Zanubrutinib (previously untreated chronic lymphocytic leukaemia)

Addendum to Project A22-130 (dossier assessment)[1]

ADDENDUM

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Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
Im Mediapark 8
50670 Köln
Germany

Phone: +49 221 35685-0
Fax: +49 221 35685-1
E-mail: berichte@iqwig.de
Internet: www.iqwig.de

IQWiG employees involved in the addendum

- Anna-Katharina Barnert
- Benjamin Becker
- Lisa Junge
- Katrin Nink

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Abbreviation	Meaning
AE	adverse event
CLL	chronic lymphocytic leukaemia
EORTC	European Organisation for Research and Treatment of Cancer
FCR	fludarabine + cyclophosphamide + rituximab
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
MedDRA	Medical Dictionary for Regulatory Activities
PT	Preferred Term
QLQ-C30	Quality of Life Questionnaire-Core 30
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SOC	System Organ Class

1 Background

On 3 May 2023, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Project A22-130 (Zanubrutinib – Benefit assessment according to § 35a Social Code Book V) [1].

The commission comprises the assessment of the additional data on the SEQUOIA study submitted by the pharmaceutical company (hereinafter referred to as the "company") following the oral hearing [2]:

- adverse events (AEs) – data up to 30 days (zanubrutinib) or 90 days (bendamustine + rituximab) or until disease progression, whichever was later

The assessment takes into account the information provided in the commenting procedure [3] and in the dossier [4].

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 randomized controlled, open-label SEQUOIA study, which compared zanubrutinib with bendamustine in combination with rituximab, was used for the benefit assessment of zanubrutinib in adult patients with previously untreated chronic lymphocytic leukaemia (CLL). A detailed description of the study can be found in dossier assessment A22-130 [1].

In compliance with the commission, the analyses of the outcomes of AEs, serious AEs (SAEs), severe AEs (Common Terminology Criteria for Adverse Events [CTCAE] grade ≥ 3), and specific AEs subsequently submitted by the company after the oral hearing are assessed below.

2.1 Analyses on side effects

As described in dossier assessment A22-130, according to the information provided by the company in Module 4 A [4] and the study documents [5], side effects were to be observed up to 30 days (zanubrutinib) or up to 90 days (bendamustine + rituximab) after the last dose of study medication or until disease progression, whichever was later. Patients who started subsequent CLL therapy before disease progression were to be observed until the end of treatment (plus 30 days or 90 days) or until the start of subsequent CLL therapy, whichever was later.

In its comments, the company confirmed that its analyses of the side effects outcomes presented in Module 4 A only covered the period until the end of treatment (plus 30 days in the intervention arm and 90 days in the comparator arm) (corresponding to the definition of treatment emergent adverse events given in the study protocol). Thus, the median treatment duration in the comparator arm was 4.8 months and the median observation period for the side effects outcomes was 7.8 months (which is approximately the treatment duration plus 90 days). At the time point of the benefit assessment, the company did not provide any analyses of outcomes in the category of side effects that cover the period until disease progression or until the start of a new CLL therapy, although the recording over a longer period of time was also predefined according to the information in Module 4 A and the study documents.

In the course of the commenting procedure [3], the company subsequently submitted event time analyses for the results of side effects with the operationalization up to 30 days (zanubrutinib) or up to 90 days (bendamustine + rituximab) after the last dose of the study medication or until disease progression, whichever was later. The median observation periods of the intervention arm and the comparator arm are comparable at approximately 36.7 months and approximately 35.9 months. However, there were uncertainties in the interpretability of the data, as the corresponding Kaplan-Meier curves did not match the reported median observation period of approximately 36.7 months in the comparator arm

and again showed many censorings between months 6 and 9. The Kaplan-Meier curves subsequently submitted by the company after the oral hearing resolve these discrepancies.

The Kaplan-Meier curves now available can be interpreted together with the event time analyses and correspond to the observation period of side effects described in the study documents of up to 30 days (zanubrutinib) and up to 90 days (bendamustine + rituximab) after the last dose of study medication or until disease progression, whichever was later. Thus, the data subsequently provided by the company are used for the benefit assessment.

The consideration of event time analyses is particularly relevant for group comparisons with different mean observation periods. However, the analyses of side effects now available are based on comparable observation periods in both study arms. In the assessment of side effects, it is primarily relevant in how many patients an event occurred. In addition, when considering the time until occurrence of the event, effects can also result solely from an earlier or later occurrence of the event and not on the basis of the proportions. For this reason, the relative risk is used as effect measure in the present assessment.

However, the outcome of discontinuation due to AEs is excluded from this. In the present data situation, this outcome only includes events that occurred during the duration of treatment with the study medication. Due to the fixed treatment duration in the comparator arm of the SEQUOIA study, the median treatment durations and, for this outcome, also the observation periods still differ between the study arms (36.3 months [zanubrutinib] versus 4.8 months [bendamustine + rituximab]). Since no further events can occur after the end of treatment in the comparator arm, the hazard ratio is still the appropriate effect measure for the outcome of discontinuation due to AEs, and the analysis already provided with the dossier is therefore decisive. As described in the dossier assessment, this analysis can only be interpreted for the first 8 months.

2.1.1 Risk of bias

The risk of bias of the results for the outcomes of SAEs, severe AEs, the specific SAEs and specific severe AEs is rated as low. For the outcomes of the category of side effects that cannot be assigned to SAEs or severe AEs, the risk of bias is rated as high due to the open-label study design.

2.1.2 Results

The analyses of the outcomes of SAEs, severe AEs, discontinuations due to AEs as well as of the SOC “blood and lymphatic system disorders” include events such as the Preferred Terms (PTs) of anaemia, neutropenia and thrombocytopenia, which can be both side effects and a reflection of the progression of the underlying disease. It cannot be conclusively clarified to

what extent the events can be assigned to the outcome category of morbidity or side effects [6]. This remains of no consequence for the present benefit assessment.

The results for the subsequently submitted data in the outcome category of side effects are presented in Table 1. The tables on common AEs, SAEs, and severe AEs are presented in Appendix A.

Table 1: Results (side effects, dichotomous) – RCT, direct comparison: zanubrutinib vs. bendamustine + rituximab (multipage table)

Study Outcome category Outcome	Zanubrutinib		Bendamustine + rituximab		Zanubrutinib vs. bendamustine + rituximab
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value[a]
SEQUOIA					
Side effects					
AEs (supplementary information)	104	101 (97.1)	101	98 (97.0)	–
SAEs	104	50 (48.1)	101	49 (48.5)	0.99 [0.75; 1.32]; > 0.999
Severe AEs[b]	104	59 (56.7)	101	82 (81.2)	0.70 [0.58; 0.85]; < 0.001
Haemorrhages (SMQ[c], AEs)	104	53 (51.0)	101	12 (11.9)	4.29 [2.44; 7.54]; < 0.001
Haemorrhages (SMQ[c], severe AEs[b])	104	4 (3.8)	101	1 (1.0)	3.88 [0.44; 34.16]; 0.245
Cardiac disorders (SOC, severe AEs[b])	104	8 (7.7)	101	4 (4.0)	1.94 [0.60; 6.25]; 0.269
Infections and infestations (SOC, severe AEs[b])	104	22 (21.2)	101	20 (19.8)	1.07 [0.62; 1.83]; 0.848
Infusion related reaction	Analysis unsuitable[d]				
Nausea (PT, AEs)	104	13 (12.5)	101	34 (33.7)	0.37 [0.21; 0.66]; < 0.001
Contusion (PT, AEs)	104	27 (26.0)	101	4 (4.0)	6.56 [2.38; 18.07]; < 0.001
Hypotension (PT, AEs)	104	3 (2.9)	101	14 (13.9)	0.21 [0.06; 0.70]; 0.005
Fever (PT, SAEs)	104	1 (1.0)	101	9 (8.9)	0.11 [0.01; 0.84]; 0.008
Blood and lymphatic system disorders (SOC, severe AEs)[b]	104	17 (16.3)	101	42 (41.6)	0.39 [0.24; 0.64]; < 0.001
Investigations (SOC, severe AEs[b])	104	6 (5.8)	101	17 (16.8)	0.34 [0.14; 0.83]; 0.012

Table 1: Results (side effects, dichotomous) – RCT, direct comparison: zanubrutinib vs. bendamustine + rituximab (multipage table)

Study Outcome category Outcome	Zanubrutinib		Bendamustine + rituximab		Zanubrutinib vs. bendamustine + rituximab
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value[a]

a. Institute's calculation, effect estimate and 95% CI asymptotic; p-value unconditional exact test, (CSZ method according to [7]).
b. Operationalized as CTCAE grade ≥ 3.
c. Without events based on laboratory values.
d. The analysis presented by the company is not suitable for the benefit assessment; however, serious and severe infusion reactions are taken into account in the overall rates of SAEs and severe AEs (see [1]).

AE: adverse event; CI: confidence interval; CSZ: convexity, symmetry, z-score; 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; SAE: serious adverse event; SMQ: Standardized MedDRA Query; SOC: System Organ Class

Side effects

SAEs

For the outcome of SAEs, no statistically significant difference between treatment groups was found. There is no hint of greater or lesser harm from zanubrutinib in comparison with bendamustine + rituximab; greater or lesser harm is therefore not proven for this outcome.

Severe AEs

A statistically significant difference between treatment groups in favour of zanubrutinib was shown for the outcome of severe AEs. There is an indication of lesser harm from zanubrutinib in comparison with bendamustine + rituximab.

Haemorrhages (AEs)

A statistically significant difference between treatment groups to the disadvantage of zanubrutinib was shown for the outcome of haemorrhages (AEs). There is a hint of greater harm from zanubrutinib in comparison with bendamustine + rituximab.

Haemorrhages (severe AEs), cardiac disorders (severe AEs), infections and infestations (severe AEs)

There was no statistically significant difference between treatment groups for any of the outcomes of haemorrhages (severe AEs), cardiac disorders (severe AEs), and infections and infestations (severe AEs). In each case, there is no hint of greater or lesser harm from zanubrutinib in comparison with bendamustine + rituximab; greater or lesser harm is therefore not proven for these outcomes.

Infusion related reaction

No suitable data are available for the outcome of infusion related reaction (see dossier assessment A22-130 [1]). There is no hint of greater or lesser harm from zanubrutinib in comparison with bendamustine + rituximab; greater or lesser harm is therefore not proven.

Further specific AEs

Nausea (AEs), hypotension (AEs)

A statistically significant difference between treatment groups in favour of zanubrutinib was shown for either of the outcomes of nausea (AEs) and hypotension (AEs). In each case, there is a hint of lesser harm from zanubrutinib in comparison with bendamustine + rituximab.

Contusion (AEs)

A statistically significant difference between treatment groups to the disadvantage of zanubrutinib was shown for the outcome of contusion (AEs). There is a hint of greater harm from zanubrutinib in comparison with bendamustine + rituximab.

Fever (SAEs), blood and lymphatic system disorders (severe AEs), investigations (severe AEs)

A statistically significant difference between treatment groups in favour of zanubrutinib was found for each of the outcomes of fever (SAEs), blood and lymphatic system disorders (severe AEs), and investigations (severe AEs). In each case, there is an indication of lesser harm from zanubrutinib in comparison with bendamustine + rituximab.

Subgroups and effect modifiers

The company did not present any subgroup analyses for the subsequently submitted analyses of the outcome category of side effects. These analyses are necessary for a comprehensive balancing of the added benefit, however. The event time analyses for the characteristics considered, i.e. age, sex and Binet stage, which are available in the dossier, do not show any effect modifications in the AE outcomes. Nevertheless, uncertainty remains, which is taken into account in the assessment of the added benefit in the certainty of conclusions.

2.1.3 Probability and extent of added benefit

2.1.3.1 Assessment of the added benefit at outcome level

The extent of the respective added benefit at outcome level is estimated from the results presented in Section 2.1.2. Table 2 presents only the results of the outcome category of side effects that are relevant in the present addendum.

Table 2: Extent of added benefit at outcome level: zanubrutinib vs. bendamustine + rituximab (multipage table)

Outcome category **Outcome**	**Zanubrutinib vs. bendamustine + rituximab** **Proportion of events (%)** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Outcomes with shortened observation period		
Side effects		
SAEs	48.1 vs. 48.5 RR: 0.99 [0.75; 1.32] p > 0.999	Greater/lesser harm not proven
Severe AEs	56.7 vs. 81.2 RR: 0.70 [0.58; 0.85] p < 0.001 Probability: indication	Outcome category: serious/severe side effects $0.75 \leq CI_u < 0.90$ Lesser harm, extent: “considerable”
Haemorrhages (AEs)	51.0 vs. 11.9 RR: 4.29 [2.44; 7.54] RR: 0.23 [0.13; 0.41][c] p < 0.001 Probability: “hint”	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ Greater harm, extent: “considerable”
Haemorrhages (severe AEs)	3.8 vs. 1.0 RR: 3.88 [0.44; 34.16] p = 0.245	Greater/lesser harm not proven
Cardiac disorders (severe AEs)	7.7 vs. 4.0 RR: 1.94 [0.60; 6.25] p = 0.269	Greater/lesser harm not proven
Infections and infestations (severe AEs)	21.2 vs. 19.8 RR: 1.07 [0.62; 1.83] p = 0.848	Greater/lesser harm not proven
Infusion related reaction	Analysis unsuitable[d]	Greater/lesser harm not proven
Nausea (AEs)	12.5 vs. 33.7 RR: 0.37 [0.21; 0.66] p < 0.001 Probability: “hint”	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ Lesser harm; extent: “considerable”
Contusion (AEs)	26.0 vs. 4.0 RR: 6.56 [2.38; 18.07]; RR: 0.15 [0.06; 0.42][c] p < 0.001 Probability: “hint”	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ Greater harm, extent: “considerable”

Table 2: Extent of added benefit at outcome level: zanubrutinib vs. bendamustine + rituximab (multipage table)

Outcome category **Outcome**	**Zanubrutinib vs. bendamustine + rituximab** **Proportion of events (%)** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Hypotension (AEs)	2.9 vs. 13.9 RR: 0.21 [0.06; 0.70] p = 0.005 Probability: "hint"	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ Lesser harm, extent: "considerable"
Fever (SAEs)	1.0 vs. 8.9 RR: 0.11 [0.01; 0.84] p = 0.008 Probability: indication	Outcome category: serious/severe side effects $0.75 \leq CI_u < 0.90$ Lesser harm, extent: "considerable"
Blood and lymphatic system disorders (severe AEs)	16.3 vs. 41.6 RR: 0.39 [0.24; 0.64] p < 0.001 Probability: indication	Outcome category: serious/severe side effects $CI_u < 0.75$; risk ≥ 5% Lesser harm, extent: "major"
Investigations (severe AEs)	5.8 vs. 16.8 RR: 0.34 [0.14; 0.83] p = 0.012 Probability: indication	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, the effect size is estimated using different limits based on the upper limit of the confidence interval (CI_u).
c. Institute's calculation; inverse direction of effect to enable use of limits to derive the extent of the added benefit.
d. The analysis presented by the company is not suitable for the benefit assessment; however, serious and severe infusion reactions are taken into account in the overall rates of SAEs and severe AEs (see [1]).

AE: adverse event; CI: confidence interval; CI_u: upper limit of confidence interval; RR: relative risk; SAE: serious adverse event

2.1.4 Overall conclusion on added benefit

Table 3 summarizes the results included in the overall conclusion on the extent of added benefit.

Table 3: Positive and negative effects from the assessment of zanubrutinib in comparison with bendamustine + rituximab

Positive effects	**Negative effects**
Outcomes with observation over the entire study duration	
–	–
Outcomes with shortened observation period[a]	
Non-serious/non-severe symptoms/late complications ▪ Nausea and vomiting: ▫ Sex (women): hint of an added benefit – extent: "considerable" ▪ Appetite loss: ▫ Age (< 65 years): hint of an added benefit – extent: "considerable"	–
Health-related quality of life ▪ Role functioning: hint of an added benefit – extent: "minor"	Health-related quality of life ▪ Cognitive functioning: ▫ Sex (women): hint of lesser benefit – extent: "minor"
Serious/severe side effects ▪ Severe AEs: indication of lesser harm – extent: "considerable" ▫ Blood and lymphatic system disorders (severe AEs): indication of lesser harm: "major" ▫ Investigations (severe AEs): indication of lesser harm – extent: "considerable" ▪ Fever (SAEs): indication of lesser harm – extent "considerable"	–
Non-serious/non-severe side effects ▪ Discontinuation due to AEs[b], nausea (AEs), hypotension (AEs): hint of lesser harm – extent: "considerable"	Non-serious/non-severe side effects ▪ Haemorrhages (AEs), contusion (AEs): hint of greater harm – extent: "considerable"
a. The outcomes of the categories of morbidity and health-related quality of life were recorded until disease progression. Side effect outcomes were recorded up to 30 days (zanubrutinib) or up to 90 days (bendamustine + rituximab) after the last dose of study medication or until disease progression, whichever was later. (See [1]). b. For the outcome of discontinuation due to AEs, the fixed treatment duration and the associated discontinuation of observation in the comparator arm mean that the hazard ratio is interpretable only for approximately the first 8 months after randomization. AE: adverse event; SAE: serious adverse event	

For the assessment of the added benefit of zanubrutinib in comparison with the appropriate comparator therapy, the company presented only data for patients without genetic risk factors for whom therapy with fludarabine + cyclophosphamide + rituximab (FCR) is unsuitable (see dossier assessment A22-130 [1]). No data are available for patients without genetic risk factors for whom therapy with FCR is suitable, and for patients with genetic risk factors.

Compared with benefit assessment A22-130, a quantification of the added benefit is possible due to the subsequently submitted results for the outcomes of the side effects category.

Overall, there are both positive and negative effects of zanubrutinib in comparison with bendamustine + rituximab for patients without genetic risk factors for whom therapy with FCR is unsuitable. There are advantages in particular in the outcome category of serious/severe side effects with indications of lesser harm with different extents. In addition, there are hints of lesser harm in the outcome category of non-serious/non-severe side effects with the extent "considerable". For the patient-reported outcomes of the outcome categories of morbidity and health-related quality of life, there are hints of added benefit of zanubrutinib in comparison with bendamustine + rituximab for individual symptom and functional scales of the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30) (partly only for subgroups) with considerable and minor extent. On the other hand, there is a hint of lesser benefit with the extent "minor" in the category of health-related quality of life (only for women) and a hint of greater harm with the extent "considerable" in the category of non-serious/non-severe side effects.

Overall, in the present situation, the added benefit is therefore based mainly on advantages in the outcome category of serious/severe side effects. Despite the low risk of bias in this outcome category, the lack of subgroup analyses and the associated uncertainty (see section on subgroup analyses) reduce the certainty of conclusions. Therefore, there is only a hint of an added benefit in the outcomes of the above-mentioned category.

In summary, there is a hint of a considerable added benefit of zanubrutinib in comparison with bendamustine + rituximab for adult patients with previously untreated CLL who have no genetic risk factors and for whom therapy with FCR is unsuitable.

2.2 Summary

The data subsequently submitted by the company in the commenting procedure have changed the conclusion on the added benefit of zanubrutinib from dossier assessment A22-130 for adult patients with previously untreated CLL who have no genetic risk factors and for whom therapy with FCR is unsuitable.

Table 4 below shows the result of the benefit assessment of zanubrutinib, taking into account both dossier assessment A22-130 and the present addendum.

Table 4: Zanubrutinib – probability and extent of added benefit

Therapeutic indication	**ACT**[a]	**Probability and extent of added benefit**
Adult patients with previously untreated CLL[b]	Ibrutinib or ibrutinib in combination with rituximab or obinutuzumab or FCR[c, d] or **bendamustine in combination with rituximab**[d, e] or chlorambucil in combination with rituximab or obinutuzumab[d, e]	▪ Patients without genetic risk factors for whom therapy with FCR is not suitable: hint of considerable added benefit ▪ All other patients in the therapeutic indication: added benefit not proven

a. Presented is the ACT specified by the G-BA. In cases where the ACT specified by the G-BA allows the company to choose a comparator therapy from several options, the respective choice of the company is printed in **bold**.
b. The G-BA assumes for the present therapeutic indication that the patients require treatment (e.g. Binet stage C). Moreover, it is assumed that allogeneic stem cell transplantation is not indicated at the time point of treatment.
c. Only for patients without genetic risk factors and < 65 years of age, for whom therapy with FCR is suitable on the basis of their general condition and comorbidities.
d. According to the G-BA, the following factors are considered genetic risk factors based on the current state of medical knowledge: presence of a 17p deletion/TP53 mutation or an unmutated immunoglobulin heavy-chain variable region.
e. Only for patients without genetic risk factors for whom therapy with FCR is not suitable. According to the G-BA, these are patients ≥ 65 years of age, and patients < 65 years for whom therapy with FCR is not suitable on the basis of their general condition and comorbidity.

17p deletion: deletion in the short arm of chromosome 17; 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.

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Appendix A Results on side effects

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

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

Table 5: Common AEs[a] – RCT, direct comparison: zanubrutinib vs. bendamustine + rituximab (multipage table)

Study	Patients with event n (%)	
SOC[b] **PT[b]**	**Zanubrutinib** **N = 104**	**Bendamustine + rituximab** **N = 101**
SEQUOIA		
Overall AE rate	101 (97.1)	98 (97.0)
Blood and lymphatic system disorders	30 (28.8)	58 (57.4)
Anaemia	6 (5.8)	20 (19.8)
Neutropenia	16 (15.4)	39 (38.6)
Thrombocytopenia	4 (3.8)	12 (11.9)
Cardiac disorders	17 (16.3)	9 (8.9)
Eye disorders	20 (19.2)	8 (7.9)
Gastrointestinal disorders	52 (50.0)	59 (58.4)
Constipation	13 (12.5)	24 (23.8)
Diarrhoea	17 (16.3)	13 (12.9)
Nausea	13 (12.5)	34 (33.7)
Vomiting	13 (12.5)	17 (16.8)
General disorders and administration site conditions	43 (41.3)	63 (62.4)
Asthenia	4 (3.8)	11 (10.9)
Chills	3 (2.9)	10 (9.9)
Fatigue	15 (14.4)	11 (10.9)
Oedema peripheral	9 (8.7)	12 (11.9)
Pyrexia	8 (7.7)	34 (33.7)
Immune system disorders	7 (6.7)	12 (11.9)
Infections and infestations	74 (71.2)	58 (57.4)
COVID-19	19 (18.3)	4 (4.0)
Nasopharyngitis	10 (9.6)	4 (4.0)
Pneumonia	7 (6.7)	10 (9.9)
Upper respiratory tract infection	15 (14.4)	11 (10.9)
Injury, poisoning and procedural complications	38 (36.5)	34 (33.7)
Contusion	27 (26.0)	4 (4.0)
Infusion related reaction	1 (1.0)	23 (22.8)
Investigations	19 (18.3)	34 (33.7)
Neutrophil count decreased	3 (2.9)	15 (14.9)
Platelet count decreased	1 (1.0)	10 (9.9)

Table 5: Common AEs[a] – RCT, direct comparison: zanubrutinib vs. bendamustine + rituximab (multipage table)

Study	**Patients with event n (%)**	
SOC[b] / **PT[b]**	**Zanubrutinib N = 104**	**Bendamustine + rituximab N = 101**
Metabolism and nutrition disorders	21 (20.2)	26 (25.7)
Musculoskeletal and connective tissue disorders	52 (50.0)	33 (32.7)
Arthralgia	21 (20.2)	13 (12.9)
Pain in extremity	11 (10.6)	5 (5.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	19 (18.3)	18 (17.8)
Nervous system disorders	37 (35.6)	31 (30.7)
Dizziness	11 (10.6)	7 (6.9)
Headache	12 (11.5)	12 (11.9)
Psychiatric disorders	14 (13.5)	10 (9.9)
Renal and urinary disorders	13 (12.5)	14 (13.9)
Respiratory, thoracic and mediastinal disorders	48 (46.2)	38 (37.6)
Cough	17 (16.3)	11 (10.9)
Skin and subcutaneous tissue disorders	52 (50.0)	44 (43.6)
Petechiae	12 (11.5)	0 (0.0)
Rash	15 (14.4)	21 (20.8)
Vascular disorders	36 (34.6)	25 (24.8)
Hypertension	18 (17.3)	13 (12.9)
Hypotension	3 (2.9)	14 (13.9)

a. Events that occurred in ≥ 10 patients in at least one study arm.
b. SOC and PT notation taken from the data subsequently submitted.

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

Table 6: Common SAEs[a] – RCT, direct comparison: zanubrutinib vs. bendamustine + rituximab

Study	**Patients with event n (%)**	
SOC[b] **PT[b]**	**Zanubrutinib** **N = 104**	**Bendamustine + rituximab** **N = 101**
SEQUOIA		
Overall SAE rate	50 (48.1)	49 (48.5)
Blood and lymphatic system disorders	3 (2.9)	5 (5.0)
Cardiac disorders	11 (10.6)	5 (5.0)
Gastrointestinal disorders	3 (2.9)	5 (5.0)
General disorders and administration site conditions	3 (2.9)	10 (9.9)
Pyrexia	1 (1.0)	9 (8.9)
Infections and infestations	27 (26.0)	17 (16.8)
COVID-19	9 (8.7)	1 (1.0)
COVID-19 pneumonia	7 (6.7)	1 (1.0)
Injury, poisoning and procedural complications	6 (5.8)	7 (6.9)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	3 (2.9)	6 (5.9)
Respiratory, thoracic and mediastinal disorders	1 (1.0)	7 (6.9)

a. Events that occurred in ≥ 5% of patients in at least one study arm.
b. SOC and PT notation taken from the data subsequently submitted.

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 7: Common severe AEs (CTCAE grade ≥ 3)[a] – RCT, direct comparison: zanubrutinib vs. bendamustine + rituximab

Study	Patients with event n (%)	
SOC[b] **PT[b]**	**Zanubrutinib** **N = 104**	**Bendamustine + rituximab** **N = 101**
SEQUOIA		
Overall rate of severe AEs (CTCAE grade ≥ 3)	59 (56.7)	82 (81.2)
Blood and lymphatic system disorders	17 (16.3)	42 (41.6)
Febrile neutropenia	1 (1.0)	8 (7.9)
Neutropenia	13 (12.5)	35 (34.7)
Thrombocytopenia	2 (1.9)	5 (5.0)
Cardiac disorders	8 (7.7)	4 (4.0)
Gastrointestinal disorders	2 (1.9)	8 (7.9)
General disorders and administration site conditions	3 (2.9)	7 (6.9)
Infections and infestations	22 (21.2)	20 (19.8)
COVID-19	9 (8.7)	1 (1.0)
COVID-19 pneumonia	7 (6.7)	1 (1.0)
Pneumonia	3 (2.9)	5 (5.0)
Injury, poisoning and procedural complications	4 (3.8)	7 (6.9)
Investigations	6 (5.8)	17 (16.8)
Neutrophil count decreased	3 (2.9)	13 (12.9)
Metabolism and nutrition disorders	4 (3.8)	6 (5.9)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	7 (6.7)	7 (6.9)
Respiratory, thoracic and mediastinal disorders	2 (1.9)	8 (7.9)
Vascular disorders	10 (9.6)	10 (9.9)
Hypertension	8 (7.7)	6 (5.9)

a. Events that occurred in ≥ 5% of patients in at least one study arm.
b. SOC and PT notation taken from the data subsequently submitted.

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