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Acalabrutinib (previously untreated chronic lymphocytic leukaemia; combination with obinutuzumab) –

Addendum to Commission A20-104[1]

Addendum

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List of abbreviations

Abbreviation	Meaning
17p deletion	deletion of the short arm of chromosome 17
AE	adverse event
CLL	chronic lymphocytic leukaemia
CTCAE	Common Terminology Criteria for Adverse Events
ECOG PS	Eastern Cooperative Oncology Group Performance Status
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
FCR	fludarabine + cyclophosphamide + rituximab
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)
MMRM	mixed-effects model with repeated measures
QLQ-C30	Quality of Life Questionnaire-Core 30
RCT	randomized controlled trial
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 A20-104 (Acalabrutinib, combination with obinutuzumab – 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 randomized controlled trial (RCT) ELEVATE-TN for the benefit assessment of acalabrutinib in combination with obinutuzumab (hereinafter referred to as "acalabrutinib + obinutuzumab") in adult patients with previously untreated chronic lymphocytic leukaemia (CLL). This study was used to derive the added benefit of acalabrutinib + obinutuzumab in adult patients with previously untreated CLL 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 treatment with fludarabine + cyclophosphamide + rituximab (FCR) is not an option (research question 2 of the benefit assessment). In the dossier submitted by the company, information on treatment and study discontinuation and on treatment duration was missing in Modules 1 to 4 B. Furthermore, the company's dossier contained no information on the severity of the discontinuations due to adverse events (AEs) and no analyses of the outcome "disease-related symptoms" recorded in the ELEVATE-TN study. The analyses presented by the company in Module 4 B for the outcome categories of morbidity and health-related quality of life, however, were not usable. With its comments, the company subsequently submitted the missing data and analyses, as well as new analyses on the included patient-reported outcomes [3].

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 following analyses presented by the company in the commenting procedure, taking into account the information in the dossier, for research question 2 (adult patients with previously untreated CLL who have no 17p deletion or TP53 mutation and for whom treatment with FCR is not an option):

- treatment and study discontinuations as well as treatment duration of all treatment components
- patient-reported outcomes recorded with Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue), European Quality of Life-5 Dimensions (EQ-5D) visual analogue scale (VAS), European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Core 30 (QLQ-C30)
- outcome "disease-related symptoms"
- outcome "treatment discontinuations due to AEs"

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

The ELEVATE-TN study is an ongoing, randomized, 3-arm, open-label phase 3 study comparing acalabrutinib or acalabrutinib + obinutuzumab with chlorambucil + obinutuzumab in adult patients with previously untreated CLL requiring treatment. Adult patients with previously untreated CLL who have no 17p deletion or TP53 mutation and for whom treatment with FCR is not an option are relevant for research question 2 of dossier assessment A20-104 considered in the present addendum (research question 2 of dossier assessment A20-104 [1]). A detailed description of the relevant subpopulation, the characteristics of the study and of the interventions, the data cut-offs and a presentation of the results on the included patient-relevant outcomes can be found in dossier assessment A20-104 [1].

2.1 Data on treatment and study discontinuation

Module 4 B contained no data on treatment and study discontinuation for the relevant subpopulation for dossier assessment A20-104. These data were subsequently submitted by the company.

Table 1 shows the data on treatment and study discontinuation for the relevant subpopulation at the second data cut-off (1 August 2019).

Table 1: Information on patients with treatment discontinuation or study discontinuation (data cut-off on 1 August 2019) – RCT, direct comparison: acalabrutinib + obinutuzumab vs. chlorambucil + obinutuzumab (patients for whom treatment with FCR is not an option)

Study Characteristic	Acalabrutinib + obinutuzumab N = 99	Chlorambucil + obinutuzumab N = 95
ELEVATE-TN		
Treatment discontinuation[a], n (%)	24 (24.2)	91 (95.8)[b]
Study discontinuation, n (%)	13 (13.1)[c]	21 (22.1)[d]

a. Discontinuation of the therapy assigned by randomization.
b. According to information from the European assessment report [4], this information includes a relevant proportion of patients who completed their treatment regimen: Of the total of N = 177 randomized patients in the chlorambucil + obinutuzumab arm, this applies to 137 patients (77.4%).
c. Including 3 deaths (3.0%).
d. Including 10 deaths (10.5%).

FCR: fludarabine + cyclophosphamide + rituximab; n: number of patients in the category; N: number of randomized patients; RCT: randomized controlled trial

Overall, markedly more patients discontinued their treatment in the comparator arm than in the intervention arm. However, according to the European assessment report [4], the data on the comparator arm also include patients who completed their treatment regimen.

2.2 Information on the course of the study

Module 4 B contained no information on treatment duration for the relevant subpopulation for dossier assessment A20-104. These data were presented by the company with its comments.

Table 2 shows the median and mean treatment duration of all drug components for the relevant subpopulation at the second data cut-off (1 August 2019).

Table 2: Information on treatment duration (data cut-off from 1 August 2019) – RCT, direct comparison: acalabrutinib + obinutuzumab vs. chlorambucil + obinutuzumab (patients for whom treatment with FCR is not an option)

Study **Duration of the study phase** **Treatment component**	**Acalabrutinib + obinutuzumab** **N = 99**	**Chlorambucil + obinutuzumab** **N = 91**
ELEVATE-TN		
Treatment duration [months]		
Acalabrutinib		Not applicable
Median [min; max]	33.3 [2.1; 45.1]	-
Mean (SD)	30.7 (10.7)	-
Chlorambucil	Not applicable	
Median [min; max]	-	5.5 [0.5; 7.2][a]
Mean (SD)	-	5.2 (1.3)[a]
Obinutuzumab		
Median [min; max]	5.5 [0.9; 7.1][a]	5.6 [0.9; 7.2][a]
Mean (SD)	5.3 (1.1)[a]	5.5 (1.3)[a]

a. Institute's calculation from data in days.

FCR: fludarabine + cyclophosphamide + rituximab; max: maximum; min: minimum; N: number of analysed patients; RCT: randomized controlled trial; SD: standard deviation

The data show that due to the different treatment regimens at the data cut-off from 1 August 2019, the treatment in the intervention arm of the relevant subpopulation was overall about 6 times longer than in the comparator arm. The results on AEs (see A20-104 [1]) and on disease-related symptoms are based on this non-prespecified data cut-off; the results on the other patient-reported outcomes are based on the prespecified data cut-off from 8 February 2019.

2.3 Results on added benefit

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)

In Module 4 B, the company had presented both analyses of mean changes and responder analyses for the following outcomes: fatigue recorded with the FACIT-Fatigue, symptoms and health-related quality of life recorded with the EORTC QLQ-C30, and health status recorded with the EQ-5D VAS. None of these analyses were rated as usable (see dossier assessment [1]). In the commenting procedure, the company presented new analyses for both types of analysis.

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 [5].

The analyses of the mean change for the EORTC QLQ-C30 are presented in Table 7 in Appendix A.

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

The responder analyses presented by the company in Module 4 B of the dossier were not used for the benefit assessment, as only time points with a response rate of at least 70% were included in the responder analyses. In addition, patients were censored at the time point of the last recording before 2 or more missed visits if symptoms had progressed thereafter. In addition, with reference to the *General Methods* 6.0 [5], it was noted in the dossier assessment for the instruments FACIT-Fatigue and EQ-5D VAS that, for a response criterion to reflect with sufficient certainty a patient-noticeable change, it should correspond to at least 15% of the scale range of an instrument when prespecified (in post-hoc analyses exactly 15% of the scale range).

The company now presented usable responder analyses with its comments. The new analyses cover all documentation times regardless of the response rates. The company only still conducted a censoring of patients at the time point of the last recording before 2 or more missed visits if symptoms had progressed thereafter. In its comments, the company justified this by stating that such censoring is comprehensible if the time between the event and the most recent visit before that event was too long to make a valid statement regarding the time point of occurrence. 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 [6,7].

- 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.

Risk of bias

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). This is due to the fact that ≥ 10% of the patients were censored at baseline and thus did not actually contribute any information to the analysis. In addition, there was a decreasing return of questionnaires, which was differential between the treatment arms, and which was not caused by deaths.

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 ELEVATE-TN study:

- unintentional weight loss ≥ 10% within the previous 6 months
- significant fatigue (e.g. Eastern Cooperative Oncology Group Performance Status [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. Thus, only 47 patients in the intervention arm (47%) and 45 patients in the comparator arm (47%) 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 8 in Appendix A.

Risk of bias

There are no usable data for the outcome "disease-related symptoms". Therefore, the risk of bias was not assessed for this outcome.

2.3.1 Results

The results on the patient-relevant outcomes subsequently submitted in the commenting procedure are presented in Table 3.

Kaplan-Meier curves for the event time analyses can be found in Appendix B.

Table 3: Results (morbidity, health-related quality of life, data cut-off from 8 February 2019) – RCT, direct comparison: acalabrutinib + obinutuzumab vs. chlorambucil + obinutuzumab (patients for whom treatment with FCR is not an option) (multipage table)

Study **Outcome category** **Outcome**	**Acalabrutinib + obinutuzumab**		**Chlorambucil + obinutuzumab**		**Acalabrutinib + obinutuzumab vs. chlorambucil + obinutuzumab**
	N[a]	**Median time to event in months [95% CI]** **Patients with event n (%)**	**N[a]**	**Median time to event in months [95% CI]** **Patients with event n (%)**	**HR [95% CI]; p-value[b]**
ELEVATE-TN					
Morbidity					
Fatigue (FACIT-Fatigue)[c]	99	NA 24 (24.2)	95	NA 16 (16.8)	1.18 [0.63; 2.26]; 0.620
Disease-related symptoms[d]			No usable data available[e]		
EORTC QLQ-C30 – symptom scales[f]					
Fatigue	99	NA 33 (33.3)	95	NA 18 (18.9)	1.54 [0.87; 2.79]; 0.143
Nausea and vomiting	99	NA 30 (30.3)	95	NA 21 (22.1)	1.15 [0.66; 2.04]; 0.627
Pain	99	11.1 [3.7; NC] 48 (48.5)	95	17.5 [6.7; NC] 33 (34.7)	1.33 [0.86; 2.09]; 0.207
Dyspnoea	99	NA 39 (39.4)	95	NA 25 (26.3)	1.36 [0.82; 2.27]; 0.241
Insomnia	99	22.3 [4.8; NC] 41 (41.4)	95	NA 28 (29.5)	1.25 [0.78; 2.05]; 0.366
Appetite loss	99	NA 28 (28.3)	95	NA 19 (20.0)	1.10 [0.62; 2.01]; 0.747
Constipation	99	33.3 [22.1; NC] 34 (34.3)	95	33.1 [12.0; NC] 30 (31.6)	0.79 [0.48; 1.31]; 0.359
Diarrhoea	99	16.7 [11.1; 33.3] 48 (48.5)	95	NA 15 (15.8)	2.67 [1.53; 4.95]; < 0.001
Health status (EQ-5D VAS)[g]	99	NA 27 (27.3)	95	NA 22 (23.2)	0.85 [0.48; 1.52]; 0.581
Health-related quality of life					
EORTC QLQ-C30 – functional scales[f]					
Global health status	99	NA 37 (37.4)	95	28.1 [16.8; NC] 27 (28.4)	1.08 [0.66; 1.79]; 0.775
Physical functioning	99	NA 25 (25.3)	95	NA 12 (12.6)	1.69 [0.86; 3.49]; 0.134
Role functioning	99	5.7 [2.8; NC] 49 (49.5)	95	16.8 [5.7; NC] 33 (34.7)	1.33 [0.86; 2.09]; 0.208
Emotional functioning	99	33.2 [27.6; NC] 34 (34.3)	95	NA 24 (25.3)	1.01 [0.60; 1.73]; 0.975

Table 3: Results (morbidity, health-related quality of life, data cut-off from 8 February 2019) – RCT, direct comparison: acalabrutinib + obinutuzumab vs. chlorambucil + obinutuzumab (patients for whom treatment with FCR is not an option) (multipage table)

Study Outcome category Outcome	Acalabrutinib + obinutuzumab		Chlorambucil + obinutuzumab		Acalabrutinib + obinutuzumab vs. chlorambucil + obinutuzumab
	N[a]	Median time to event in months [95% CI] Patients with event n (%)	N[a]	Median time to event in months [95% CI] Patients with event n (%)	HR [95% CI]; p-value[b]
Cognitive functioning	99	16.7 [4.7; NC] 47 (47.5)	95	28.1 [11.0; NC] 30 (31.6)	1.30 [0.82; 2.07]; 0.277
Social functioning	99	11.1 [3.1; NC] 48 (48.5)	95	16.6 [4.6; NC] 36 (37.9)	1.11 [0.72; 1.72]; 0.650

a. In the event time analyses, all patients without evaluable visits or without baseline data on the day of randomization were censored. This amounts to ≥ 10% of randomized patients who did not actually contribute any information to the event time analysis.
b. HR (incl. 95% CI) calculated using an unstratified Cox proportional hazards model. The p-value was calculated using an unstratified log-rank test.
c. Time to first deterioration; defined as a decrease in score by ≥ 7.8 points compared with baseline (scale range: 0-52).
d. 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.
e. See Section 2.3 of the present addendum for reasons.
f. Time to first deterioration, defined as an increase in score by ≥ 15 points (for the symptom scales) or a decrease in score by ≥ 15 points (for the functional scales) in comparison with baseline (scale range: 0-100).
g. Time to first deterioration; defined as a decrease in score by ≥ 15 points in comparison with baseline (scale range: 0-100).

CI: confidence interval; ECOG PS: Eastern Cooperative Oncology Group Performance Status; EORTC: European Organisation for Research and Treatment of Cancer; EQ-5D: European Quality of Life-5 Dimensions; FACIT: Functional Assessment of Chronic Illness Therapy; FCR: fludarabine + cyclophosphamide + rituximab; HR: hazard ratio; n: number of patients with (at least one) event; N: number of analysed patients; NA: not achieved; NC: not calculable; QLQ-C30: Quality of Life Questionnaire-Core 30; RCT: randomized controlled trial; VAS: visual analogue scale

Morbidity

Fatigue (FACIT-Fatigue), health status (EQ-5D VAS)

No statistically significant difference between the treatment groups was shown for the time to first deterioration for each of the outcomes "fatigue" (FACIT-Fatigue) and "health status" (EQ-5D VAS). In each case, this resulted in no hint of an added benefit of acalabrutinib + obinutuzumab in comparison with chlorambucil + obinutuzumab; an added benefit is therefore not proven.

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 + obinutuzumab in comparison with chlorambucil + obinutuzumab; an added benefit is therefore not proven.

Symptoms (EORTC QLQ-C30 [symptom scales])

A statistically significant difference to the disadvantage of acalabrutinib + obinutuzumab in comparison with chlorambucil + obinutuzumab was shown for the symptom scale "diarrhoea" for the time to first deterioration. This resulted in a hint of lesser benefit of acalabrutinib + obinutuzumab in comparison with chlorambucil + obinutuzumab. No statistically significant difference between the treatment groups was shown for the time to first deterioration for each of the other EORTC QLQ-C30 symptom scales. In each case, this resulted in no hint of an added benefit or lesser benefit of acalabrutinib + obinutuzumab in comparison with chlorambucil + obinutuzumab; an added benefit is therefore not proven.

Health-related quality of life

EORTC QLQ-C30 (functional scales)

For the outcome "health-related quality of life" recorded with the global health status and the EORTC QLQ-C30 functional scales, there was no statistically significant difference between the treatment groups for the time to first deterioration. In each case, this resulted in no hint of an added benefit of acalabrutinib + obinutuzumab in comparison with chlorambucil + obinutuzumab; an added benefit is therefore not proven.

2.4 Assessment of the added benefit at outcome level

Based on the results presented in the present addendum in Section 2.3.1 and the assessment of the outcome category for the outcome "discontinuation due to AEs" presented below, the extent of the respective added benefit is estimated at outcome level (see Table 4).

Determination of the outcome category for the outcome "discontinuation due to AEs" (≥ 1 component)

In its comments, the company subsequently submitted data on the severity grade of the AEs that led to the discontinuation of therapy. These data show that a large proportion of these AEs (intervention arm: 75%; comparator arm: 90%) were severe AEs (Common Terminology Criteria for Adverse Events [CTCAE] grade ≥ 3). Deviating from the assessment in benefit assessment A20-104 [1], the outcome "discontinuation due to AEs" is assigned to the outcome category of serious/severe side effects.

Table 4: Extent of added benefit at outcome level: acalabrutinib + obinutuzumab vs. chlorambucil + obinutuzumab (patients for whom treatment with FCR is not an option) (multipage table)

Outcome category **Outcome**	**Acalabrutinib + obinutuzumab vs. chlorambucil + obinutuzumab** **Median time to event (months)** **Effect estimation [95% CI]; p-value** **Probability[a]**	**Derivation of extent[b]**
Morbidity		
Fatigue (FACIT-Fatigue)	Median: NA vs. NA HR: 1.18 [0.63; 2.26]; p = 0.620	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: 1.54 [0.87; 2.79]; p = 0.143	Lesser benefit/added benefit not proven
Nausea and vomiting	Median: NA vs. NA HR: 1.15 [0.66; 2.04]; p = 0.627	Lesser benefit/added benefit not proven
Pain	Median: 11.1 vs. 17.5 HR: 1.33 [0.86; 2.09]; p = 0.207	Lesser benefit/added benefit not proven
Dyspnoea	Median: NA vs. NA HR: 1.36 [0.82; 2.27]; p = 0.241	Lesser benefit/added benefit not proven
Insomnia	Median: 22.3 vs. NA HR: 1.25 [0.78; 2.05]; p = 0.366	Lesser benefit/added benefit not proven
Appetite loss	Median: NA vs. NA HR: 1.10 [0.62; 2.01]; p = 0.747	Lesser benefit/added benefit not proven
Constipation	Median: 33.3 vs. 33.1 HR: 0.79 [0.48; 1.31]; p = 0.359	Lesser benefit/added benefit not proven
Diarrhoea	Median: 16.7 vs. NA HR: 2.67 [1.53; 4.95]; p < 0.001 HR: 0.37 [0.20; 0.65][c] probability: “hint”	Outcome category: non-serious/non-severe symptoms/late complications $CI_u < 0.80$ lesser benefit, extent: “considerable”
Health status (EQ-5D VAS)	Median: NA vs. NA HR: 0.85 [0.48; 1.52]; p = 0.581	Lesser benefit/added benefit not proven
Health-related quality of life		
EORTC QLQ-C30 – functional scales		
Global health status	Median: NA vs. 28.1 HR: 1.08 [0.66; 1.79]; p = 0.775	Lesser benefit/added benefit not proven
Physical functioning	Median: NA vs. NA HR: 1.69 [0.86; 3.49]; p = 0.134	Lesser benefit/added benefit not proven
Role functioning	Median: 5.7 vs. 16.8 HR: 1.33 [0.86; 2.09]; p = 0.208	Lesser benefit/added benefit not proven
Emotional functioning	Median: 33.2 vs. NA HR: 1.01 [0.60; 1.73]; p = 0.975	Lesser benefit/added benefit not proven
Cognitive functioning	Median: 16.7 vs. 28.1 HR: 1.30 [0.82; 2.07]; p = 0.277	Lesser benefit/added benefit not proven

Table 4: Extent of added benefit at outcome level: acalabrutinib + obinutuzumab vs. chlorambucil + obinutuzumab (patients for whom treatment with FCR is not an option) (multipage table)

Outcome category **Outcome**	**Acalabrutinib + obinutuzumab vs. chlorambucil + obinutuzumab** **Median time to event (months)** **Effect estimation [95% CI]; p-value** **Probability[a]**	**Derivation of extent[b]**
Social functioning	Median: 11.1 vs. 16.6 HR: 1.11 [0.72; 1.72]; p = 0.650	Lesser benefit/added benefit not proven
Side effects		
Discontinuation due to AEs (≥ 1 component)	Median: NA vs. NA HR: 0.39 [0.18; 0.81]; p = 0.011 probability: "hint"	Outcome category: serious/severe side effects $0.75 \leq CI_u < 0.90$ lesser harm, extent: "considerable"

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 the confidence interval; EORTC: European Organisation for Research and Treatment of Cancer; EQ-5D: European Quality of Life-5 Dimensions; FACIT: Functional Assessment of Chronic Illness Therapy; FCR: fludarabine + cyclophosphamide + rituximab; HR: hazard ratio; NA: not achieved; QLQ-C30: Quality of Life Questionnaire-Core 30; RCT: randomized controlled trial; VAS: visual analogue scale

2.5 Overall conclusion on added benefit

Table 5 summarizes the results considered in the overall conclusion on the extent of added benefit.

Table 5: Positive and negative effects from the assessment of acalabrutinib + obinutuzumab in comparison with chlorambucil + obinutuzumab (patients for whom treatment with FCR is not an option) (multipage table)

Positive effects	**Negative effects**
–	Non-serious/non-severe symptoms/late complications ▪ **EORTC QLQ-C30 – symptom scale "diarrhoea": hint of lesser benefit – extent: "considerable"**
Serious/severe side effects[a] ▪ Severe AEs: hint of lesser harm – extent: "major" including ▫ blood and lymphatic system disorders: hint of lesser harm – extent: "major" including - febrile neutropenia: hint of lesser harm – extent: "considerable" ▫ metabolism and nutrition disorders: hint of lesser harm – extent: "major" including - tumour lysis syndrome: indication of lesser harm – extent: "major" ▪ **Discontinuation due to AEs hint of lesser harm – extent: "considerable"**	–
Non-serious/non-severe side effects[a] ▪ infusion related reaction: hint of lesser harm – extent "considerable" ▪ nausea: hint of lesser harm – extent: "considerable"	Non-serious/non-severe side effects[a] ▪ headache: hint of greater harm – extent: "considerable"
a. When interpreting the results on side effects, it should be noted that the great differences in observation periods between the treatment arms mean that the hazard ratio only reflects approximately the first 7 months. Results printed in **bold** result from the analyses subsequently submitted by the company with the written comments. AE: adverse event; EORTC: European Organisation for Research and Treatment of Cancer; FCR: fludarabine + cyclophosphamide + rituximab; QLQ-C30: Quality of Life Questionnaire-Core 30	

With the data subsequently submitted in the comments, the changed allocation of the outcome "discontinuation due to AEs" to the outcome category of serious/severe side effects resulted in an additional hint of lesser harm with the extent "considerable " in serious/severe side effects for the outcome "discontinuation due to AEs" for acalabrutinib + obinutuzumab in comparison with chlorambucil + obinutuzumab.

In addition, there is a hint of lesser benefit with the extent "considerable" for acalabrutinib + obinutuzumab compared to chlorambucil + obinutuzumab for the symptom scale "diarrhoea" of the EORTC QLQ-C30.

Overall, the positive effects of acalabrutinib + obinutuzumab predominate in the present situation. The added benefit is based exclusively on advantages in the category of side effects. Due to the large differences in observation periods, the underlying analyses represent only the

approximately first 7 months of the study. The data on morbidity and health-related quality of life subsequently submitted by the company, which allow a comparison over an observation period that was almost twice as long, do not support these advantages. Therefore, it cannot be deduced from this that advantages of acalabrutinib also exist beyond the first 7 months. In this specific data situation, it is therefore not possible to quantify the added benefit, even under consideration of the data subsequently submitted.

In summary, there is therefore a hint of a non-quantifiable added benefit of acalabrutinib + obinutuzumab in comparison with chlorambucil + obinutuzumab for adult patients with previously untreated CLL who have no 17p deletion or TP53 mutation and for whom treatment with FCR is not an option.

2.6 Summary

The data subsequently submitted by the company in the commenting procedure have not changed the conclusion on the added benefit of acalabrutinib + obinutuzumab from dossier assessment A20-104.

The following Table 6 shows the result of the benefit assessment of acalabrutinib + obinutuzumab under consideration of dossier assessment A20-104 and the present addendum.

Table 6: Acalabrutinib + obinutuzumab – probability and extent of added benefit

Research question	Subindication	ACT[a]	Probability and extent of added benefit
1	Adult patients with previously untreated CLL who have no 17p deletion or TP53 mutation and for whom treatment with FCR is an option	FCR	Added benefit not proven
2	Adult patients with previously untreated CLL who have no 17p deletion or TP53 mutation and for whom treatment with FCR is not an option	▪ Bendamustine in combination with rituximab or ▪ **chlorambucil in combination** with rituximab or **obinutuzumab**	Hint of non-quantifiable added benefit
3	Adult patients with previously untreated CLL with 17p deletion or TP53 mutation or for whom chemo-immunotherapy is not indicated for other reasons	Ibrutinib	Added benefit not proven

a. The G-BA assumes for the present therapeutic indication that the patients require treatment. Moreover, it is assumed 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**.

17p: deletion of the short arm of chromosome 17; ACT: appropriate comparator therapy; CLL: chronic lymphocytic leukaemia; FCR: fludarabine + cyclophosphamide + rituximab; 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: patients for whom treatment with FCR is not an option

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

Table 7: Results (morbidity, health-related quality of life, continuous – supplementary presentation on the EORTC QLQ-C30, data cut-off from 8 February 2019) – RCT, direct comparison: acalabrutinib + obinutuzumab vs. chlorambucil + obinutuzumab (patients for whom treatment with FCR is not an option) (multipage table)

Study Outcome category Outcome	Acalabrutinib + obinutuzumab			Chlorambucil + obinutuzumab			Acalabrutinib + obinutuzumab vs. chlorambucil + obinutuzumab
	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]
ELEVATE-TN							
Morbidity							
EORTC QLQ-C30 – symptom scales[c]							
Fatigue	86	34.50 (22.22)	−7.40 (1.50)	76	36.40 (24.52)	−10.79 (1.72)	3.40 [−1.09; 7.88]; 0.137
Nausea and vomiting	86	4.46 (12.11)	−0.54 (0.66)	76	4.17 (13.64)	−1.98 (0.74)	1.44 [−0.53; 3.41]; 0.151
Pain	86	22.87 (26.33)	−2.42 (1.49)	76	16.01 (23.80)	−5.71 (1.70)	3.30 [−1.20; 7.79]; 0.149
Dyspnoea	86	16.67 (24.92)	−2.55 (1.62)	76	18.86 (23.94)	−7.17 (1.84)	4.62 [−0.22; 9.46]; 0.061
Insomnia	86	28.68 (26.65)	−5.68 (1.58)	76	25.88 (25.30)	−9.74 (1.82)	4.06 [−0.70; 8.82]; 0.094
Appetite loss	86	15.50 (22.69)	−6.22 (1.23)	76	12.72 (23.07)	−6.54 (1.41)	0.32 [−3.37; 4.02]; 0.863
Constipation	86	15.50 (26.91)	−4.28 (1.32)	76	10.96 (20.65)	−3.00 (1.53)	−1.28 [−5.28; 2.73]; 0.529
Diarrhoea	86	6.59 (14.298)	1.93 (1.05)	76	8.33 (18.95)	−2.47 (1.21)	4.39 [1.23; 7.55]; 0.007 Hedges' g: 0.43 [0.12; 0.75]
Health-related quality of life							
EORTC QLQ-C30 – functional scales[d]							
Global health status	86	67.05 (21.27)	4.56 (1.21)	76	66.45 (22.19)	7.59 (1.30)	−3.04 [−6.69; 0.62]; 0.103
Physical functioning	86	79.75 (19.10)	2.25 (1.23)	76	79.91 (20.61)	4.28 (1.39)	−2.03 [−5.71; 1.64]; 0.276
Role functioning	86	76.74 (24.69)	3.87 (1.53)	76	79.82 (25.14)	5.48 (1.78)	−1.61 [−6.27; 3.06]; 0.496
Emotional functioning	86	78.00 (21.00)	6.91 (1.19)	76	79.28 (18.03)	6.88 (1.33)	0.02 [−3.50; 3.54]; 0.990

Table 7: Results (morbidity, health-related quality of life, continuous – supplementary presentation on the EORTC QLQ-C30, data cut-off from 8 February 2019) – RCT, direct comparison: acalabrutinib + obinutuzumab vs. chlorambucil + obinutuzumab (patients for whom treatment with FCR is not an option) (multipage table)

Study **Outcome category** **Outcome**	**Acalabrutinib + obinutuzumab**			**Chlorambucil + obinutuzumab**			**Acalabrutinib + obinutuzumab vs. chlorambucil + obinutuzumab**
	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]**
Cognitive functioning	86	84.88 (17.83)	0.49 (1.15)	76	84.87 (21.63)	1.34 (1.32)	−0.86 [−4.32; 2.60]; 0.626
Social functioning	86	85.47 (21.81)	1.63 (1.27)	76	84.65 (20.32)	4.41 (1.50)	−2.78 [−6.67; 1.10]; 0.159

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

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

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

Table 8: Results (morbidity – supplementary presentation on the outcome "disease-related symptoms", data cut-off from 1 August 2019) – RCT, direct comparison: acalabrutinib + obinutuzumab vs. chlorambucil + obinutuzumab (patients for whom treatment with FCR is not an option)

Study Outcome category Outcome	Acalabrutinib + obinutuzumab		Chlorambucil + obinutuzumab		Acalabrutinib vs. chlorambucil + obinutuzumab
	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]
ELEVATE-TN					
Morbidity					
Patients with at least one disease-related symptom[b] at baseline					
Time to first absence of any disease-related symptoms	47	1.1 [1.1; 1.8] 44 (93.6)	45	1.4 [1.1; 1.9] 38 (84.4)	1.17 [0.75; 1.81]; 0.562

a. HR (incl. 95% CI) calculated using an unstratified Cox proportional hazards model. The p-value was calculated using an unstratified 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; ECOG PS: Eastern Cooperative Oncology Group Performance Status; FCR: fludarabine + cyclophosphamide + rituximab; 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: patients for whom treatment with FCR is not an option

B.1 – Morbidity

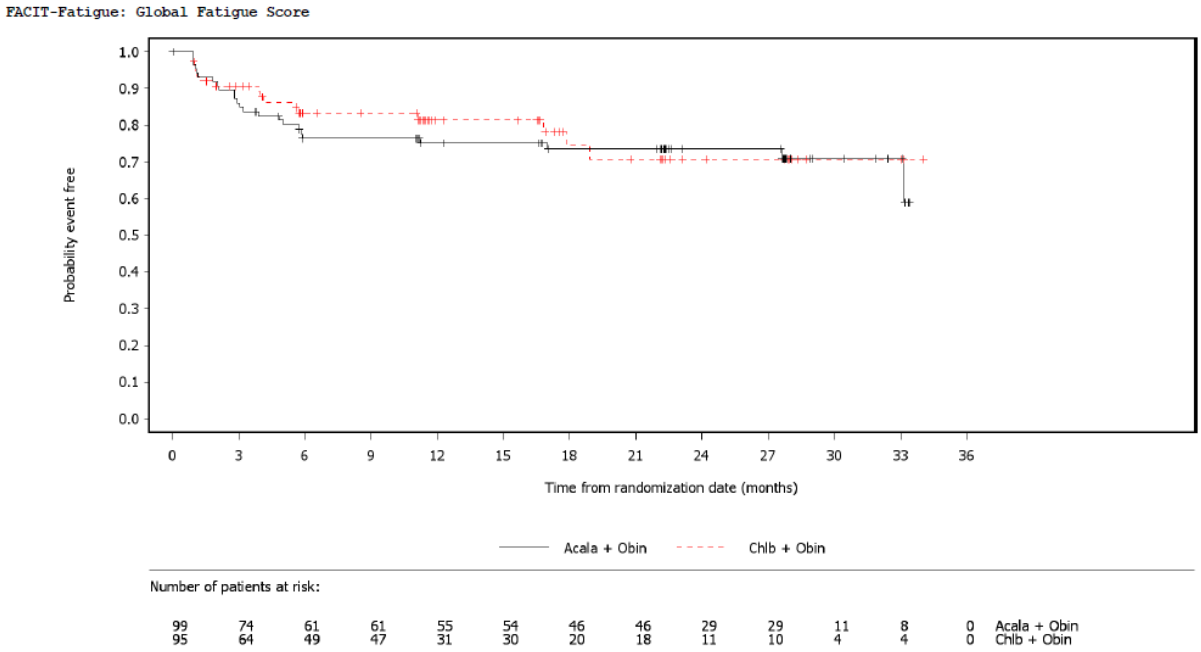

Figure 1: Kaplan-Meier-curves for fatigue (FACIT-Fatigue, time to first deterioration ≥ 7.8 points, data cut-off from 8 February 2019)

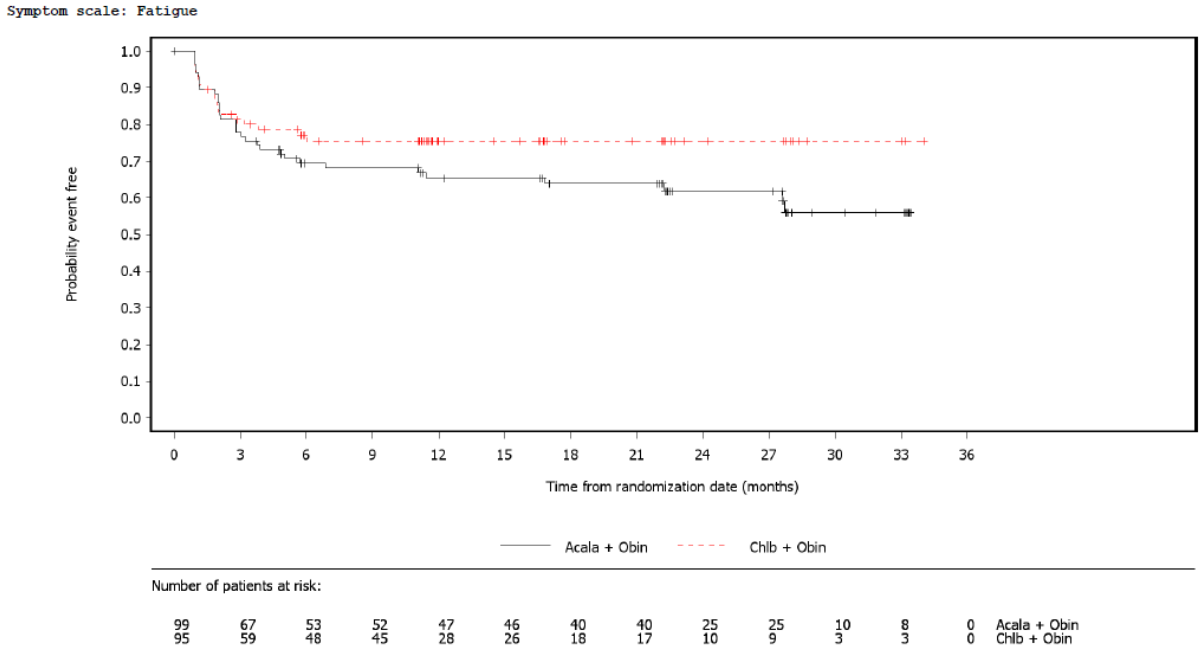

Figure 2: Kaplan-Meier-curves for symptoms, symptom scale "fatigue" (EORTC QLQ-C30, time to first deterioration ≥ 15 points, data cut-off from 8 February 2019)

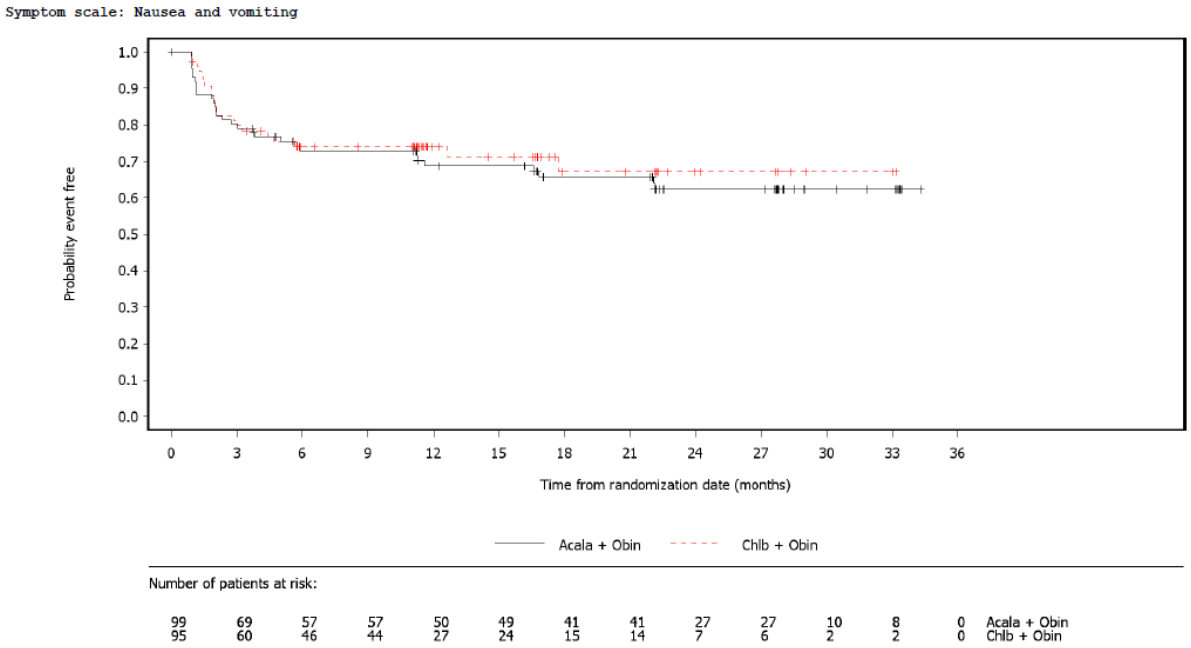

Figure 3: Kaplan-Meier-curves for symptoms, symptom scale "nausea and vomiting" (EORTC QLQ-C30, time to first deterioration ≥ 15 points, data cut-off from 8 February 2019)

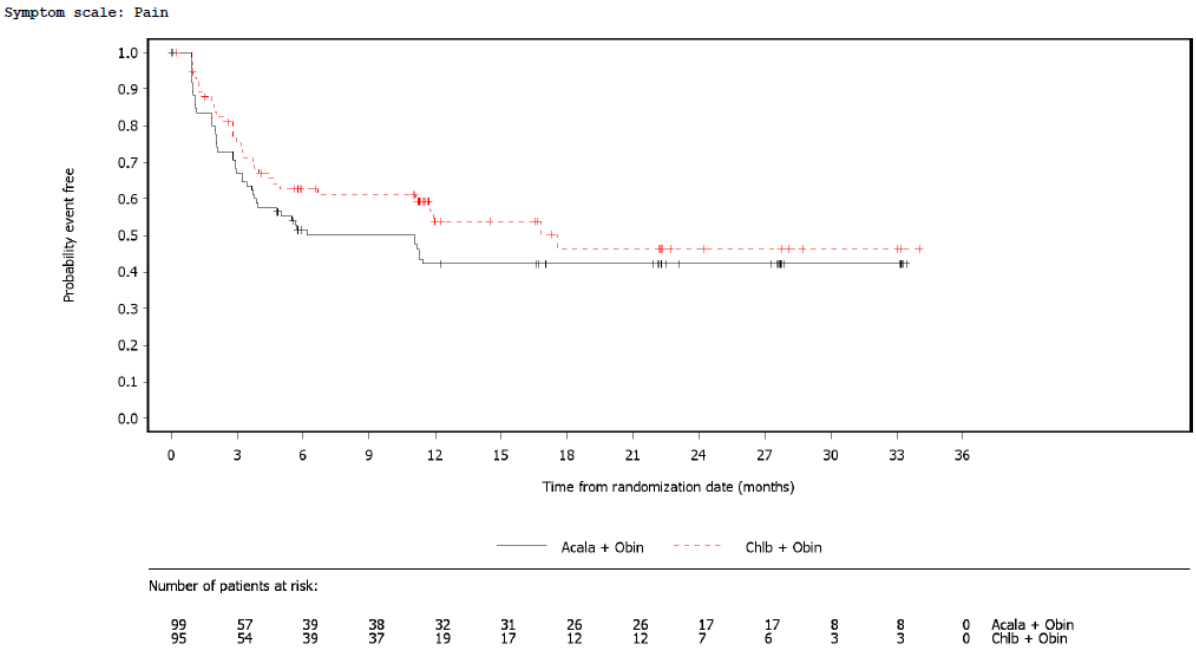

Figure 4: Kaplan-Meier-curves for symptoms, symptom scale "pain" (EORTC QLQ-C30, time to first deterioration ≥ 15 points, data cut-off from 8 February 2019)

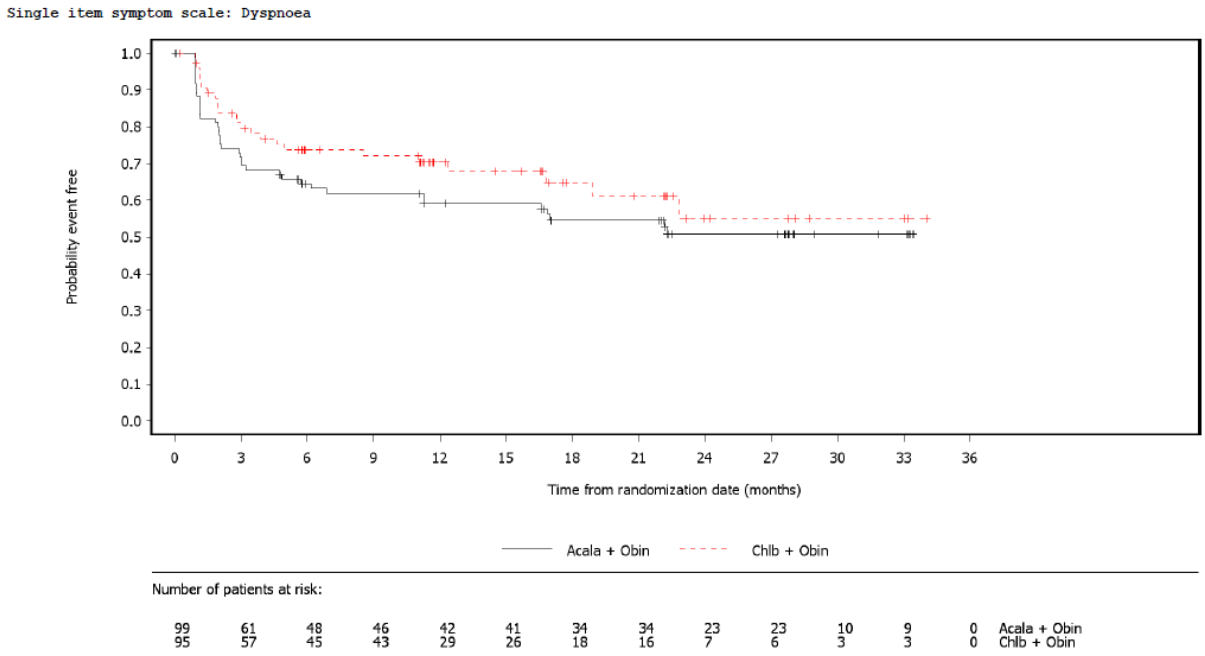

Figure 5: Kaplan-Meier-curves for symptoms, symptom scale "dyspnoea" (EORTC QLQ-C30, time to first deterioration ≥ 15 points, data cut-off from 8 February 2019)

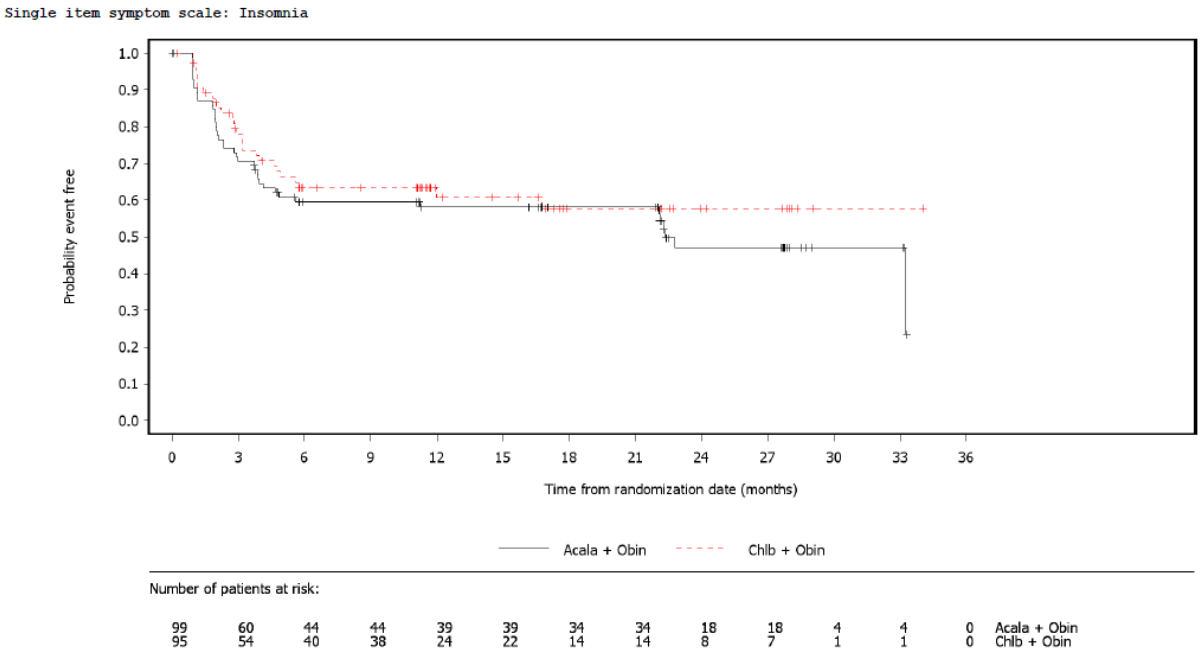

Figure 6: Kaplan-Meier-curves for symptoms, symptom scale "insomnia" (EORTC QLQ-C30, time to first deterioration ≥ 15 points, data cut-off from 8 February 2019)

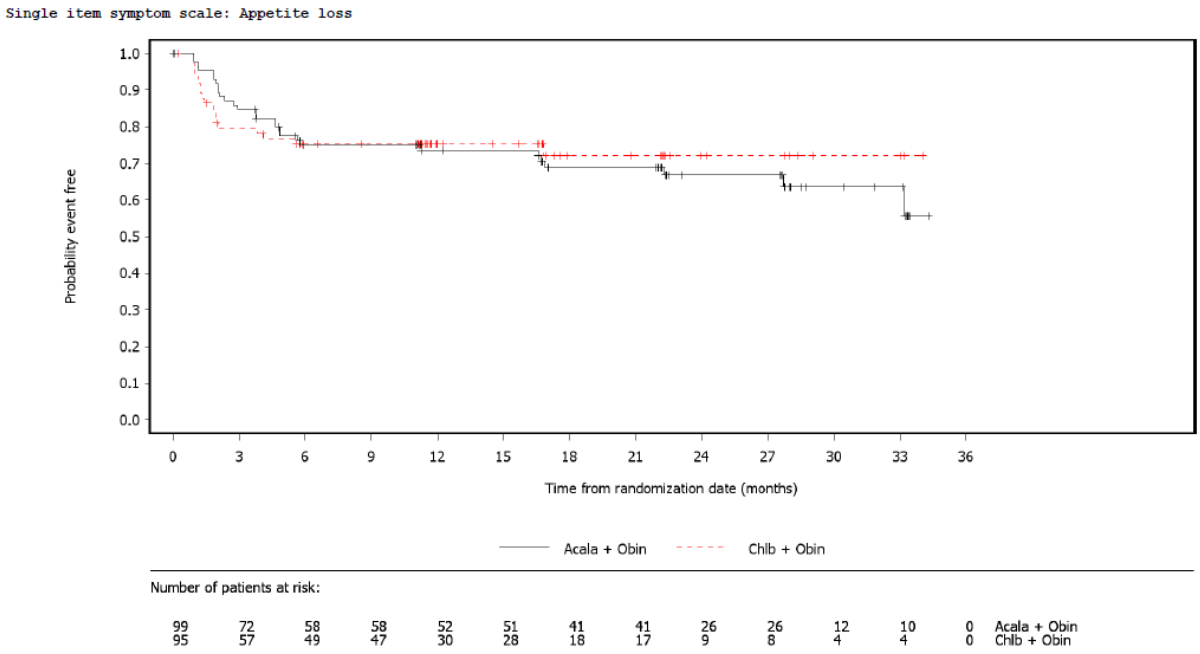

Figure 7: Kaplan-Meier-curves for symptoms, symptom scale "appetite loss" (EORTC QLQ-C30, time to first deterioration ≥ 15 points, data cut-off from 8 February 2019)

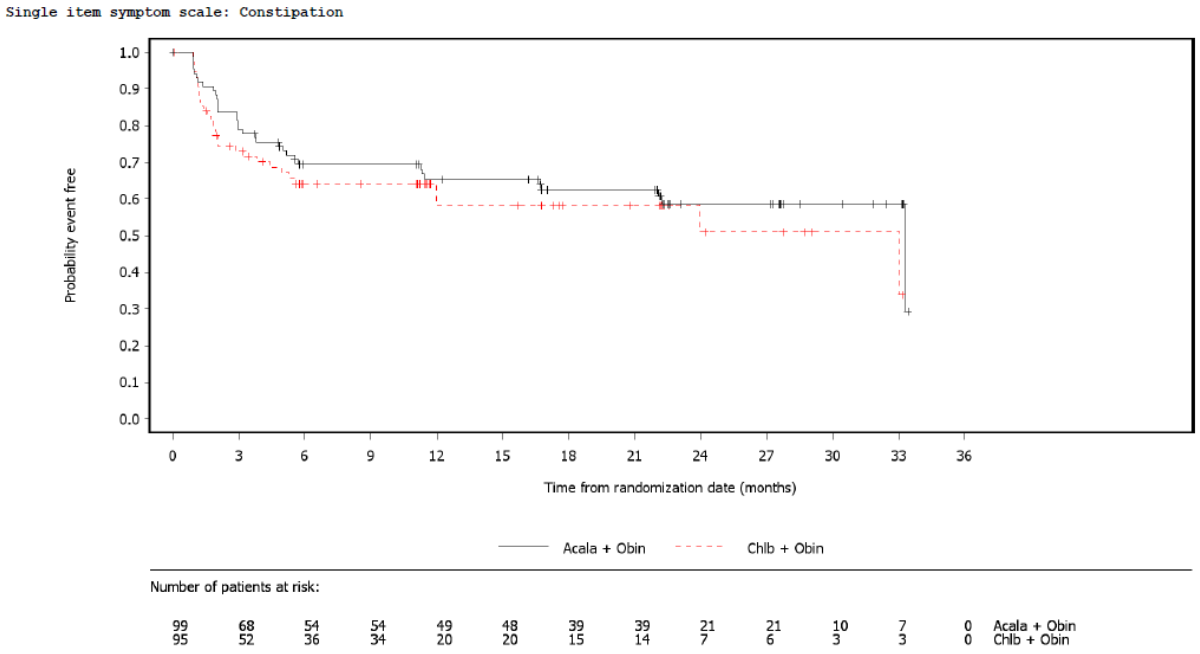

Figure 8: Kaplan-Meier-curves for symptoms, symptom scale "constipation" (EORTC QLQ-C30, time to first deterioration ≥ 15 points, data cut-off from 8 February 2019)

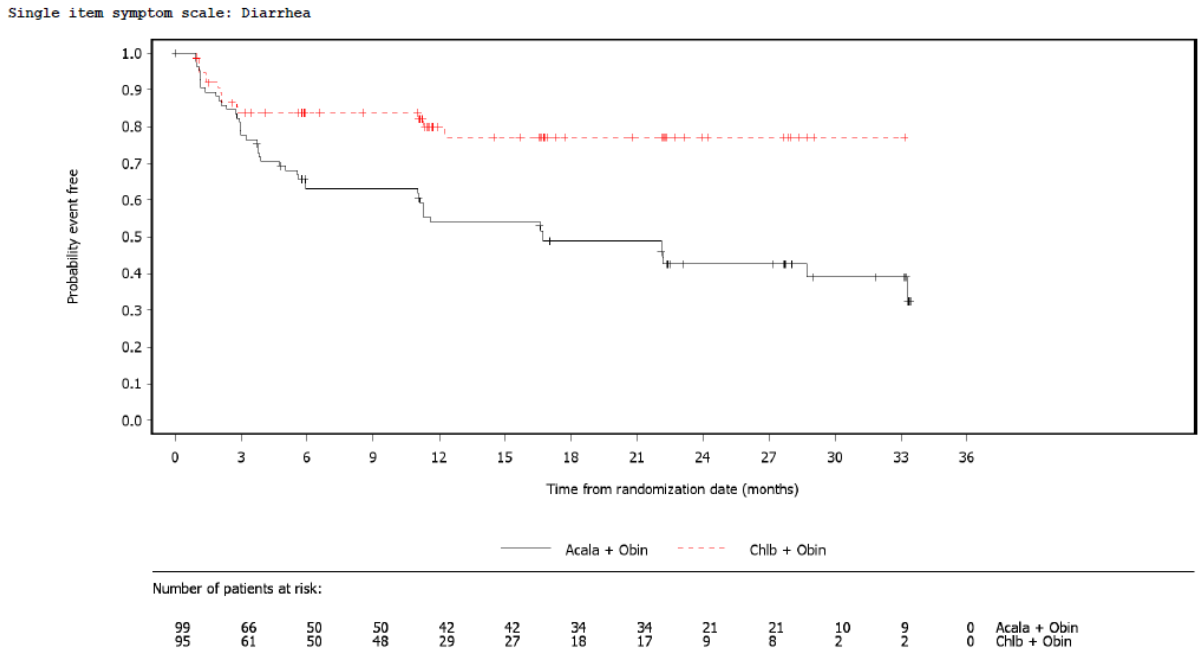

Figure 9: Kaplan-Meier-curves for symptoms, symptom scale "diarrhoea" (EORTC QLQ-C30, time to first deterioration ≥ 15 points, data cut-off from 8 February 2019)

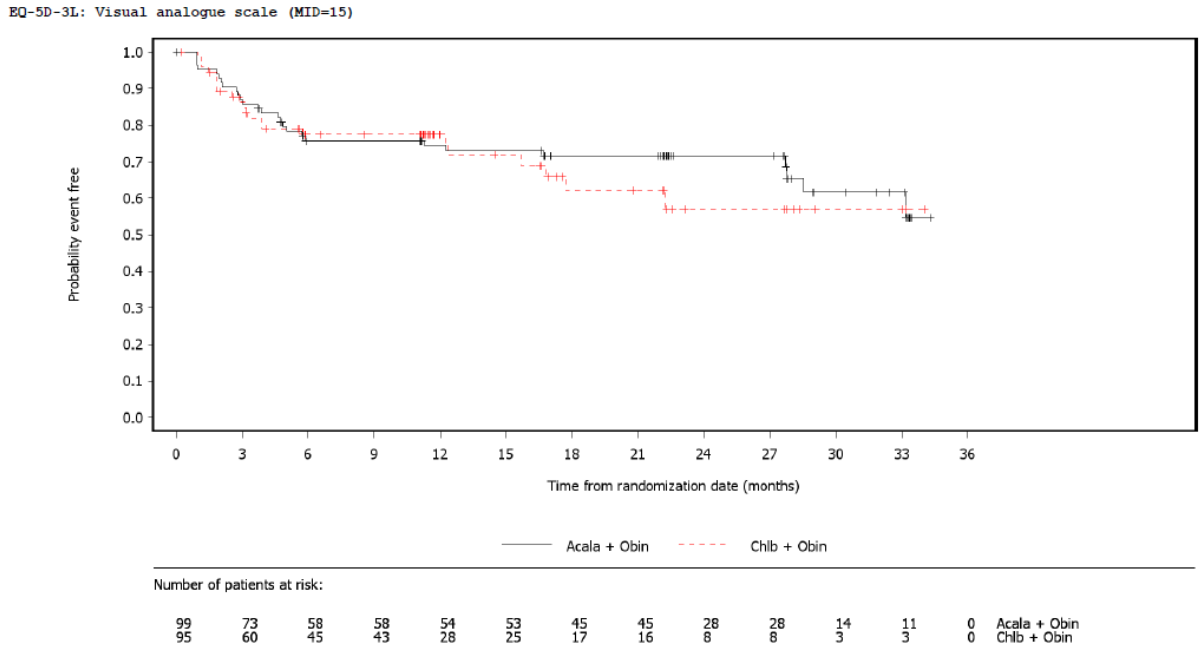

Figure 10: Kaplan-Meier curves for health status (EQ-5D VAS, time to first deterioration ≥ 15 points, data cut-off from 8 February 2019)

B.2 – Health-related quality of life

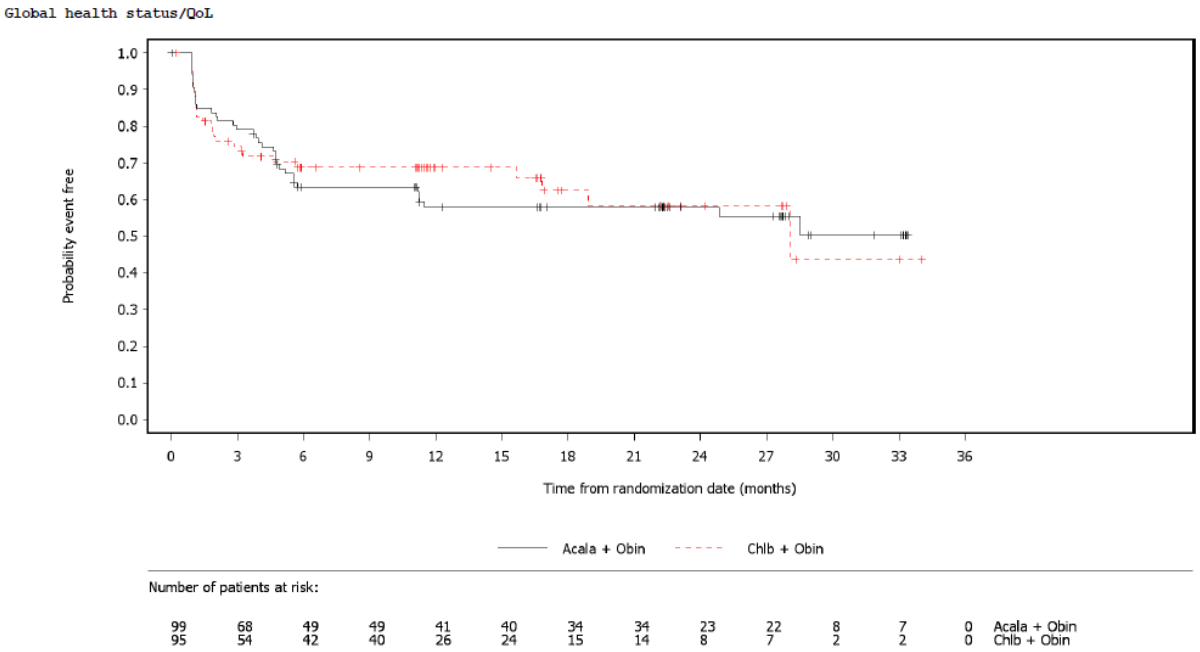

Figure 11: Kaplan-Meier curves for health-related quality of life, global health status (EORTC QLQ-C30, time to first deterioration ≥ 15 points, data cut-off from 8 February 2019)

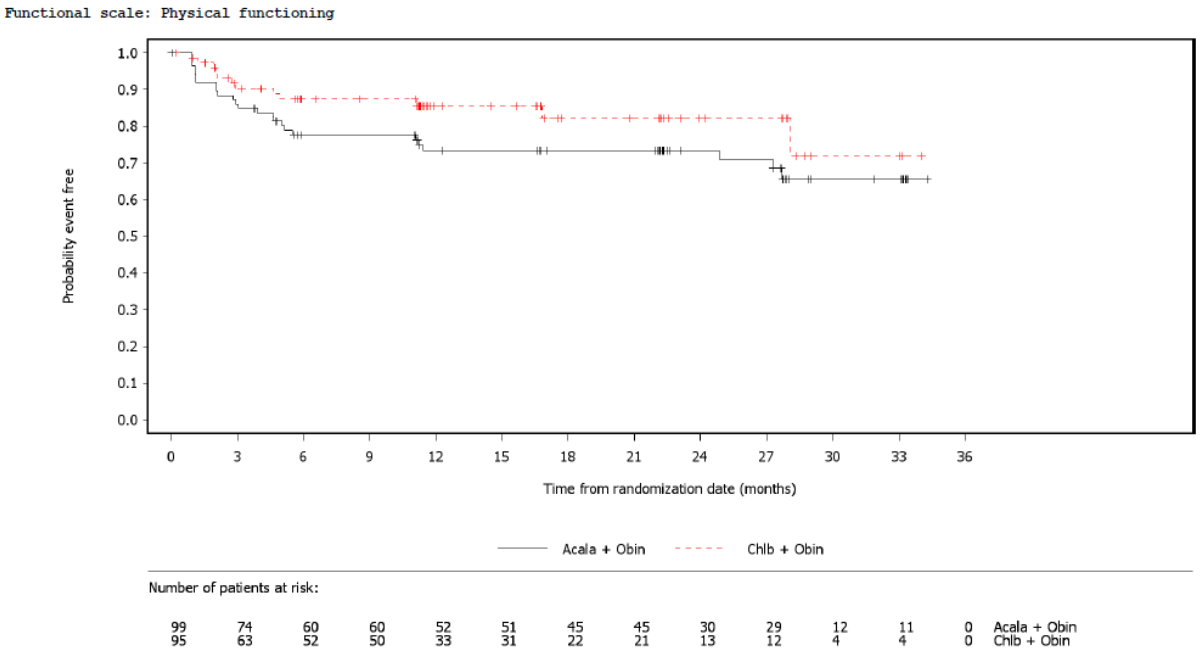

Figure 12: Kaplan-Meier curves for health-related quality of life, functional scale "physical functioning" (EORTC QLQ-C30, time to first deterioration ≥ 15 points, data cut-off from 8 February 2019)

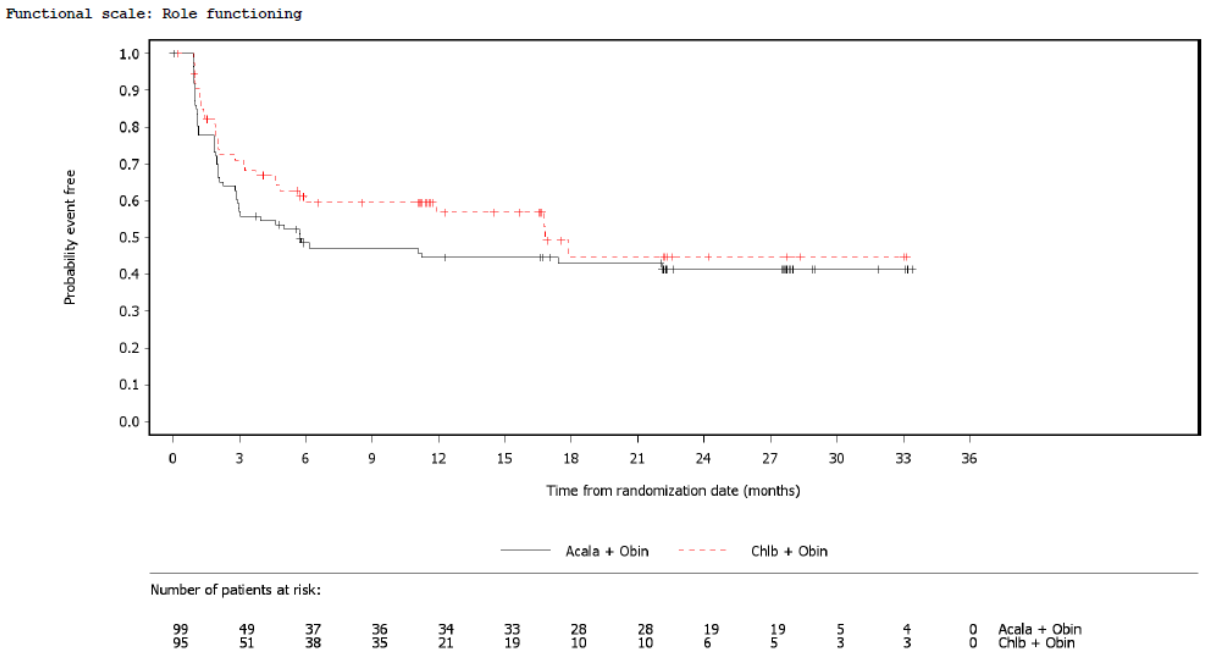

Figure 13: Kaplan-Meier curves for health-related quality of life, functional scale "role functioning" (EORTC QLQ-C30, time to first deterioration ≥ 15 points, data cut-off from 8 February 2019)

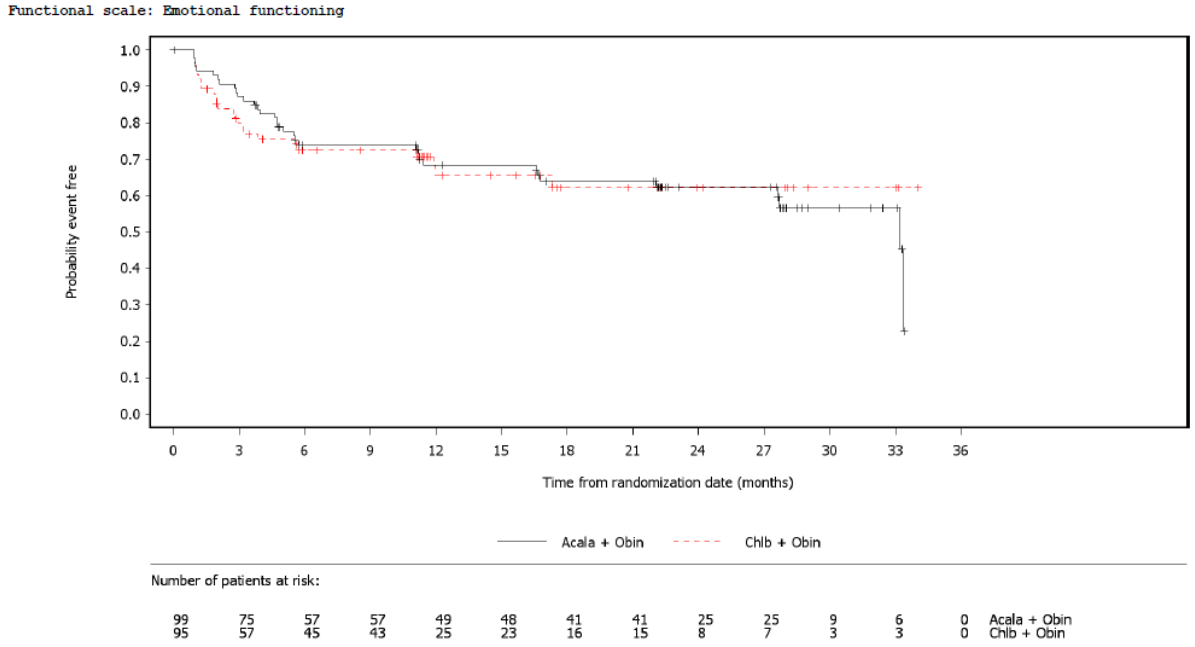

Figure 14: Kaplan-Meier curves for health-related quality of life, functional scale "emotional functioning" (EORTC QLQ-C30, time to first deterioration ≥ 15 points, data cut-off from 8 February 2019)

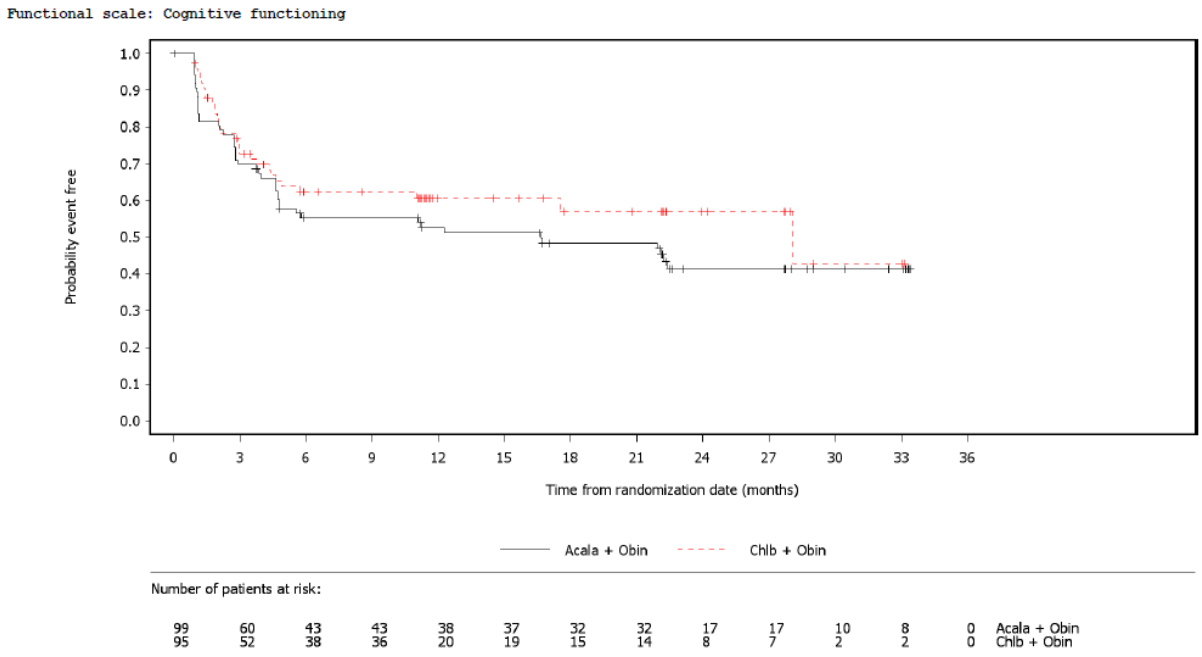

Figure 15: Kaplan-Meier curves for health-related quality of life, functional scale "cognitive functioning" (EORTC QLQ-C30, time to first deterioration ≥ 15 points, data cut-off from 8 February 2019)

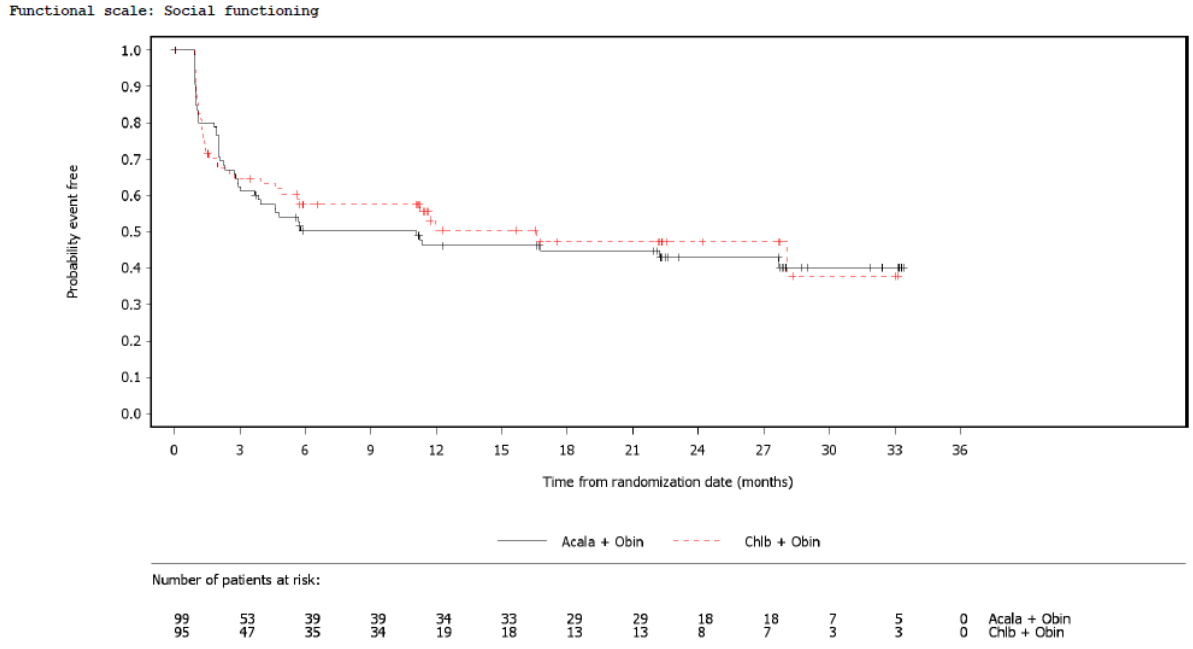

Figure 16: Kaplan-Meier curves for health-related quality of life, functional scale "social functioning" (EORTC QLQ-C30, time to first deterioration ≥ 15 points, data cut-off from 8 February 2019)