median: NA vs. NA HR: NC; p = 0.008 probability: "hint"	Outcome category: serious/severe side effects lesser harm, extent: "non-quantifiable"
Blood and lymphatic system disorders (severe AE)	Median: NA vs. 8.3 HR: 0.40 [0.21; 0.75]; p = 0.004 probability: "hint"	Outcome category: serious/severe side effects $0.75 \leq CI_u < 0.90$ lesser harm, extent: "considerable"
Gastrointestinal disorders (severe AE)	Median: NA vs. NA HR: 0.05 [0.01; 0.16]; p < 0.001 probability: "hint"	Outcome category: serious/severe side effects $CI_u < 0.75$, risk ≥ 5% lesser harm, extent: "major"
Hepatobiliary disorders (severe AE)	Median: NA vs. NA HR: NC; 0.002 probability: "hint"	Outcome category: serious/severe side effects lesser harm, extent: "non-quantifiable"
Metabolism and nutrition disorders (severe AE)	Median: NA vs. NA HR: 0.18 [0.03; 0.78]; p = 0.018 probability: "hint"	Outcome category: serious/severe side effects $0.75 \leq CI_u < 0.90$ lesser harm, extent: "considerable"
Investigations (severe AE)	Median: NA vs. NA HR: 0.19 [0.04; 0.66]; p = 0.007 probability: "hint"	Outcome category: serious/severe side effects $CI_u < 0.75$, risk ≥ 5% lesser harm, extent: "major"

a. Probability provided if there is a statistically significant and relevant effect.
b. Depending on the outcome category, estimations of effect size are made with different limits based on the upper limit of the confidence interval (CI_u).
c. Institute's calculation; reversed direction of effect to enable use of limits to derive the extent of the added benefit.

AE: adverse event; CI: confidence interval; CI_u: upper limit of confidence interval; CLL: chronic lymphocytic leukaemia; EORTC: European Organisation for Research and Treatment of Cancer; FACIT: Functional Assessment of Chronic Illness Therapy; NA: not achieved; NC: not calculable; QLQ-C30: Quality of Life Questionnaire-Core-30; SAE: serious adverse event; VAS: visual analogue scale

2.2.3.2 Overall conclusion on added benefit

Table 12 summarizes the results considered in the overall conclusion on the extent of added benefit.

Table 12: Positive and negative effects from the assessment of acalabrutinib in comparison with idelalisib + rituximab (adults with CLL; one prior therapy; chemo-immunotherapy unsuitable)

Positive effects	Negative effects
Serious/severe side effects ▪ SAEs: hint of lesser harm – extent: "major" ▪ Severe AEs: hint of lesser harm – extent: "major" including ▫ Infections and infestations: hint of lesser harm – extent: "minor" ▫ General disorders and administration site conditions : hint of lesser harm – extent: "non-quantifiable" ▫ Respiratory, thoracic and mediastinal disorders: hint of lesser harm – extent: "non-quantifiable" ▫ Skin and subcutaneous tissue disorders: hint of lesser harm – extent: "considerable" ▫ Renal failure: hint of lesser harm – extent: "non-quantifiable" ▫ Blood and lymphatic system disorders: hint of lesser harm – extent: "considerable" ▫ Gastrointestinal disorders: hint of lesser harm – extent: "major" ▫ Hepatobiliary disorders: hint of lesser harm – extent: "non-quantifiable" ▫ Metabolism and nutrition disorders: hint of lesser harm – extent: "considerable" ▫ Investigations: hint of lesser harm – extent: "major" ▪ Discontinuation due to AEs: hint of lesser harm – extent: "major"	Non-serious/non-severe side effects ▪ Headache (AE): hint of greater harm – extent: "considerable"
AE: adverse event; CLL: chronic lymphocytic leukaemia; SAE: serious adverse event	

With the exception of one negative effect in the non-serious/non-severe side effects, the overall view of the data shows exclusively positive effects for acalabrutinib in comparison with idelalisib + rituximab. These effects are shown exclusively in the outcome category of side effects in serious/severe side effects. There is a hint of lesser harm, each of major extent, in the overall rates of SAEs, severe AEs, and discontinuation due to AEs. Among the severe AEs, there are several AEs at SOC and PT level in favour of acalabrutinib with different extent.

In summary, there is therefore a hint of major added benefit of acalabrutinib in comparison with idelalisib + rituximab for adult patients with CLL after one prior therapy who have 17p deletion or TP53 mutation or for whom chemo-immunotherapy is not indicated for other reasons.

2.3 Research question 3: adults with CLL; at least 2 prior therapies

2.3.1 Results on added benefit

The company assigned all patients in the ASCEND study with at least 2 prior therapies (73 patients in the intervention arm, 88 in the comparator arm) to research question 3 (adults with CLL; at least 2 prior therapies).

The data presented by the company are unsuitable for the assessment of the added benefit of acalabrutinib in comparison with the ACT. The reason for this is that, in deviation from the ACT specified by the G-BA, the decision for the therapy option in the comparator arm was not made on an individual patient basis, but that all patients in the subpopulation operationalized by the company in research question 3 received bendamustine + rituximab or idelalisib + rituximab. The company did not explain why other therapy options specified by the G-BA were not considered for the patients. (For reasons, see also dossier assessment A20-105 [1].

2.3.2 Probability and extent of added benefit

The company did not subsequently submit any relevant data to assess the added benefit of acalabrutinib in adult patients with CLL after at least 2 prior therapies in comparison with the ACT. This resulted in no change in comparison with dossier assessment A20-105 [1]; an added benefit is not proven.

2.4 Summary

The data subsequently submitted by the company in the commenting procedure changed the conclusion on the added benefit of acalabrutinib from dossier assessment A20-105 for research question 2: For adult patients with CLL after one prior therapy who have 17p deletion or TP53 mutation or for whom chemo-immunotherapy is not indicated for other reasons, there is a hint of major added benefit. For the other research questions, there was no change in comparison with dossier assessment A20-105.

The following Table 13 shows the result of the benefit assessment of acalabrutinib under consideration of dossier assessment A20-105 and the present addendum.

Table 13: Acalabrutinib – probability and extent of added benefit

Research question	Subindication[a]	ACT[b]	Probability and extent of added benefit[c]
1	Adult patients with CLL after one prior therapy who have no 17p deletion or TP53 mutation and for whom chemo-immunotherapy[c] is indicated	Patient-specific therapy[e] choosing from FCR, BR, venetoclax in combination with rituximab and ClbR	Added benefit not proven
2	Adult patients with CLL after one prior therapy who have 17p deletion or TP53 mutation or for whom chemo-immunotherapy[d] is not indicated for other reasons	Ibrutinib or **idelalisib + rituximab** or best supportive care[f, g]	**Hint of major added benefit[h]**
3	Adult patients with CLL after at least 2 prior therapies	Patient-specific therapy[d] choosing from ibrutinib, idelalisib in combination with rituximab, venetoclax in combination with rituximab, FCR, BR, ClbR, ibrutinib in combination with BR, and best supportive care[f]	Added benefit not proven

a. It is assumed that the patients require treatment and that allogeneic stem cell transplantation is not indicated at the time point of treatment.
b. Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in **bold**.
c. Changes in comparison with dossier assessment A20-105 are printed in **bold**.
d. Or therapy with rituximab in combination with venetoclax.
e. Taking into account the molecular-cytogenetic characteristics of the disease, the general condition and the success and tolerability of the prior therapy. For the implementation of patient-specific therapy, it is expected that a choice of several treatment options is available, allowing a patient-specific therapy decision (multi-comparator study). The choice and, if necessary, limitation of treatment options must be justified.
f. Only for patients with failure of a previous therapy with ibrutinib as monotherapy or idelalisib + rituximab.
g. Best supportive care refers to the therapy that provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life.
h. Only patients with chemo-immunotherapy as pretreatment were included in the ASCEND study. It remains unclear whether the observed effects can be transferred to patients with another pretreatment.

17p deletion: deletion of the short arm of chromosome 17; ACT: appropriate comparator therapy;
BR: rituximab in combination with bendamustine; ClbR: rituximab in combination with chlorambucil;
CLL: chronic lymphocytic leukaemia; FCR: rituximab in combination with fludarabine and cyclophosphamide;
G-BA: Federal Joint Committee; TP53 mutation: mutation of the tumour protein p53

The G-BA decides on the added benefit.

3 References

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

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

Table 14: Results (morbidity, health-related quality of life, continuous – supplementary presentation for the EORTC QLQ-C30) – RCT, direct comparison: acalabrutinib vs. idelalisib + rituximab (adults with CLL; one prior therapy; chemo-immunotherapy unsuitable) (multipage table)

Study Outcome category Outcome	Acalabrutinib			Idelalisib + rituximab			Acalabrutinib vs. 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	60	31.48 (21.47)	–5.27 (2.01)	37	35.74 (24.45)	–8.19 (2.45)	2.92 [–2.48; 8.32]; 0.286
Nausea and vomiting	60	4.44 (8.61)	–1.32 (0.94)	37	5.86 (12.56)	–1.39 (1.12)	0.07 [–2.45; 2.58]; 0.958
Pain	60	15.00 (20.05)	–1.69 (2.07)	37	21.62 (25.42)	–4.40 (2.54)	2.71 [–3.03; 8.46]; 0.350
Appetite loss	60	10.56 (19.88)	–3.57 (1.57)	37	17.12 (29.00)	–3.66 (1.89)	0.09 [–3.98; 4.15]; 0.966
Diarrhoea	60	6.11 (17.88)	1.39 (1.73)	37	5.41 (14.73)	2.46 (2.08)	–1.06 [–5.75; 3.63]; 0.654
Dyspnoea	60	17.78 (24.90)	–6.35 (1.88)	37	19.82 (28.82)	–8.18 (2.27)	1.83 [–3.28; 6.94]; 0.478
Insomnia	60	26.11 (29.49)	–3.76 (2.66)	37	26.13 (31.56)	–2.96 (3.14)	–0.79 [–7.83; 6.24]; 0.823
Constipation	60	12.22 (23.74)	–3.54 (1.48)	37	3.60 (10.49)	–3.97 (1.83)	0.43 [–3.79; 4.65]; 0.839
Health-related quality of life							
EORTC QLQ-C30 – functional scales[d]							
Global health status	60	61.94 (21.61)	4.97 (1.76)	37	63.06 (21.48)	2.36 (2.08)	2.61 [–2.05; 7.26]; 0.269
Physical functioning	60	77.56 (17.95)	5.17 (1.63)	37	77.12 (19.22)	7.12 (1.98)	–1.95 [–6.48; 2.57]; 0.393
Role functioning	60	83.33 (20.59)	0.16 (2.32)	37	76.13 (25.62)	–0.02 (2.82)	0.19 [–6.02; 6.39]; 0.953
Cognitive functioning	60	85.28 (16.83)	–0.57 (1.75)	37	84.68 (17.29)	1.56 (2.08)	–2.13 [–6.81; 2.56]; 0.369
Emotional functioning	60	81.11 (20.41)	2.65 (1.83)	37	77.93 (17.81)	3.04 (2.22)	–0.39 [–5.45; 4.68]; 0.880

Table 14: Results (morbidity, health-related quality of life, continuous – supplementary presentation for the EORTC QLQ-C30) – RCT, direct comparison: acalabrutinib vs. idelalisib + rituximab (adults with CLL; one prior therapy; chemo-immunotherapy unsuitable) (multipage table)

Study Outcome category Outcome	Acalabrutinib			Idelalisib + rituximab			Acalabrutinib vs. 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]
Social functioning	60	84.17 (20.91)	2.32 (2.44)	37	78.83 (25.35)	0.09 (2.95)	2.22 [–4.38; 8.83]; 0.505

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 idelalisib + rituximab) indicate an advantage for acalabrutinib.
d. Higher values indicate better quality of life; positive effects (acalabrutinib minus idelalisib + rituximab) indicate an advantage for acalabrutinib.

CI: confidence interval; CLL: chronic lymphocytic leukaemia; EORTC: European Organisation for Research and Treatment of Cancer; 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 15: Results (morbidity – supplementary presentation for the outcome "disease-related symptoms", data cut from 1 August 2019) – RCT, direct comparison: acalabrutinib vs. idelalisib + rituximab (adults with CLL; one prior therapy; chemo-immunotherapy unsuitable)

Study Outcome category Outcome	Acalabrutinib N	Acalabrutinib Median time to event in months [95% CI] Patients with event n (%)	Idelalisib + rituximab N	Idelalisib + rituximab Median time to event in months [95% CI] Patients with event n (%)	Acalabrutinib vs. idelalisib + rituximab 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	35	1.1 [1.0; 1.8] 34 (97.1)	31	1.9 [1.1; 2.5] 29 (93.5)	1.11 [0.66; 1.89]; 0.725

a. HR (incl. 95% CI) calculated using Cox proportional hazards model stratified by 17p deletion status (yes vs. no); 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 B – Kaplan-Meier curves: adults with CLL; one prior therapy; chemo-immunotherapy unsuitable

B.1 – Mortality

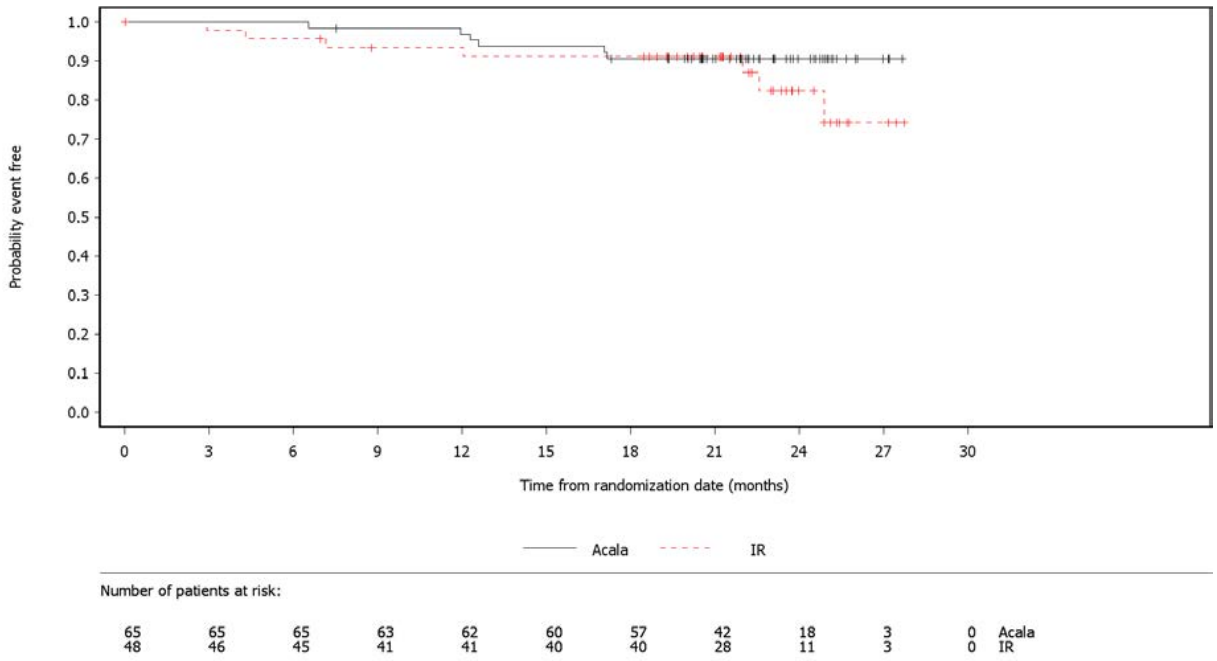

Figure 1: Kaplan-Meier curves, outcome “overall survival”, ASCEND study, data cut-off from 1 August 2019

B.2 – **Morbidity**

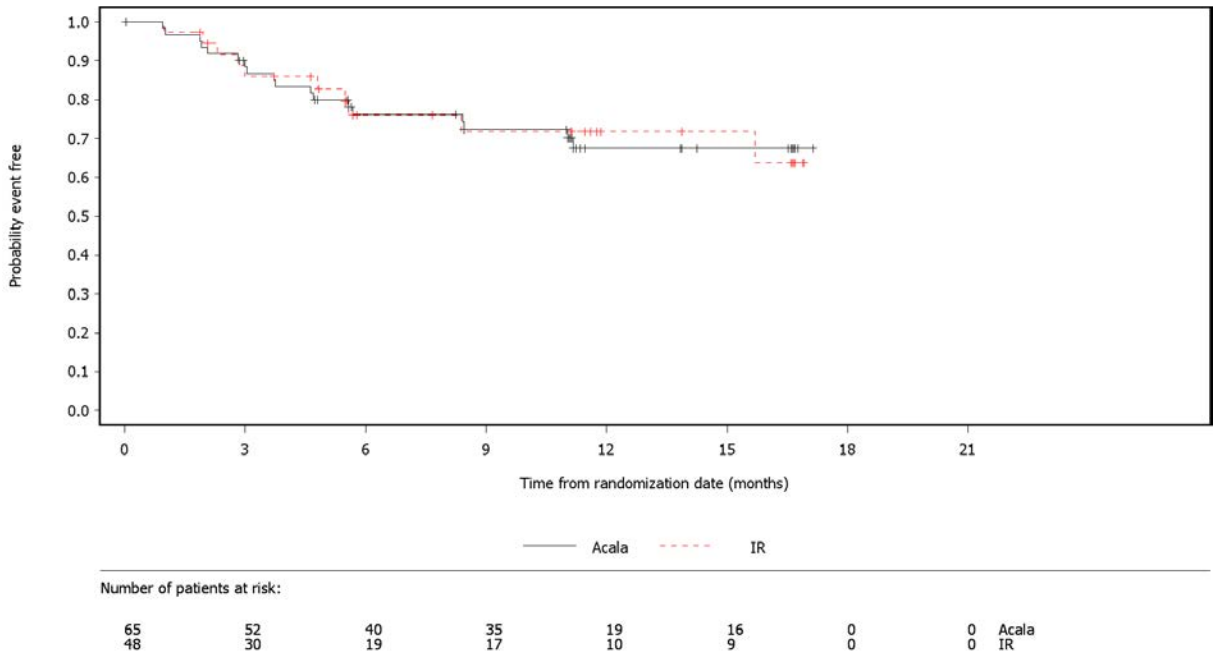

Figure 2: Kaplan-Meier-curves for symptoms, outcome “fatigue” (FACIT-Fatigue, time to clinically relevant deterioration by ≥ 7.8 points), ASCEND study, data cut-off from 15 January 2019

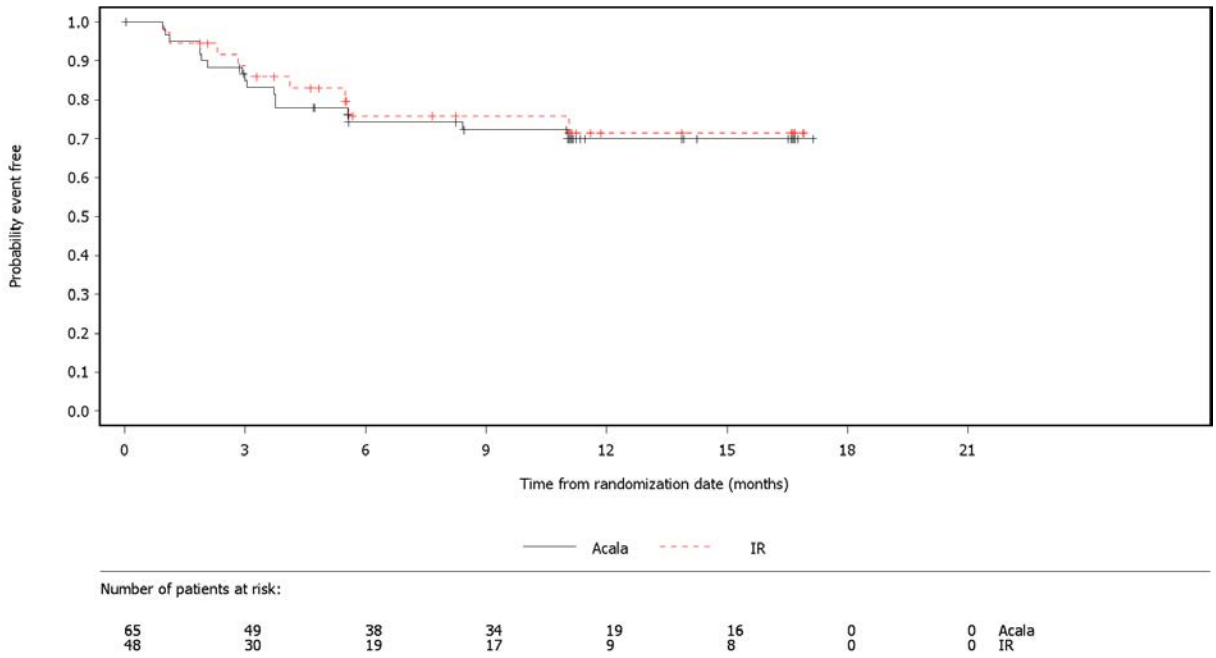

Figure 3: Kaplan-Meier-curves for symptoms, outcome "fatigue" (EORTC QLQ-C30, time to clinically relevant deterioration by ≥ 15 points), ASCEND study, data cut-off from 15 January 2019

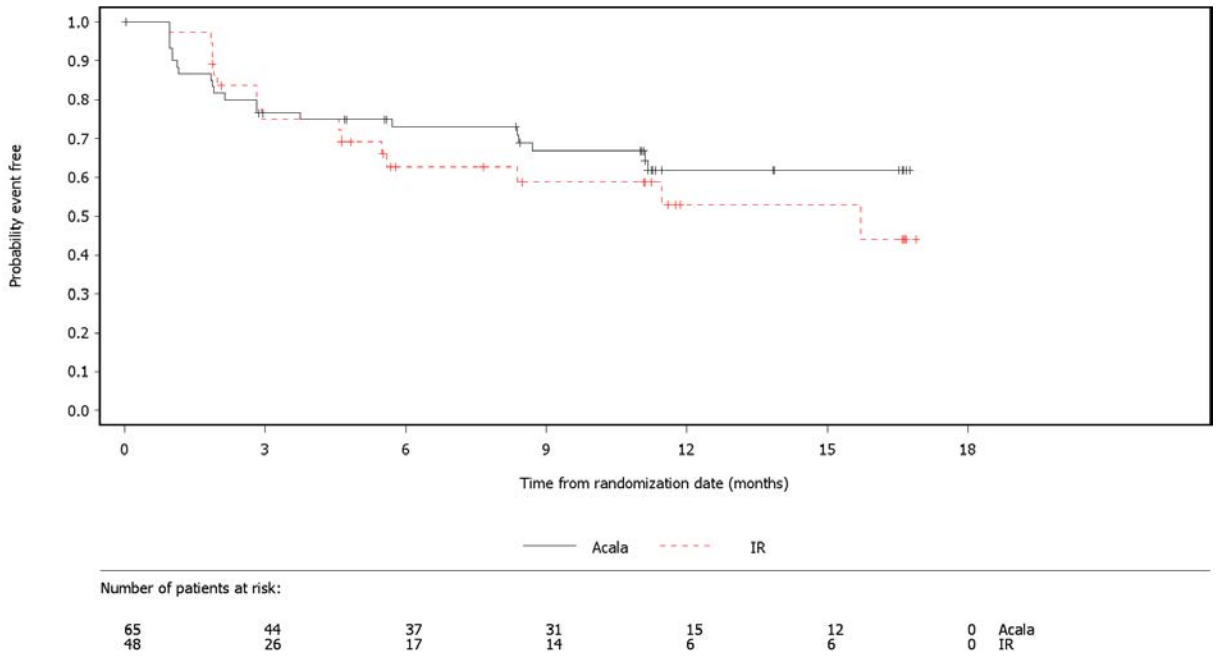

Figure 4: Kaplan-Meier-curves for symptoms, outcome "nausea and vomiting" (EORTC QLQ-C30, time to clinically relevant deterioration by ≥ 15 points), ASCEND study, data cut-off from 15 January 2019

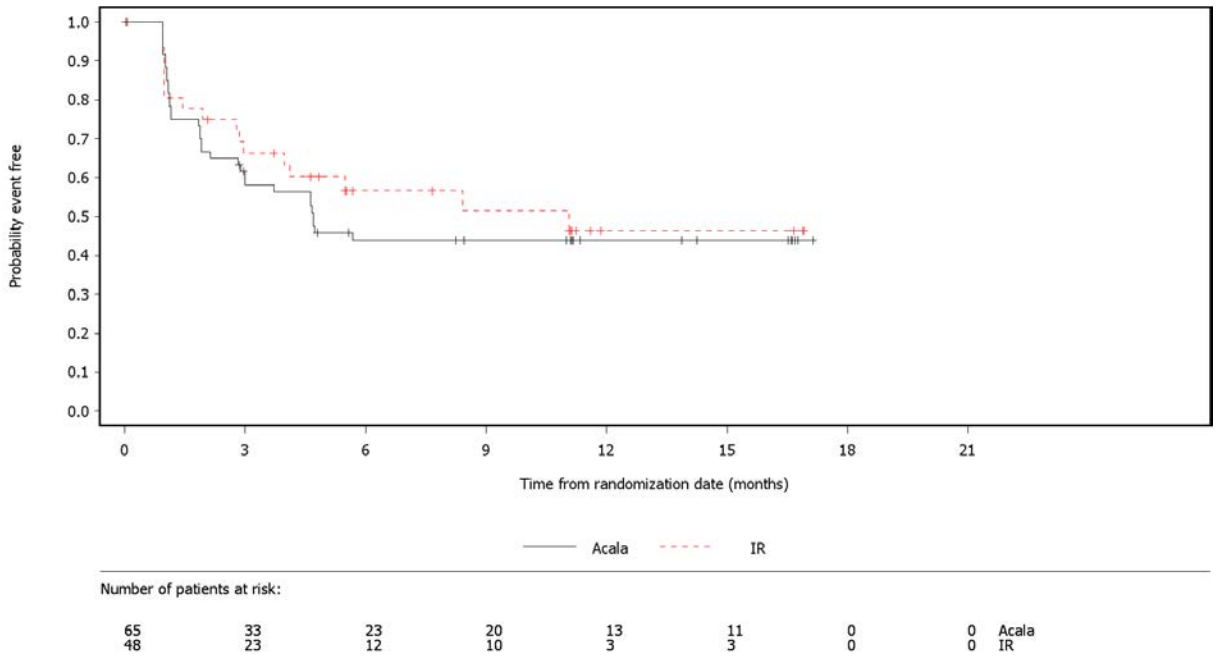

Figure 5: Kaplan-Meier-curves for symptoms, outcome "pain" (EORTC QLQ-C30, time to clinically relevant deterioration by ≥ 15 points), ASCEND study, data cut-off from 15 January 2019

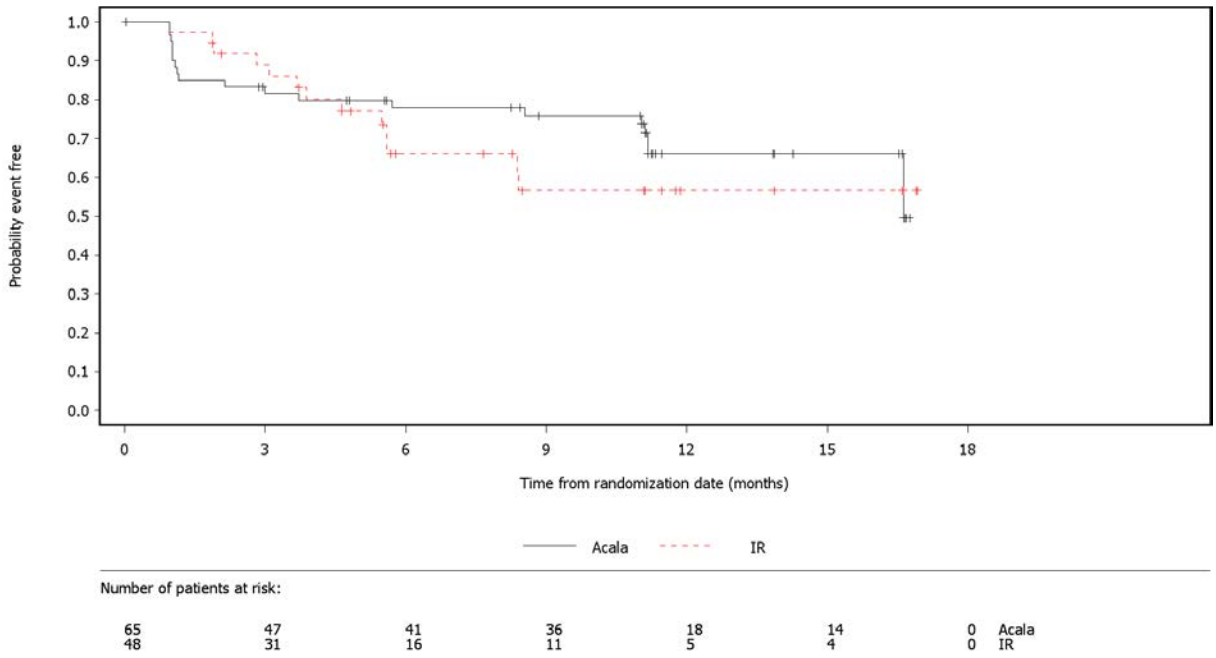

Figure 6: Kaplan-Meier-curves for symptoms, outcome "appetite loss" (EORTC QLQ-C30, time to clinically relevant deterioration by ≥ 15 points), ASCEND study, data cut-off from 15 January 2019

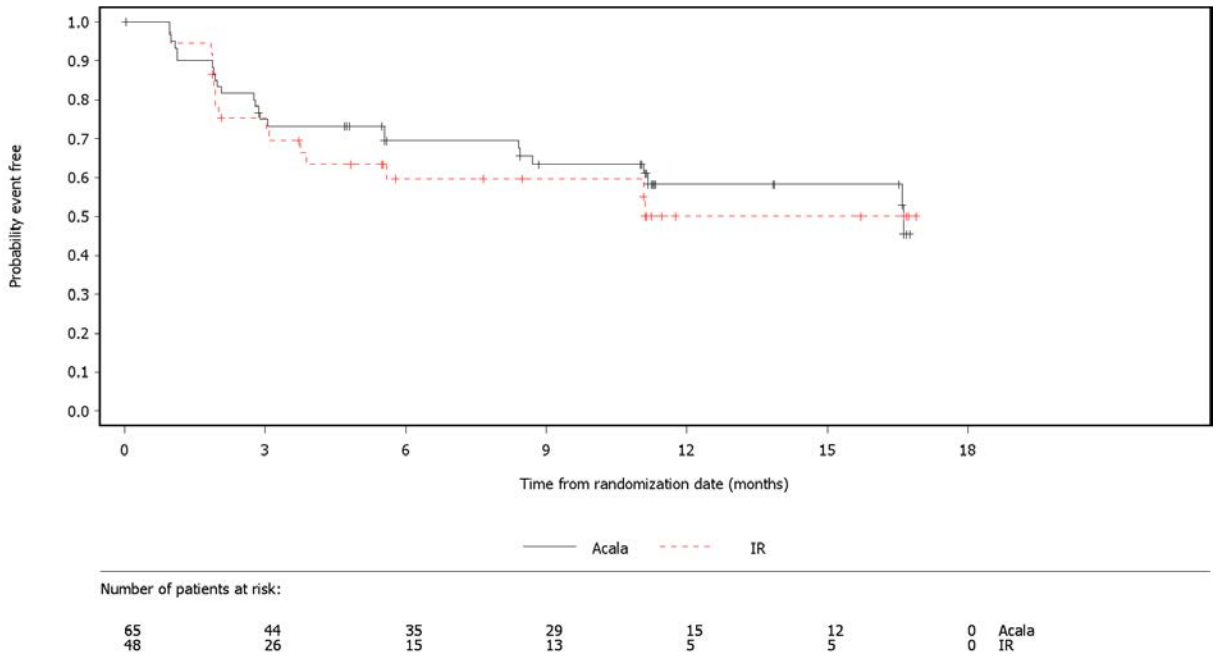

Figure 7: Kaplan-Meier-curves for symptoms, outcome "diarrhoea" (EORTC QLQ-C30, time to clinically relevant deterioration by ≥ 15 points), ASCEND study, data cut-off from 15 January 2019

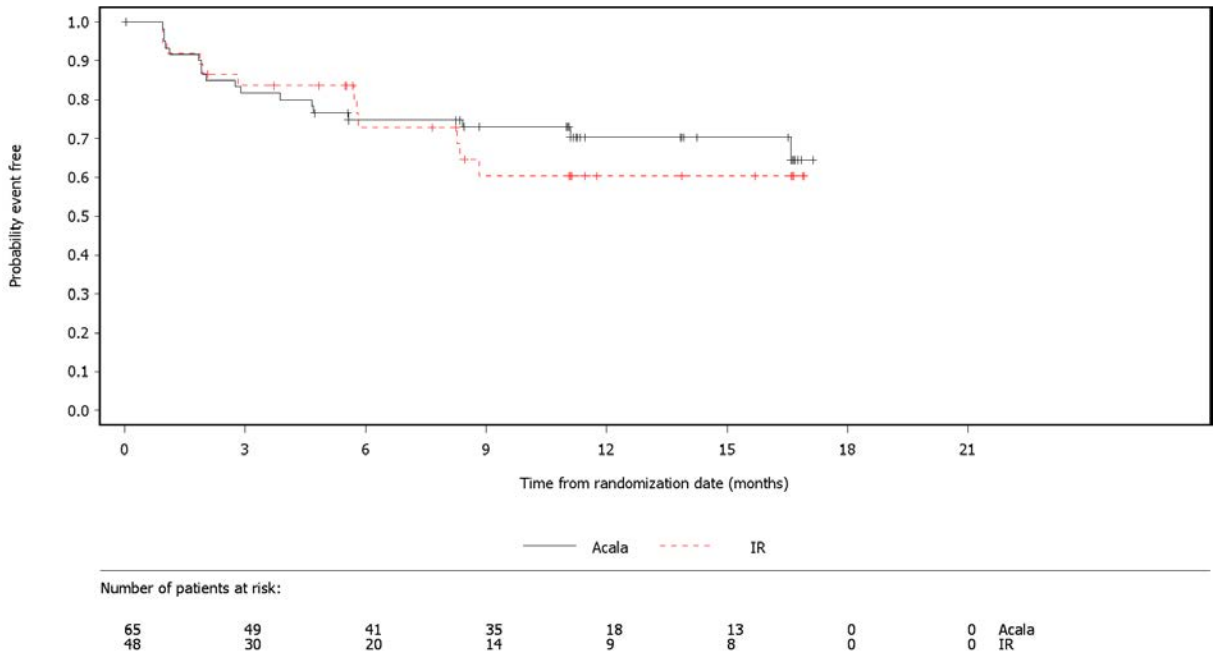

Figure 8: Kaplan-Meier-curves for symptoms, outcome "dyspnoea" (EORTC QLQ-C30, time to clinically relevant deterioration by ≥ 15 points), ASCEND study, data cut-off from 15 January 2019

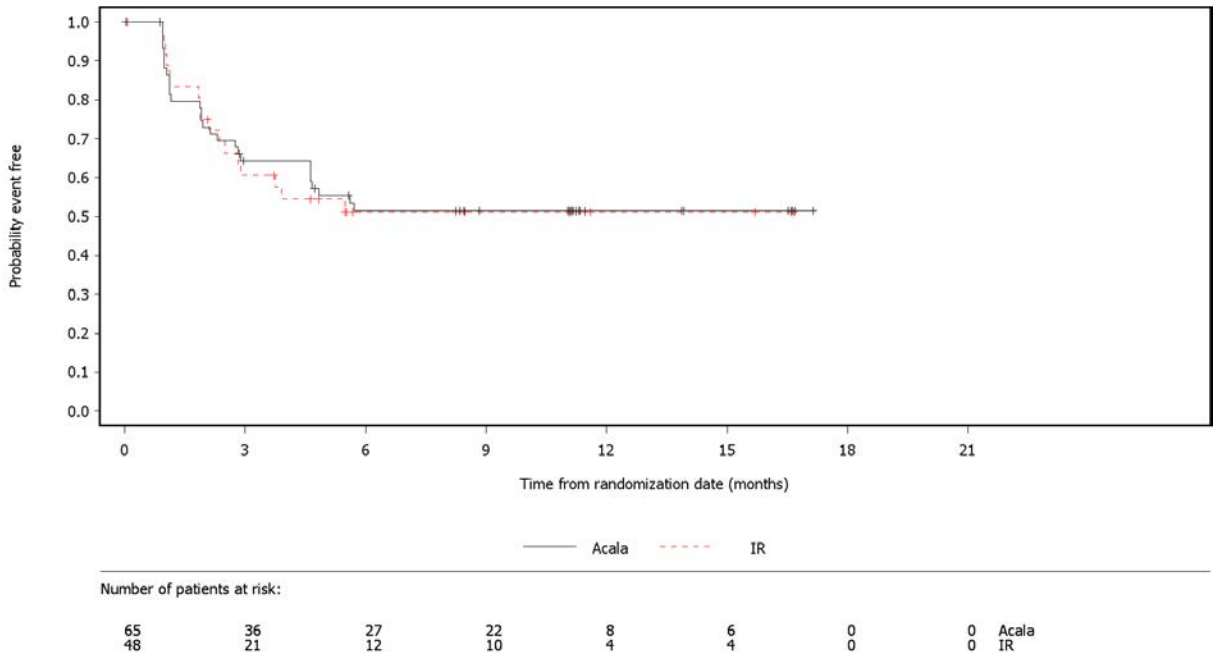

Figure 9: Kaplan-Meier-curves for symptoms, outcome "insomnia" (EORTC QLQ-C30, time to clinically relevant deterioration by ≥ 15 points), ASCEND study, data cut-off from 15 January 2019

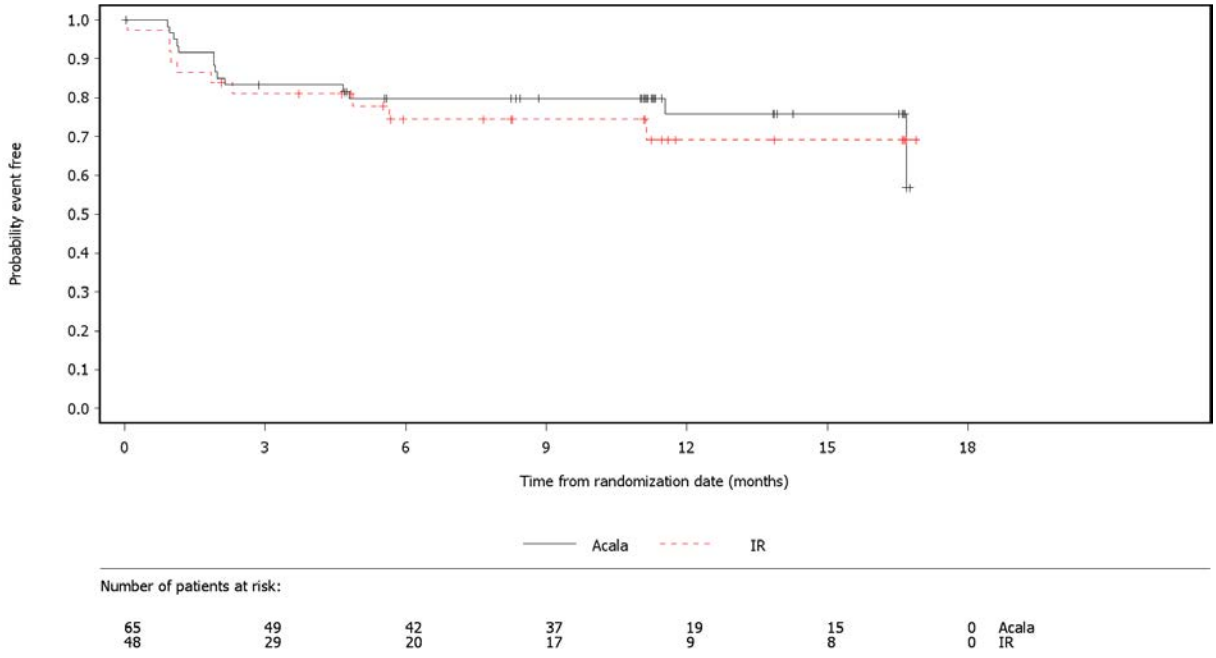

Figure 10: Kaplan-Meier-curves for symptoms, outcome "constipation" (EORTC QLQ-C30, time to clinically relevant deterioration by ≥ 15 points), ASCEND study, data cut-off from 15 January 2019

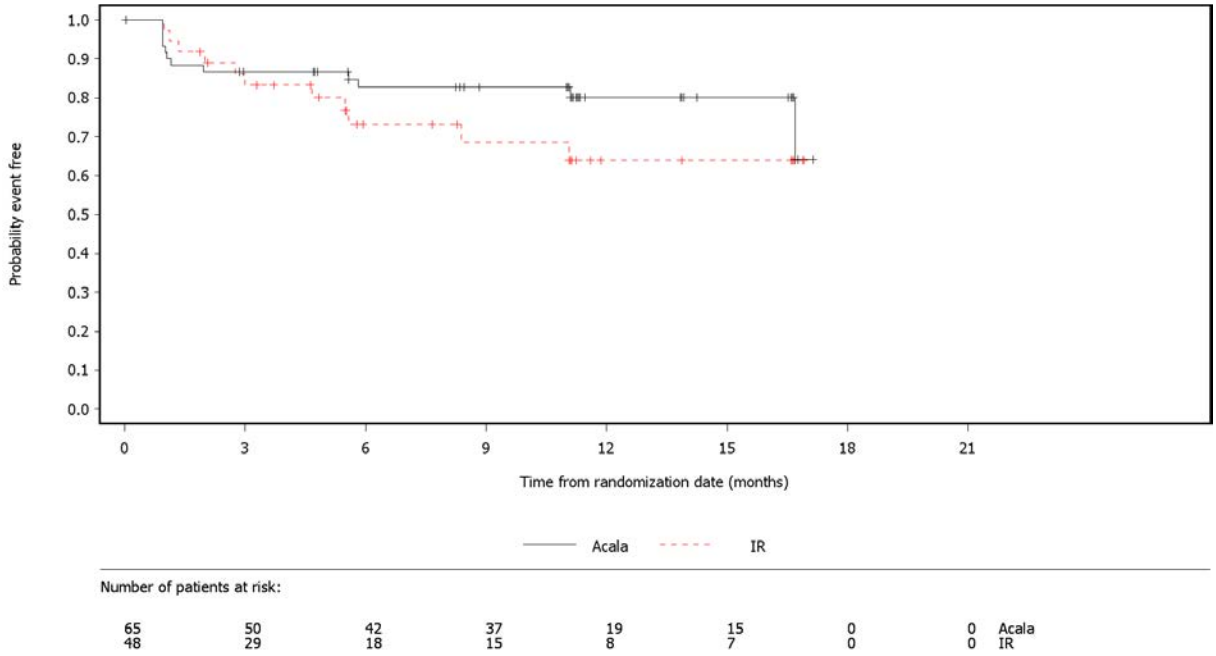

Figure 11: Kaplan-Meier-curves for symptoms, outcome "health status" (EQ-5D VAS, time to clinically relevant deterioration by ≥ 15 points), ASCEND study, data cut-off from 15 January 2019

B.3 – **Health-related quality of life**

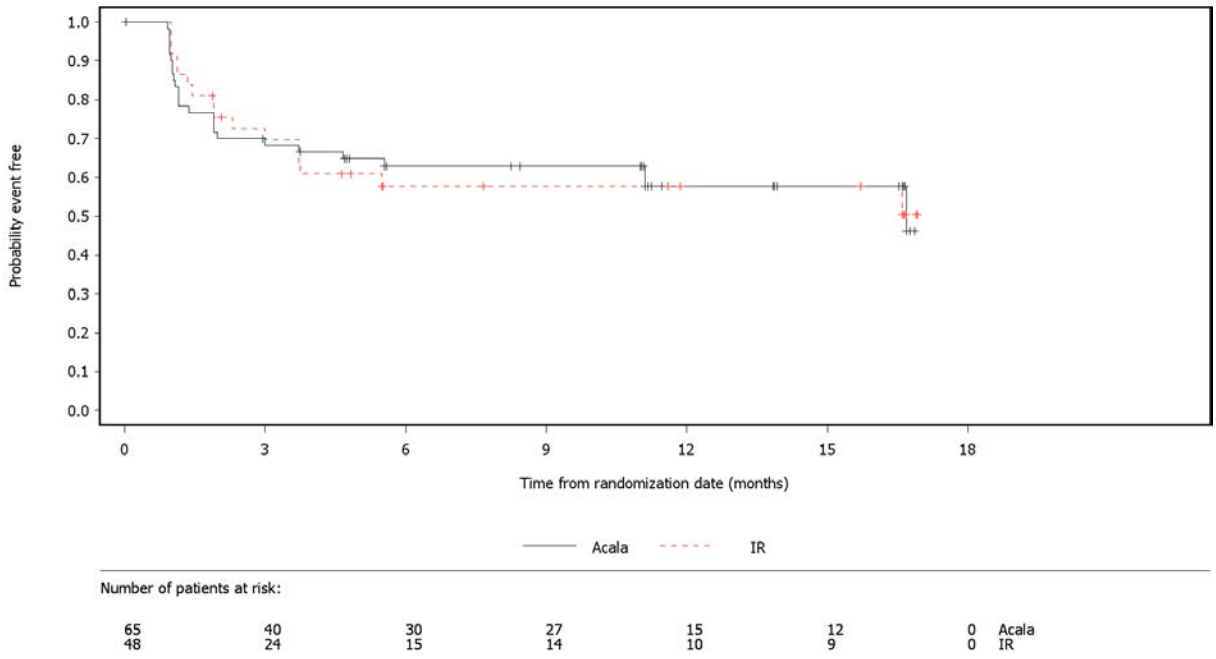

Figure 12: Kaplan-Meier-curves for symptoms, outcome "global health status" (EORTC QLQ-C30, time to clinically relevant deterioration by ≥ 15 points), ASCEND study, data cut-off from 15 January 2019

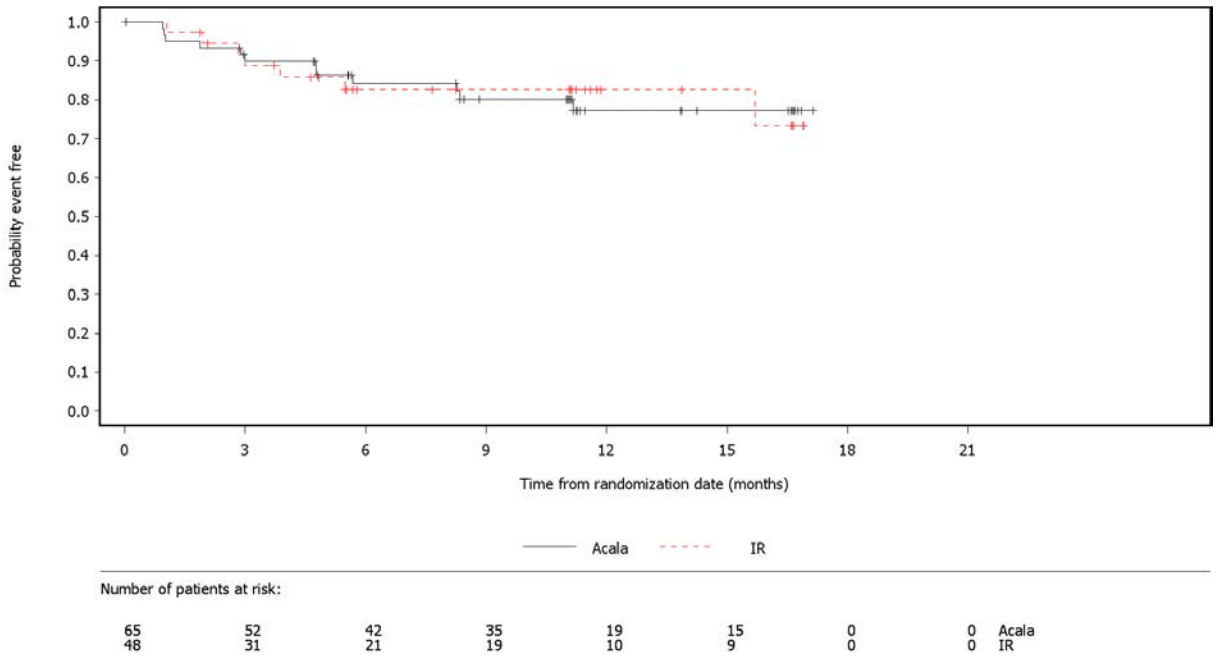

Figure 13: Kaplan-Meier-curves for symptoms, outcome "physical functioning" (EORTC QLQ-C30, time to clinically relevant deterioration by ≥ 15 points), ASCEND study, data cut-off from 15 January 2019

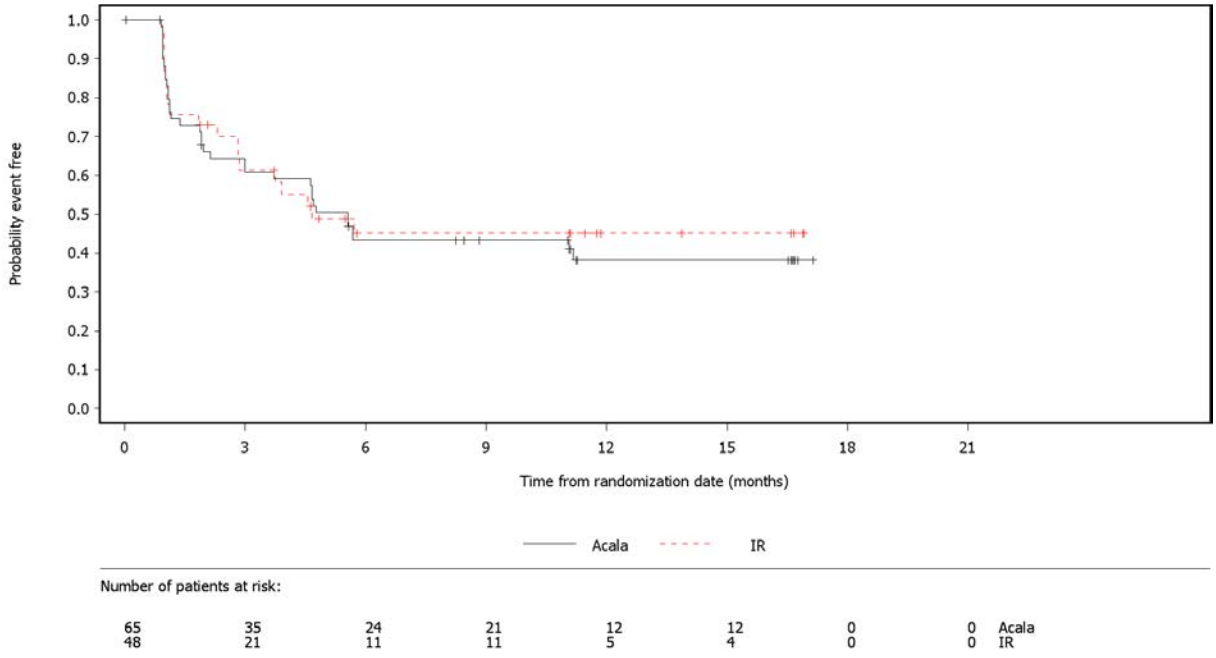

Figure 14: Kaplan-Meier-curves for symptoms, outcome "role functioning" (EORTC QLQ-C30, time to clinically relevant deterioration by ≥ 15 points), ASCEND study, data cut-off from 15 January 2019

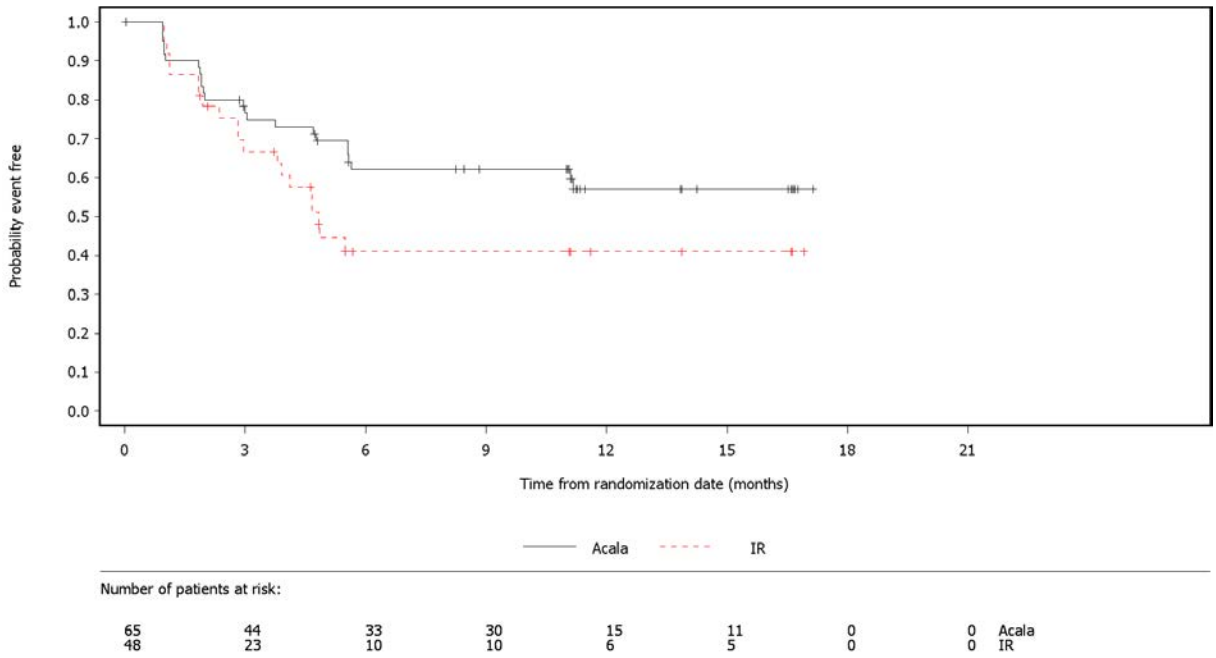

Figure 15: Kaplan-Meier-curves for symptoms, outcome "cognitive functioning" (EORTC QLQ-C30, time to clinically relevant deterioration by ≥ 15 points), ASCEND study, data cut-off from 15 January 2019

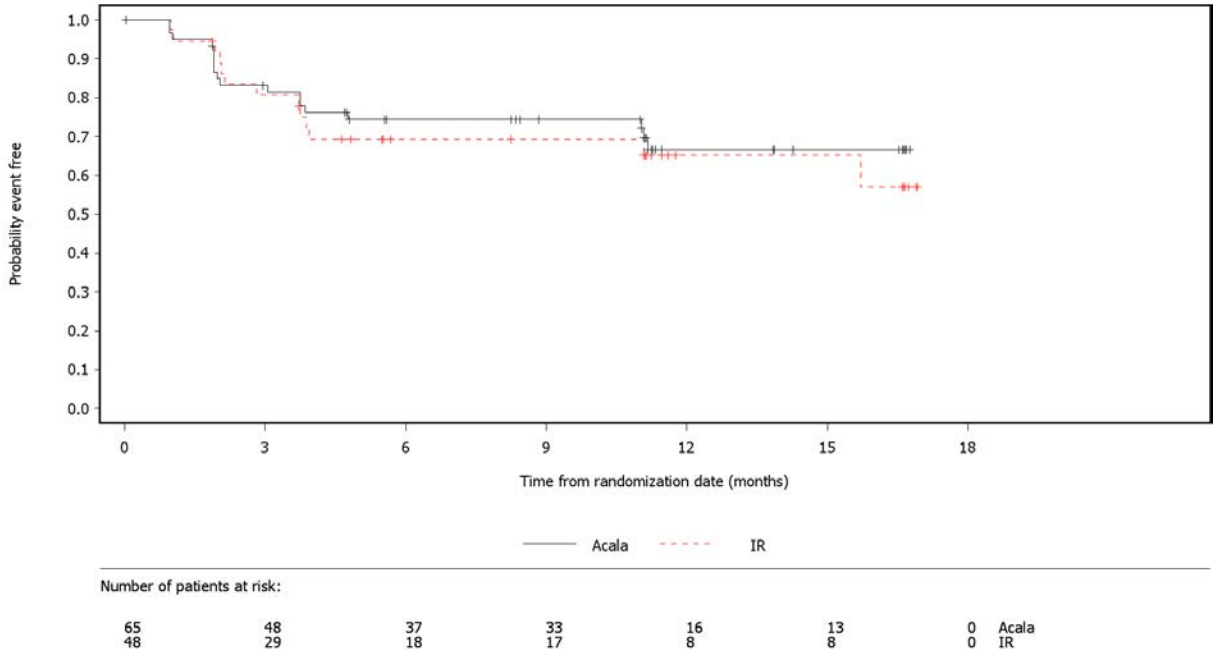

Figure 16: Kaplan-Meier-curves for symptoms, outcome "emotional functioning" (EORTC QLQ-C30, time to clinically relevant deterioration by ≥ 15 points), ASCEND study, data cut-off from 15 January 2019

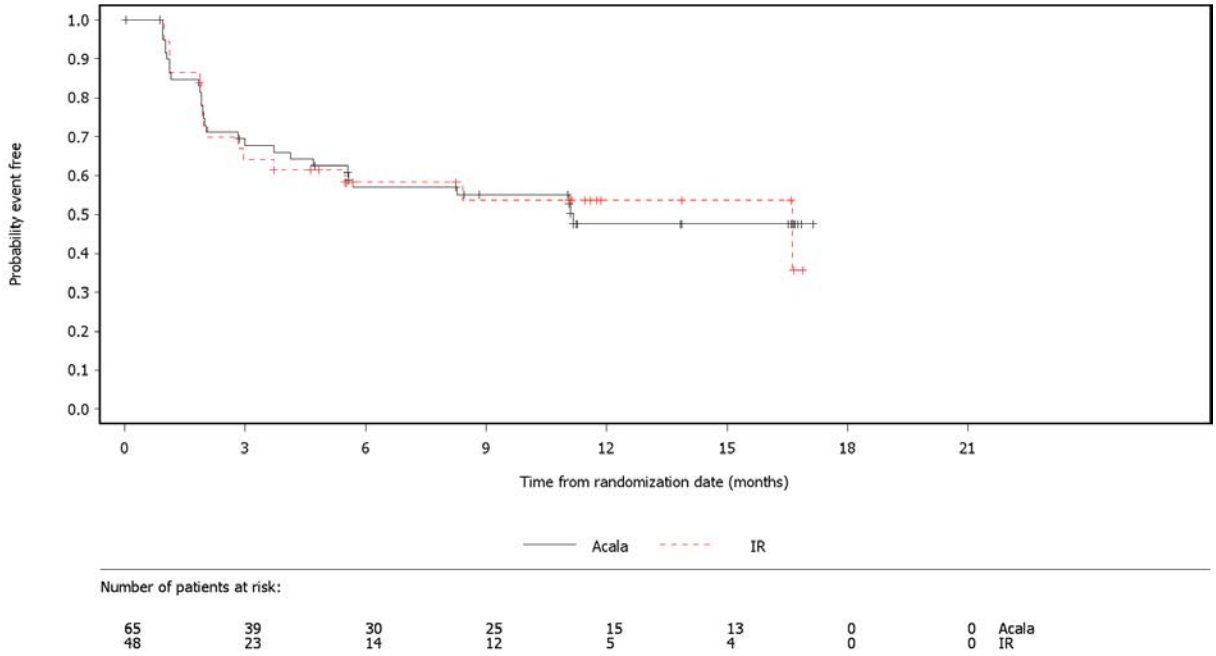

Figure 17: Kaplan-Meier-curves for symptoms, outcome "social functioning" (EORTC QLQ-C30, time to clinically relevant deterioration by ≥ 15 points), ASCEND study, data cut-off from 15 January 2019

B.4 – **Side effects**

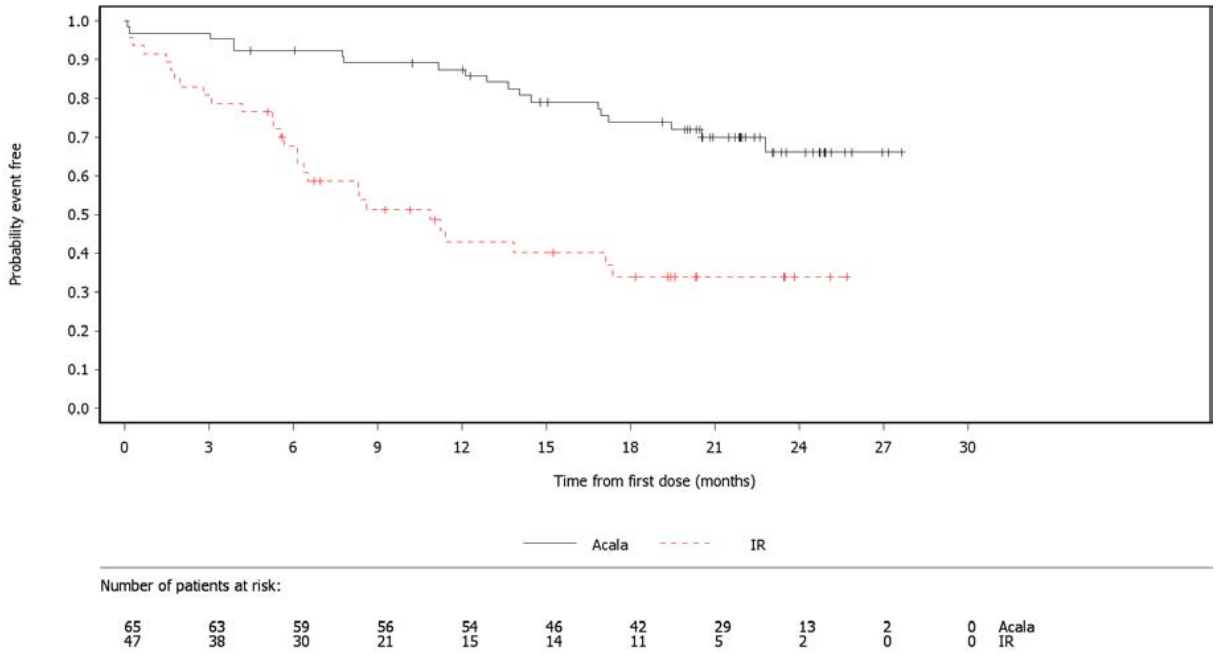

Figure 18: Kaplan-Meier curves, outcome "SAEs", ASCEND study, data cut-off from 1 August 2019

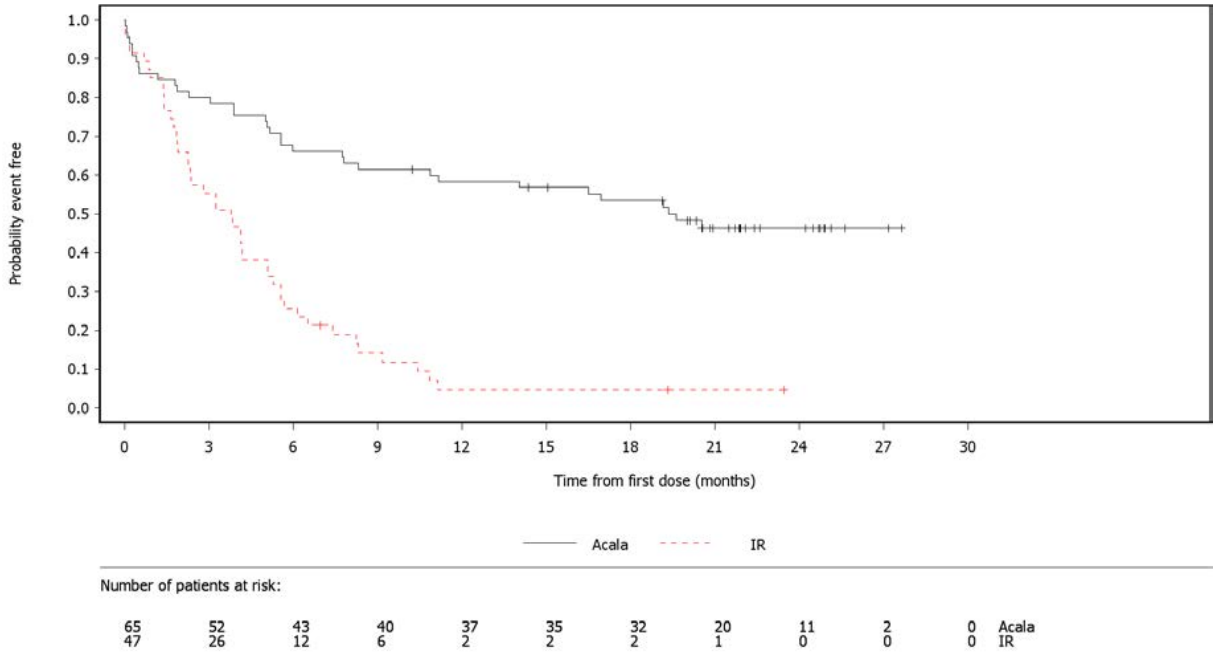

Figure 19: Kaplan-Meier curves, outcome "severe AEs" (CTCAE grade ≥ 3), ASCEND study, data cut-off from 1 August 2019

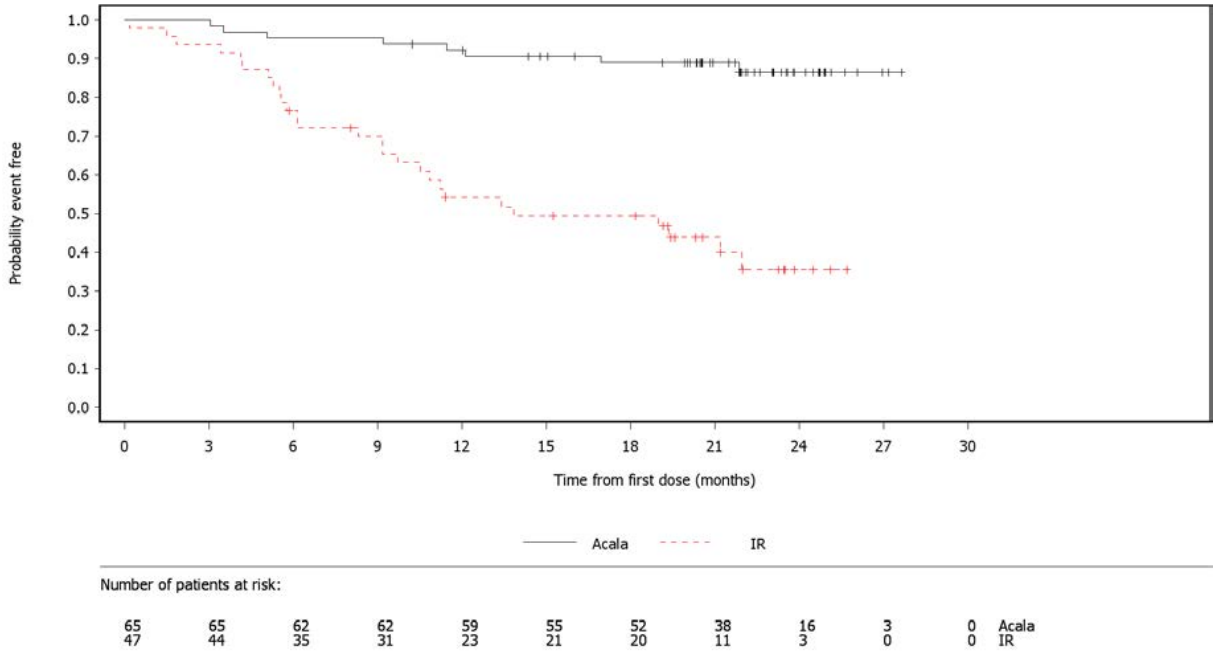

Figure 20: Kaplan-Meier curves, outcome "discontinuation due to AEs", ASCEND study, data cut-off from 1 August 2019

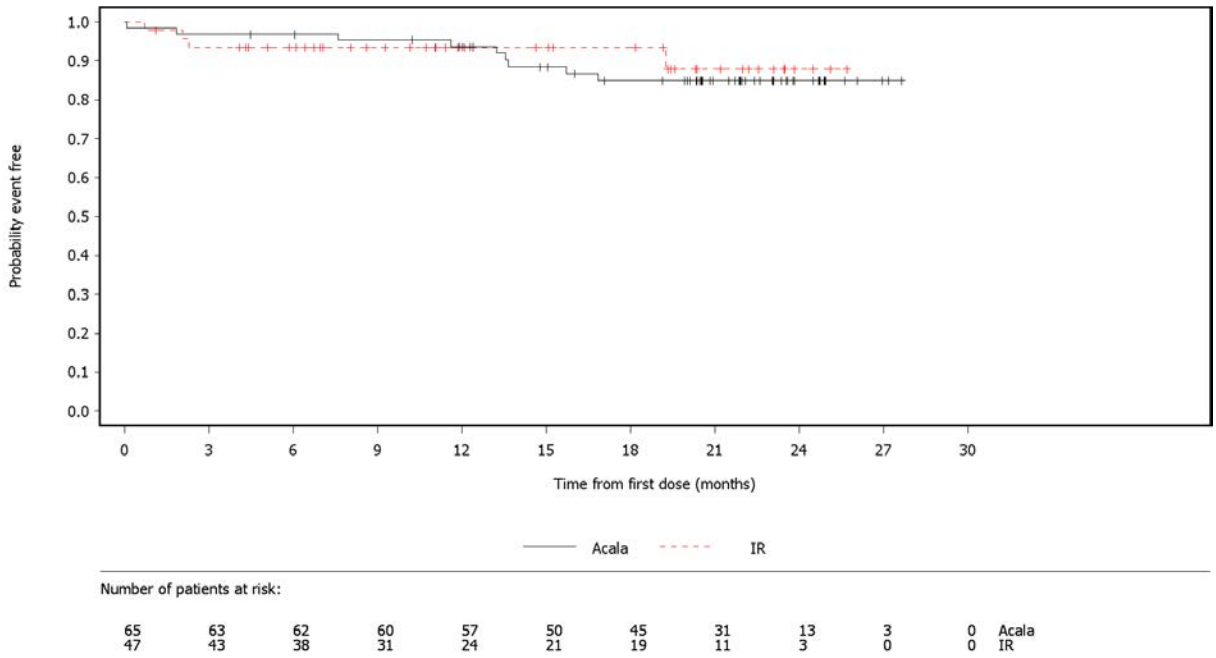

Figure 21: Kaplan-Meier curves, outcome "cardiac disorders" (SOC, AEs), ASCEND study, data cut-off from 1 August 2019

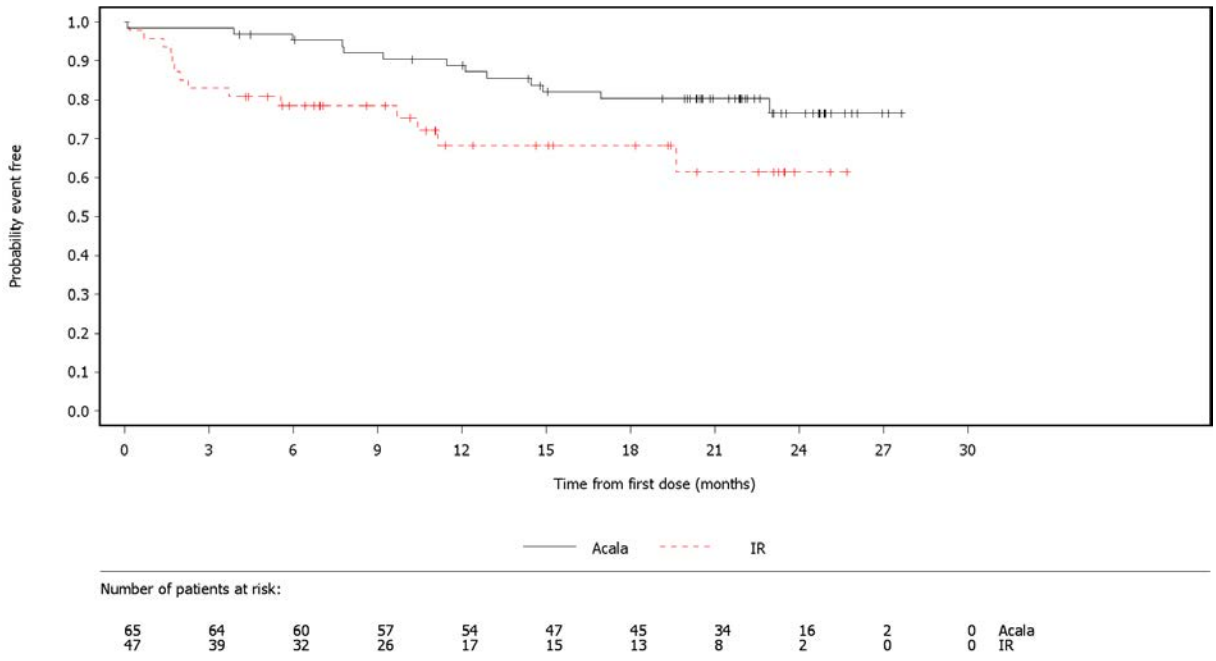

Figure 22: Kaplan-Meier curves, outcome "infections and infestations" (SOC, severe AEs [CTCAE ≥ 3]), ASCEND study, data cut-off from 1 August 2019

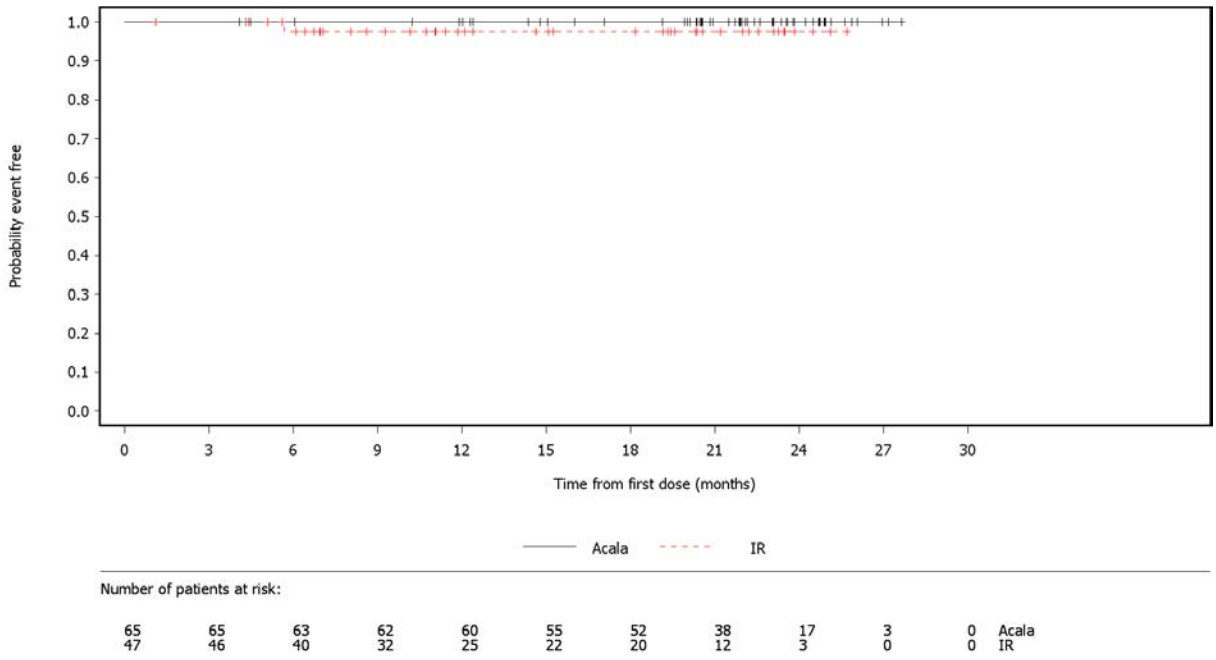

Figure 23: Kaplan-Meier curves, outcome "haemorrhages" (severe AEs [CTCAE ≥ 3]), ASCEND study, data cut-off from 1 August 2019

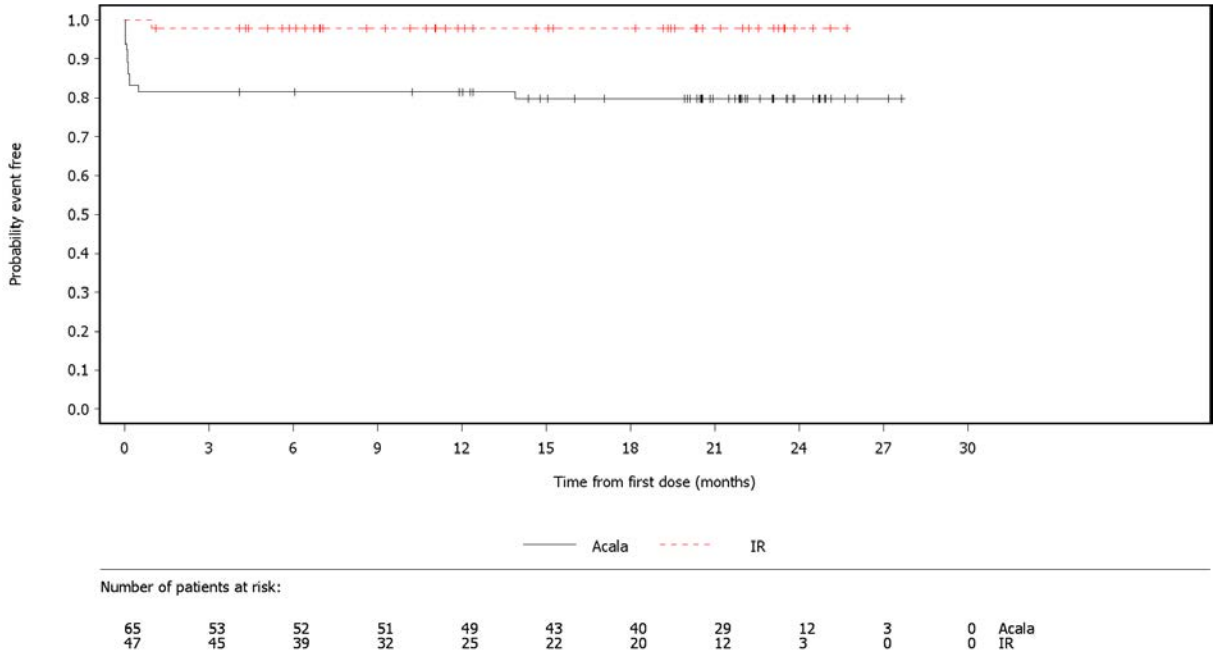

Figure 24: Kaplan-Meier curves, outcome "headache" (PT, AEs), ASCEND study, data cut-off from 1 August 2019

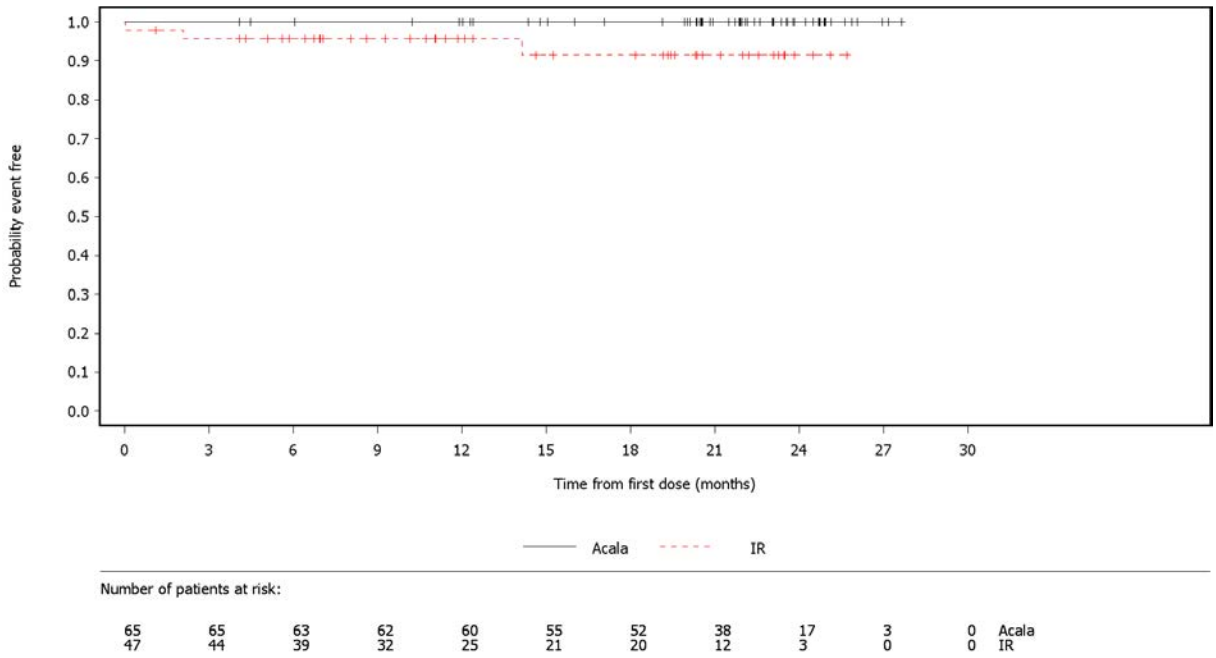

Figure 25: Kaplan-Meier curves, outcome "general disorders and administration site conditions" (SOC, severe AEs [CTCAE ≥ 3]), ASCEND study, data cut-off from 1 August 2019

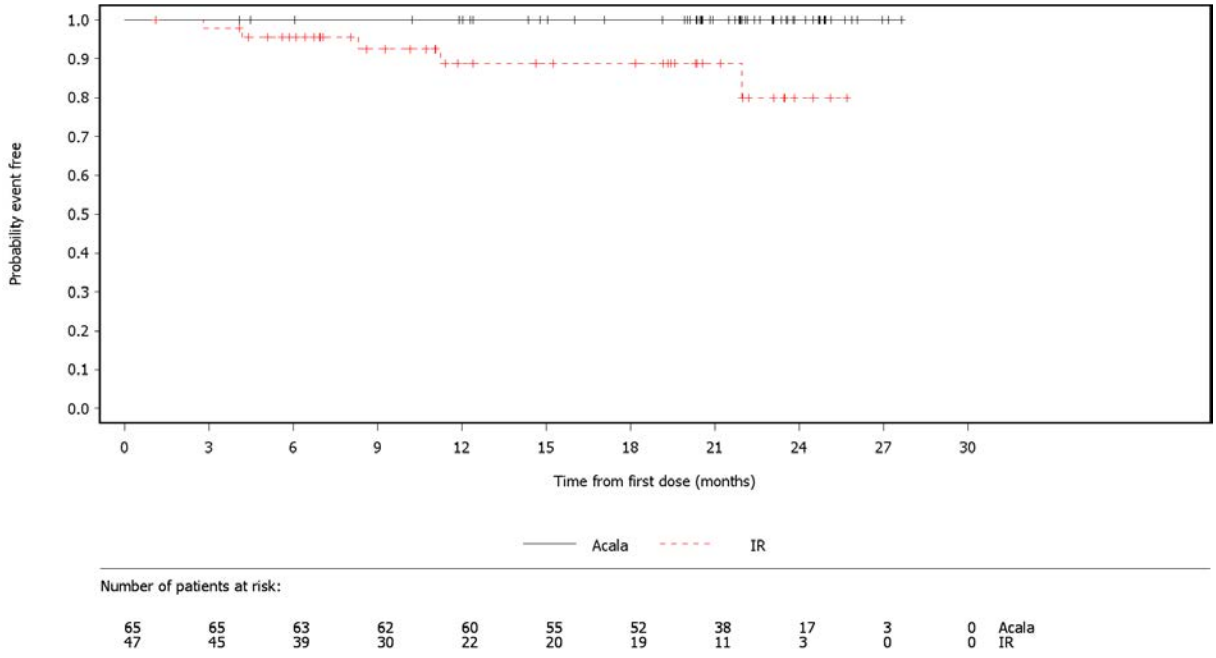

Figure 26: Kaplan-Meier curves, outcome "respiratory, thoracic and mediastinal disorders" (SOC, severe AEs [CTCAE ≥ 3]), ASCEND study, data cut-off from 1 August 2019

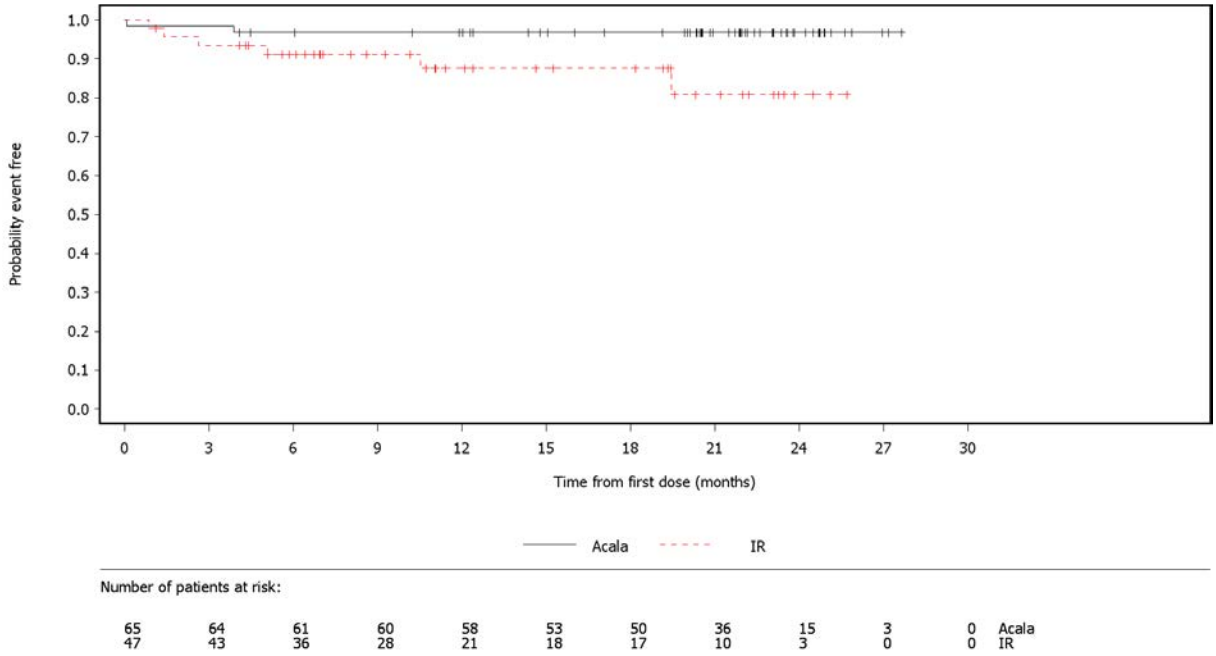

Figure 27: Kaplan-Meier curves, outcome "skin and subcutaneous tissue disorders" (SOC, severe AEs [CTCAE ≥ 3]), ASCEND study, data cut-off from 1 August 2019

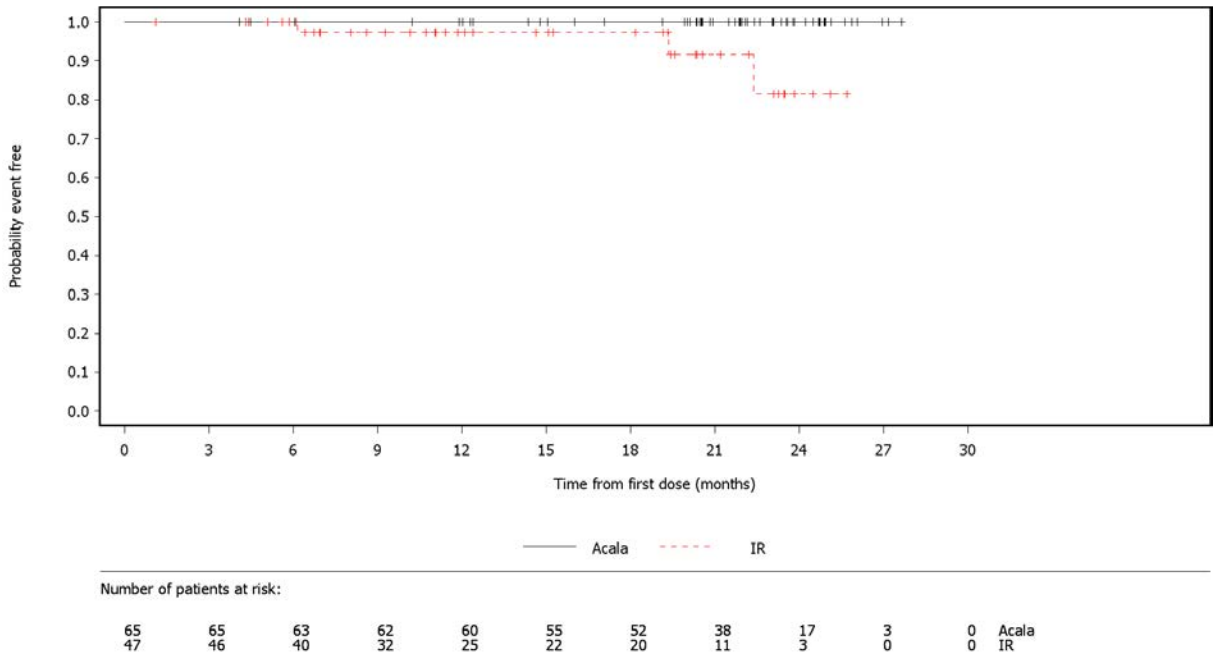

Figure 28: Kaplan-Meier curves, outcome "renal failure" (PT, severe AEs [CTCAE ≥ 3]), ASCEND study, data cut-off from 1 August 2019

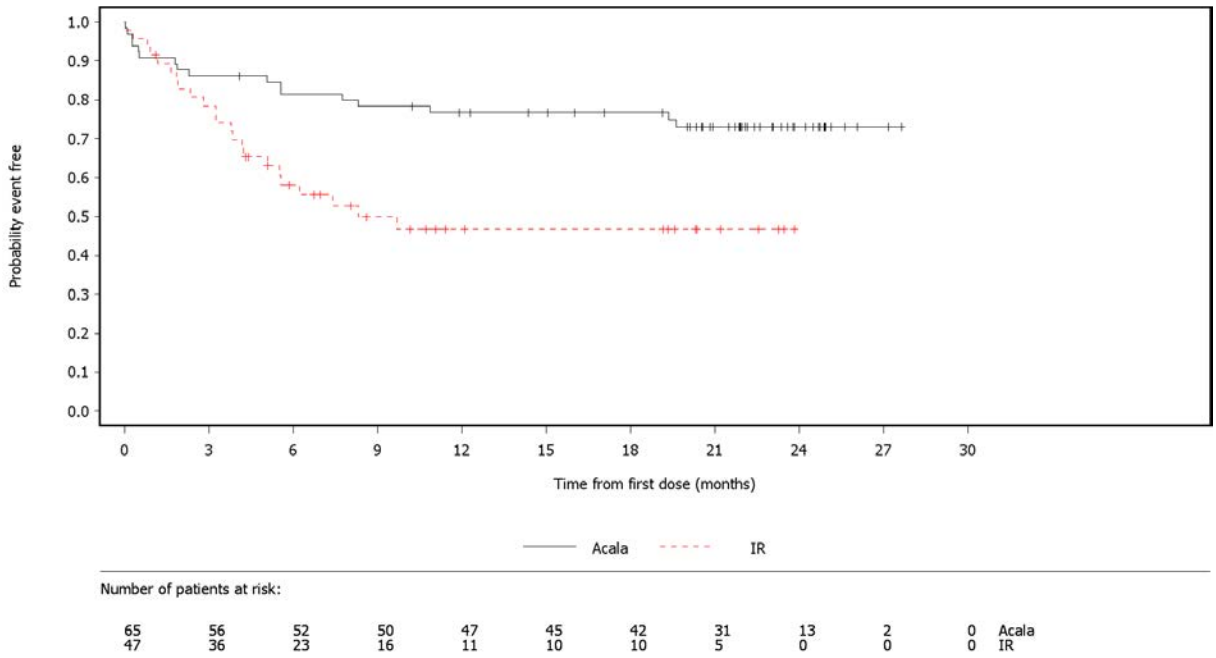

Figure 29: Kaplan-Meier curves, outcome "blood and lymphatic system disorders" (SOC, severe AEs [CTCAE ≥ 3]), ASCEND study, data cut-off from 1 August 2019

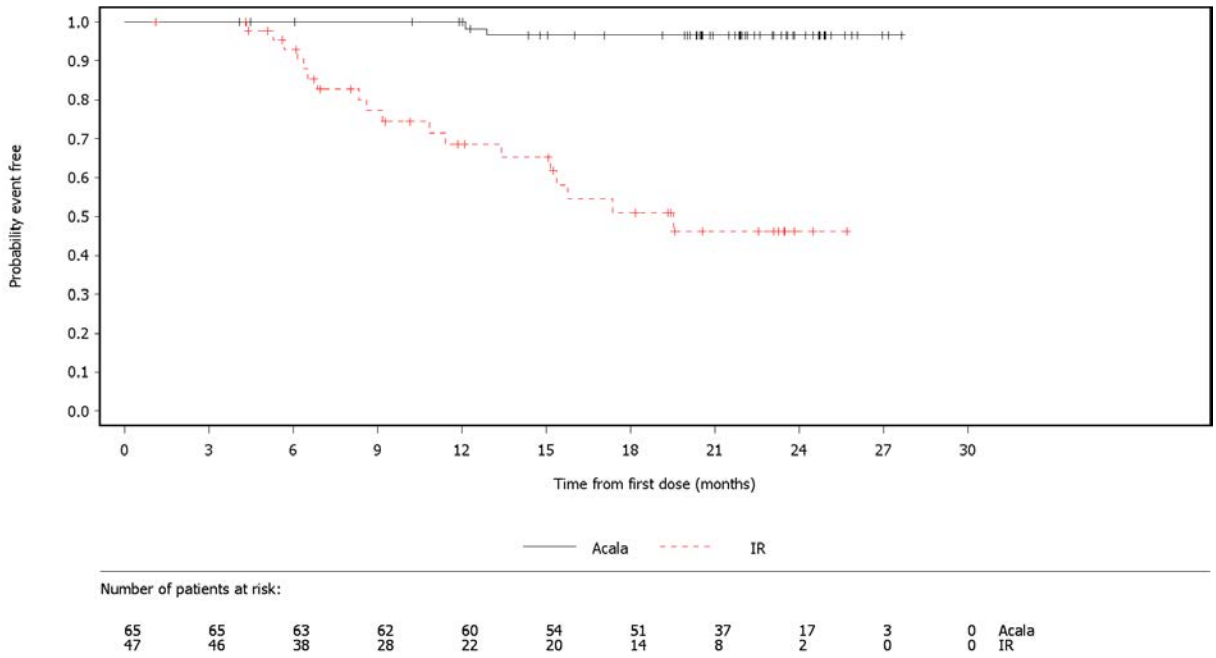

Figure 30: Kaplan-Meier curves, outcome "gastrointestinal disorders" (SOC, severe AEs [CTCAE ≥ 3]), ASCEND study, data cut-off from 1 August 2019

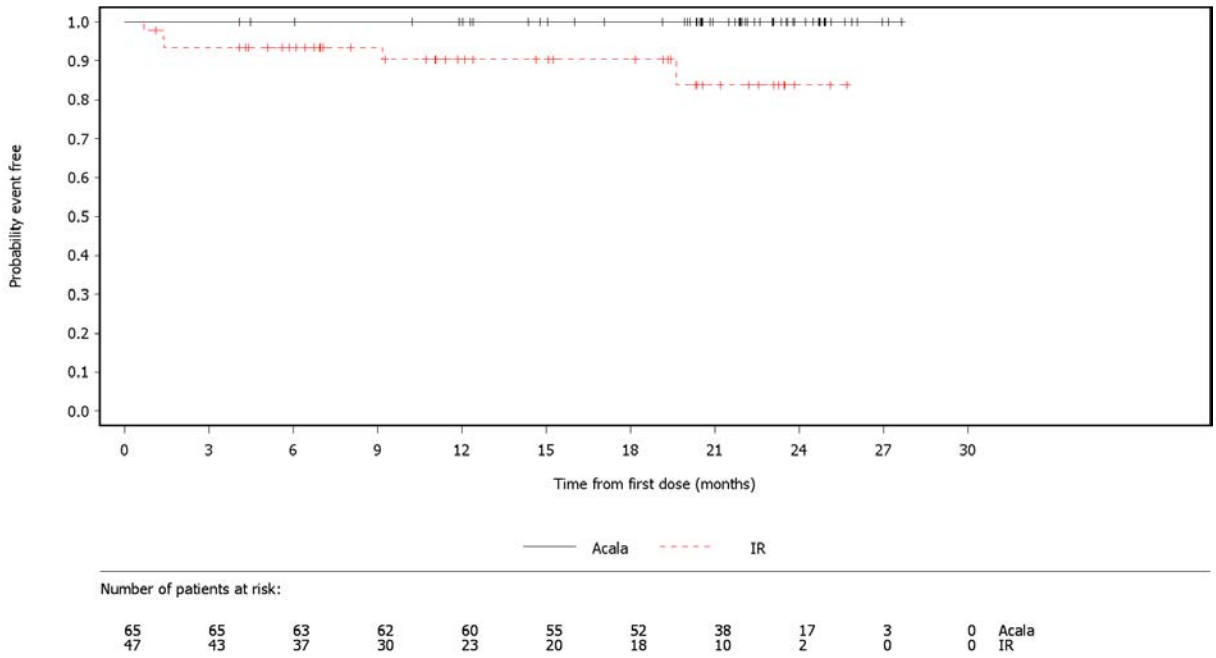

Figure 31: Kaplan-Meier curves, outcome "hepatobiliary disorders" (SOC, severe AEs [CTCAE ≥ 3]), ASCEND study, data cut-off from 1 August 2019

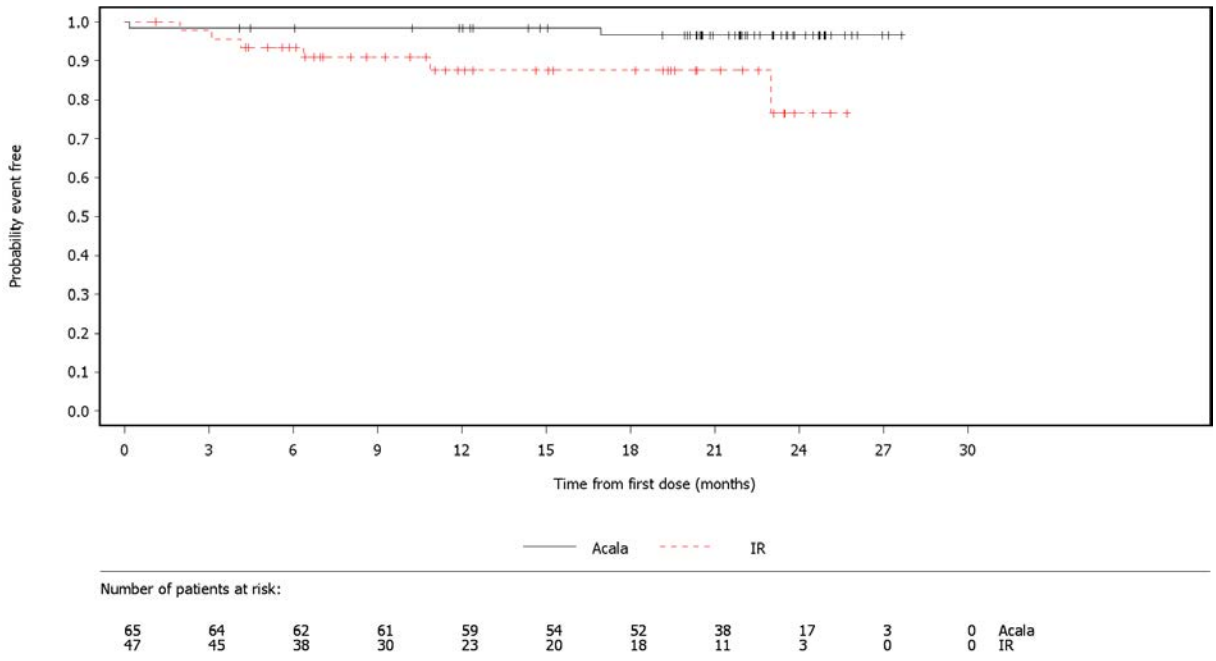

Figure 32: Kaplan-Meier curves, outcome "metabolism and nutrition disorders" (SOC, severe AEs [CTCAE ≥ 3]), ASCEND study, data cut-off from 1 August 2019

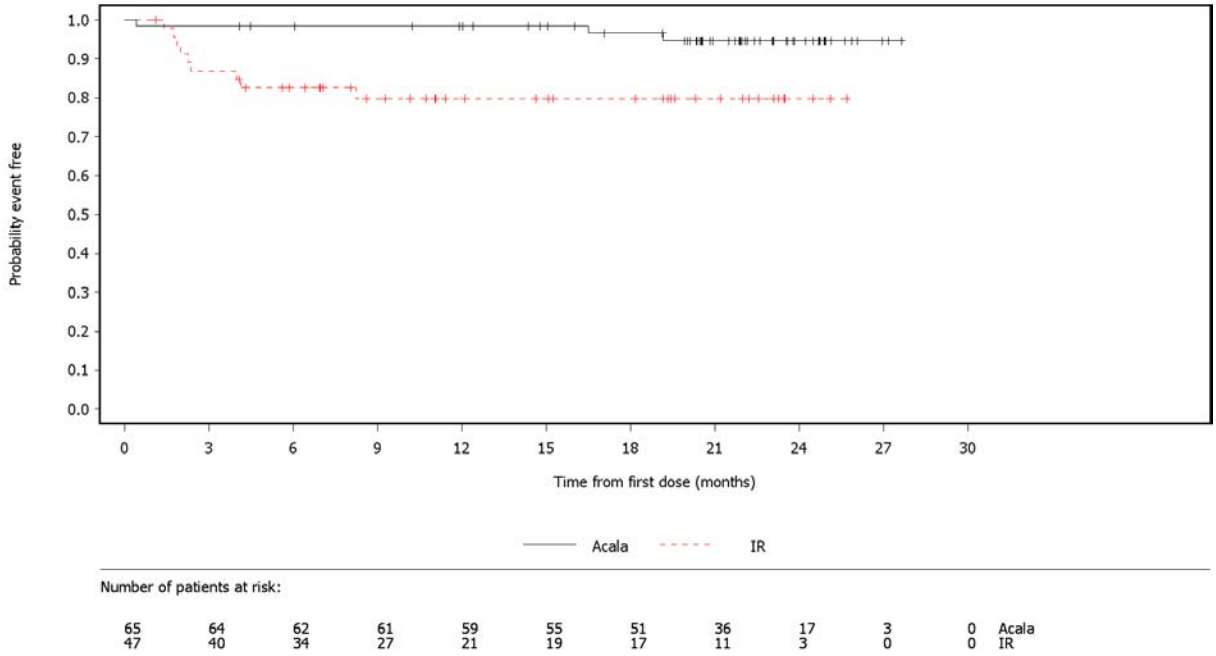

Figure 33: Kaplan-Meier curves, outcome "investigations" (SOC, severe AEs [CTCAE ≥ 3]), ASCEND study, data cut-off from 1 August 2019

Appendix C – Results on side effects: Adults with CLL; one prior therapy; chemo-immunotherapy unsuitable

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

Study	**Patients with event n (%)**	
SOC[b] **PT[b]**	**Acalabrutinib** **N = 65**	**Idelalisib + rituximab** **N = 47**
ASCEND		
Overall AE rate	62 (95.4)	47 (100.0)
General disorders and administration site conditions	15 (23.1)	15 (31.9)
Pyrexia	5 (7.7)	8 (17.0)
Respiratory, thoracic and mediastinal disorders	18 (27.7)	14 (29.8)
Cough	9 (13.8)	6 (12.8)
Skin and subcutaneous tissue disorders	24 (36.9)	19 (40.4)
Rash	3 (4.6)	9 (19.1)
Pruritus	2 (3.1)	5 (10.6)
Renal and urinary disorders	7 (10.8)	6 (12.8)
Blood and lymphatic system disorders	26 (40.0)	27 (57.4)
Anaemia	9 (13.8)	4 (8.5)
Neutropenia	17 (26.2)	20 (42.6)
Thrombocytopenia	9 (13.8)	6 (12.8)
Gastrointestinal disorders	32 (49.2)	33 (70.2)
Diarrhoea	16 (24.6)	25 (53.2)
Constipation	3 (4.6)	5 (10.6)
Nervous system disorders	19 (29.2)	6 (12.8)
Headache	13 (20.0)	1 (2.1)
Vascular disorders	8 (12.3)	8 (17.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	10 (15.4)	2 (4.3)
Cardiac disorders	9 (13.8)	4 (8.5)
Infections and infestations	38 (58.5)	31 (66.0)
Respiratory tract infection	8 (12.3)	2 (4.3)
Upper respiratory tract infection	11 (16.9)	9 (19.1)
Nasopharyngitis	3 (4.6)	5 (10.6)
Pneumonia	7 (10.8)	5 (10.6)
Hepatobiliary disorders	1 (1.5)	8 (17.0)
Musculoskeletal and connective tissue disorders	16 (24.6)	13 (27.7)
Arthralgia	4 (6.2)	5 (10.6)
Back pain	7 (10.8)	3 (6.4)
Metabolism and nutrition disorders	13 (20.0)	15 (31.9)
Hypokalaemia	1 (1.5)	6 (12.8)

Table 16: Common AEs[a] – RCT, direct comparison: acalabrutinib vs. idelalisib + rituximab (adults with CLL; one prior therapy; chemo-immunotherapy unsuitable) (multipage table)

Study	**Patients with event n (%)**	
SOC[b] **PT[b]**	**Acalabrutinib** **N = 65**	**Idelalisib + rituximab** **N = 47**
Investigations	12 (18.5)	21 (44.7)
Alanine aminotransferase increased	2 (3.1)	8 (17.0)
Aspartate aminotransferase increased	2 (3.1)	7 (14.9)
Transaminases increased	0 (0)	6 (12.8)
Injury, poisoning and procedural complications	10 (15.4)	8 (17.0)

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 analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class

Table 17: Common severe AEs[a] (CTCAE grade ≥ 3) – RCT, direct comparison: acalabrutinib vs. idelalisib + rituximab (adults with CLL; one prior therapy; chemo-immunotherapy unsuitable)

Study	**Patients with event n (%)**	
SOC[b] **PT[b]**	**Acalabrutinib** **N = 65**	**Idelalisib + rituximab** **N = 47**
ASCEND		
Overall rate of severe AEs (CTCAE grade ≥ 3)	34 (52.3)	44 (93.6)
General disorders and administration site conditions	0 (0)	3 (6.4)
Respiratory, thoracic and mediastinal disorders	0 (0)	5 (10.6)
Skin and subcutaneous tissue disorders	2 (3.1)	6 (12.8)
Renal and urinary disorders	0 (0)	4 (8.5)
Renal failure	0 (0)	3 (6.4)
Blood and lymphatic system disorders	17 (26.2)	23 (48.9)
Anaemia	6 (9.2)	2 (4.3)
Neutropenia	13 (20.0)	19 (40.4)
Thrombocytopenia	3 (4.6)	3 (6.4)
Gastrointestinal disorders	2 (3.1)	18 (38.3)
Diarrhoea	1 (1.5)	13 (27.7)
Vascular disorders	3 (4.6)	3 (6.4)
Infections and infestations	13 (20.0)	14 (29.8)
Pneumonia	4 (6.2)	4 (8.5)
Hepatobiliary disorders	0 (0)	5 (10.6)
Metabolism and nutrition disorders	2 (3.1)	6 (12.8)
Hypokalaemia	0 (0)	3 (6.4)
Investigations	3 (4.6)	9 (19.1)
Alanine aminotransferase increased	1 (1.5)	4 (8.5)
Transaminases increased	0 (0)	5 (10.6)

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 analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class

Table 18: Common SAEs[a] – RCT, direct comparison: acalabrutinib vs. idelalisib + rituximab (adults with CLL; one prior therapy; chemo-immunotherapy unsuitable)

Study	**Patients with event n (%)**	
SOC[b] **PT[b]**	**Acalabrutinib** **N = 65**	**Idelalisib + rituximab** **N = 47**
ASCEND		
Overall SAE rate	19 (29.2)	28 (59.6)
Respiratory, thoracic and mediastinal disorders	0 (0)	5 (10.6)
Renal and urinary disorders	1 (1.5)	3 (6.4)
Gastrointestinal disorders	2 (3.1)	13 (27.7)
Diarrhoea	1 (1.5)	8 (17.0)
Cardiac disorders	4 (6.2)	0 (0)
Infections and infestations	10 (15.4)	12 (25.5)
Pneumonia	3 (4.6)	4 (8.5)

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 analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class

Table 19: Discontinuation due to AEs – RCT, direct comparison: acalabrutinib vs. idelalisib + rituximab (adults with CLL; one prior therapy; chemo-immunotherapy unsuitable)(multipage table)

Study	**Patients with event n (%)**	
SOC[a] **PT[a]**	**Acalabrutinib** **N = 65**	**Idelalisib + rituximab** **N = 47**
ASCEND		
Overall rate of discontinuations due to AEs[b]	8 (12.3)	27 (57.4)
Respiratory, thoracic and mediastinal disorders	1 (1.5)	4 (8.5)
Interstitial lung disease	0 (0)	3 (6.4)
Pneumonitis	0 (0)	1 (2.1)
Pulmonary mass	1 (1.5)	0 (0)
Skin and subcutaneous tissue disorders	0 (0)	1 (2.1)
Pruritus	0 (0)	1 (2.1)
Renal and urinary disorders	1 (1.5)	0 (0)
Haematuria	1 (1.5)	0 (0)
Blood and lymphatic system disorders	1 (1.5)	0 (0)
Cytopenia	1 (1.5)	0 (0)
Gastrointestinal disorders	0 (0)	12 (25.5)
Diarrhoea	0 (0)	9 (19.1)
Colitis	0 (0)	2 (4.3)
Oesophagitis	0 (0)	1 (2.1)
Ear and labyrinth disorders	0 (0)	1 (2.1)
Vertigo	0 (0)	1 (2.1)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2 (3.1)	1 (2.1)
Bladder transitional cell carcinoma	1 (1.5)	0 (0)
Epstein-Barr virus positive mucocutaneous ulcer	0 (0)	1 (2.1)
Lung neoplasm malignant	1 (1.5)	0 (0)
Infections and infestations	3 (4.6)	3 (6.4)
Respiratory tract infection	1 (1.5)	0 (0)
Rash pustular	0 (0)	1 (2.1)
Hepatitis B	1 (1.5)	0 (0)
Peritonitis	1 (1.5)	0 (0)
Pneumonia	0 (0)	1 (2.1)
Pneumonia legionella	0 (0)	1 (2.1)
Septic shock	0 (0)	1 (2.1)
Hepatobiliary disorders	0 (0)	1 (2.1)
Hepatocellular injury	0 (0)	1 (2.1)

Table 19: Discontinuation due to AEs – RCT, direct comparison: acalabrutinib vs. idelalisib + rituximab (adults with CLL; one prior therapy; chemo-immunotherapy unsuitable)(multipage table)

Study	**Patients with event n (%)**	
SOC[a] **PT[a]**	**Acalabrutinib** **N = 65**	**Idelalisib + rituximab** **N = 47**
Metabolism and nutrition disorders	1 (1.5)	0 (0)
Dehydration	1 (1.5)	0 (0)
Investigations	0 (0)	5 (10.6)
Alanine aminotransferase increased	0 (0)	1 (2.1)
Hepatitis B DNA assay positive	0 (0)	1 (2.1)
Transaminases increased	0 (0)	3 (6.4)

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 analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class