



## Clinical trial results:

### A Phase 3, Randomized, Open-Label, Multicenter Study Comparing the Efficacy and Safety of the Bruton's Tyrosine Kinase (BTK) Inhibitors BGB-3111 and Ibrutinib in Subjects with Waldenström's Macroglobulinemia (WM)

#### Summary

|                          |                                  |
|--------------------------|----------------------------------|
| EudraCT number           | 2016-002980-33                   |
| Trial protocol           | DE BE SE ES NL PL GR GB CZ FR IT |
| Global end of trial date | 21 June 2022                     |

#### Results information

|                                |                                                                                                                                         |
|--------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------|
| Result version number          | v2 (current)                                                                                                                            |
| This version publication date  | 10 November 2023                                                                                                                        |
| First version publication date | 14 April 2023                                                                                                                           |
| Version creation reason        | <ul style="list-style-type: none"><li>Changes to summary attachments</li><li>Removal of incorrect secondary identifier number</li></ul> |

#### Trial information

##### Trial identification

|                       |              |
|-----------------------|--------------|
| Sponsor protocol code | BGB-3111-302 |
|-----------------------|--------------|

##### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT03053440 |
| WHO universal trial number (UTN)   | -           |

Notes:

#### Sponsors

|                              |                                                                                          |
|------------------------------|------------------------------------------------------------------------------------------|
| Sponsor organisation name    | BeiGene                                                                                  |
| Sponsor organisation address | 1840 Gateway Drive, San Mateo, CA , United States, 94404                                 |
| Public contact               | BeiGene Clinical Support, BeiGene USA, Inc., +1 877-828-5568, clinicaltrials@beigene.com |
| Scientific contact           | BeiGene Clinical Support, BeiGene USA, Inc., +1 877-828-5568, clinicaltrials@beigene.com |

Notes:

#### Paediatric regulatory details

|                                                                      |    |
|----------------------------------------------------------------------|----|
| Is trial part of an agreed paediatric investigation plan (PIP)       | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

## Results analysis stage

|                                                      |              |
|------------------------------------------------------|--------------|
| Analysis stage                                       | Final        |
| Date of interim/final analysis                       | 29 July 2022 |
| Is this the analysis of the primary completion data? | No           |

|                                  |              |
|----------------------------------|--------------|
| Global end of trial reached?     | Yes          |
| Global end of trial date         | 21 June 2022 |
| Was the trial ended prematurely? | No           |

Notes:

## General information about the trial

Main objective of the trial:

To compare the efficacy of zanubrutinib (BGB-3111) vs ibrutinib in subjects with MYD88MUT WM

Protection of trial subjects:

This study was conducted in accordance with sponsor procedures, which comply with the principles of GCP, International Council on Harmonisation Guidelines, the Declaration of Helsinki, and applicable local regulatory requirements.

Background therapy: -

Evidence for comparator: -

|                                                           |                  |
|-----------------------------------------------------------|------------------|
| Actual start date of recruitment                          | 16 December 2016 |
| Long term follow-up planned                               | No               |
| Independent data monitoring committee (IDMC) involvement? | No               |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                    |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | Australia: 62      |
| Country: Number of subjects enrolled | United States: 19  |
| Country: Number of subjects enrolled | Netherlands: 5     |
| Country: Number of subjects enrolled | Poland: 16         |
| Country: Number of subjects enrolled | Spain: 18          |
| Country: Number of subjects enrolled | Sweden: 7          |
| Country: Number of subjects enrolled | United Kingdom: 30 |
| Country: Number of subjects enrolled | Czechia: 7         |
| Country: Number of subjects enrolled | France: 1          |
| Country: Number of subjects enrolled | Germany: 2         |
| Country: Number of subjects enrolled | Greece: 11         |
| Country: Number of subjects enrolled | Italy: 23          |
| Worldwide total number of subjects   | 201                |
| EEA total number of subjects         | 90                 |

Notes:

### Subjects enrolled per age group

|                                        |   |
|----------------------------------------|---|
| In utero                               | 0 |
| Preterm newborn - gestational age < 37 | 0 |

|                                          |     |
|------------------------------------------|-----|
| wk                                       |     |
| Newborns (0-27 days)                     | 0   |
| Infants and toddlers (28 days-23 months) | 0   |
| Children (2-11 years)                    | 0   |
| Adolescents (12-17 years)                | 0   |
| Adults (18-64 years)                     | 58  |
| From 65 to 84 years                      | 134 |
| 85 years and over                        | 9   |

## Subject disposition

### Recruitment

Recruitment details:

A total of 229 participants were randomized to Arms A and B in 12 countries in European Union, United Kingdom and United States.

### Pre-assignment

Screening details:

The screening period consisted of Days -35 to -1.

### Period 1

|                              |                                 |
|------------------------------|---------------------------------|
| Period 1 title               | Overall period (overall period) |
| Is this the baseline period? | Yes                             |
| Allocation method            | Randomised - controlled         |
| Blinding used                | Not blinded                     |

### Arms

|                              |                  |
|------------------------------|------------------|
| Are arms mutually exclusive? | Yes              |
| <b>Arm title</b>             | Arm A: Ibrutinib |

Arm description:

Participants diagnosed with WM with mutated MYD88 gene received 420 mg ibrutinib once daily orally until progressive disease, unacceptable toxicity, death, withdrawal of consent, or study termination by sponsor

|                                        |              |
|----------------------------------------|--------------|
| Arm type                               | Experimental |
| Investigational medicinal product name | Ibrutinib    |
| Investigational medicinal product code |              |
| Other name                             |              |
| Pharmaceutical forms                   | Capsule      |
| Routes of administration               | Oral use     |

Dosage and administration details:

Ibrutinib 420 milligrams (mg) once a day

|                  |                     |
|------------------|---------------------|
| <b>Arm title</b> | Arm B: Zanubrutinib |
|------------------|---------------------|

Arm description:

Participants diagnosed with WM with mutated MYD88 gene received 160 mg zanubrutinib twice daily orally until progressive disease, unacceptable toxicity, death, withdrawal of consent, or study termination by sponsor

|                                        |                    |
|----------------------------------------|--------------------|
| Arm type                               | Experimental       |
| Investigational medicinal product name | Zanubrutinib       |
| Investigational medicinal product code |                    |
| Other name                             | Brukinsa, BGB-3111 |
| Pharmaceutical forms                   | Capsule            |
| Routes of administration               | Oral use           |

Dosage and administration details:

Zanubrutinib 160 mg twice a day

| <b>Number of subjects in period 1</b> | Arm A: Ibrutinib | Arm B: Zanubrutinib |
|---------------------------------------|------------------|---------------------|
| Started                               | 99               | 102                 |
| Completed                             | 0                | 0                   |
| Not completed                         | 99               | 102                 |
| Adverse event, serious fatal          | 19               | 14                  |
| Consent withdrawn by subject          | 9                | 8                   |
| Physician decision                    | 2                | 1                   |
| Sponsor's decision to end study       | 20               | 13                  |
| Lost to follow-up                     | 1                | -                   |
| Enrolled in Long-term extension study | 48               | 66                  |

## Baseline characteristics

### Reporting groups

|                       |                  |
|-----------------------|------------------|
| Reporting group title | Arm A: Ibrutinib |
|-----------------------|------------------|

Reporting group description:

Participants diagnosed with WM with mutated MYD88 gene received 420 mg ibrutinib once daily orally until progressive disease, unacceptable toxicity, death, withdrawal of consent, or study termination by sponsor

|                       |                     |
|-----------------------|---------------------|
| Reporting group title | Arm B: Zanubrutinib |
|-----------------------|---------------------|

Reporting group description:

Participants diagnosed with WM with mutated MYD88 gene received 160 mg zanubrutinib twice daily orally until progressive disease, unacceptable toxicity, death, withdrawal of consent, or study termination by sponsor

| Reporting group values             | Arm A: Ibrutinib | Arm B: Zanubrutinib | Total |
|------------------------------------|------------------|---------------------|-------|
| Number of subjects                 | 99               | 102                 | 201   |
| Age categorical<br>Units: Subjects |                  |                     |       |

|                                                                         |                |                 |     |
|-------------------------------------------------------------------------|----------------|-----------------|-----|
| Age continuous<br>Units: years<br>arithmetic mean<br>standard deviation | 69.9<br>± 8.58 | 69.2<br>± 10.26 | -   |
| Gender categorical<br>Units: Subjects                                   |                |                 |     |
| Female                                                                  | 34             | 33              | 67  |
| Male                                                                    | 65             | 69              | 134 |
| Ethnicity<br>Units: Subjects                                            |                |                 |     |
| Hispanic or Latino                                                      | 4              | 4               | 8   |
| Not Hispanic or Latino                                                  | 91             | 82              | 173 |
| Unknown or Not Reported                                                 | 4              | 16              | 20  |
| Race<br>Units: Subjects                                                 |                |                 |     |
| Asian                                                                   | 0              | 4               | 4   |
| White                                                                   | 94             | 88              | 182 |
| Unknown or Not Reported                                                 | 5              | 10              | 15  |

## End points

### End points reporting groups

|                                                                                                                                                                                                                                                        |                     |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------|
| Reporting group title                                                                                                                                                                                                                                  | Arm A: Ibrutinib    |
| Reporting group description:<br>Participants diagnosed with WM with mutated MYD88 gene received 420 mg ibrutinib once daily orally until progressive disease, unacceptable toxicity, death, withdrawal of consent, or study termination by sponsor     |                     |
| Reporting group title                                                                                                                                                                                                                                  | Arm B: Zanubrutinib |
| Reporting group description:<br>Participants diagnosed with WM with mutated MYD88 gene received 160 mg zanubrutinib twice daily orally until progressive disease, unacceptable toxicity, death, withdrawal of consent, or study termination by sponsor |                     |

### Primary: Percentage of participants achieving either a complete response (CR) or very good partial response (VGPR) using an adaptation of the response criteria updated at the Sixth IWWM as assessed by an independent review committee (IRC)

|                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                                                                                                                                                                                                                                       |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title                                                                                                                                                                                                                                                                                                                                                                                                                                             | Percentage of participants achieving either a complete response (CR) or very good partial response (VGPR) using an adaptation of the response criteria updated at the Sixth IWWM as assessed by an independent review committee (IRC) |
| End point description:<br>Percentage of participants with CR, defined as normal serum immunoglobulin M (IgM) levels, disappearance of monoclonal protein by immunofixation, and negative cryoglobulinemia if cryoglobulinemia was positive at baseline, or VGPR, defined as $\geq 90\%$ reduction in serum IgM level from baseline or normal serum IgM values. Intent to Treat (ITT) Analysis Set: Includes all randomized participants assigned to an arm. |                                                                                                                                                                                                                                       |
| End point type                                                                                                                                                                                                                                                                                                                                                                                                                                              | Primary                                                                                                                                                                                                                               |
| End point timeframe:<br>Up to approximately 2 years and 7 months                                                                                                                                                                                                                                                                                                                                                                                            |                                                                                                                                                                                                                                       |

| End point values                  | Arm A:<br>Ibrutinib | Arm B:<br>Zanubrutinib |  |  |
|-----------------------------------|---------------------|------------------------|--|--|
| Subject group type                | Reporting group     | Reporting group        |  |  |
| Number of subjects analysed       | 99                  | 102                    |  |  |
| Units: Percentage of Participants |                     |                        |  |  |
| number (confidence interval 95%)  | 19.2 (12.0 to 28.3) | 28.4 (19.9 to 38.2)    |  |  |

### Statistical analyses

|                            |                                        |
|----------------------------|----------------------------------------|
| Statistical analysis title | Statistical analysis 1                 |
| Comparison groups          | Arm A: Ibrutinib v Arm B: Zanubrutinib |

|                                         |                         |
|-----------------------------------------|-------------------------|
| Number of subjects included in analysis | 201                     |
| Analysis specification                  | Pre-specified           |
| Analysis type                           | superiority             |
| P-value                                 | = 0.0921 <sup>[1]</sup> |
| Method                                  | Cochran-Mantel-Haenszel |
| Parameter estimate                      | Risk difference (RD)    |
| Point estimate                          | 10.2                    |
| Confidence interval                     |                         |
| level                                   | 95 %                    |
| sides                                   | 2-sided                 |
| lower limit                             | -1.5                    |
| upper limit                             | 22                      |

Notes:

[1] - Based on Cochran-Mantel-Haenszel test stratified by the stratification factors per IRT. p Value is 2-sided

### Secondary: Percentage of Participants Achieving Major Response Rate (MRR) as assessed by IRC

|                 |                                                                                   |
|-----------------|-----------------------------------------------------------------------------------|
| End point title | Percentage of Participants Achieving Major Response Rate (MRR) as assessed by IRC |
|-----------------|-----------------------------------------------------------------------------------|

End point description:

MRR defined as the proportion of participants achieving a best response of response of CR, VGPR, or partial response (PR). MRR defined as the proportion of participants achieving a best response of response of CR, VGPR, or partial response (PR). ITT Analysis Set

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Up to approximately 2 years and 7 months

| End point values                  | Arm A:<br>Ibrutinib | Arm B:<br>Zanubrutinib |  |  |
|-----------------------------------|---------------------|------------------------|--|--|
| Subject group type                | Reporting group     | Reporting group        |  |  |
| Number of subjects analysed       | 99                  | 100                    |  |  |
| Units: Percentage of Participants |                     |                        |  |  |
| number (confidence interval 95%)  | 77.8 (68.3 to 85.5) | 77.5 (68.1 to 85.1)    |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Duration of Response (DOR) as assessed by IRC

|                 |                                               |
|-----------------|-----------------------------------------------|
| End point title | Duration of Response (DOR) as assessed by IRC |
|-----------------|-----------------------------------------------|

End point description:

DOR defined as the time from first determination of response (CR, VGPR or PR) until first documentation of progression or death, whichever comes first. ITT Analysis set

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Up to approximately 2 years and 7 months

| End point values                 | Arm A:<br>Ibrutinib | Arm B:<br>Zanubrutinib |  |  |
|----------------------------------|---------------------|------------------------|--|--|
| Subject group type               | Reporting group     | Reporting group        |  |  |
| Number of subjects analysed      | 99 <sup>[2]</sup>   | 102 <sup>[3]</sup>     |  |  |
| Units: Months                    |                     |                        |  |  |
| median (confidence interval 95%) | 9999 (9999 to 9999) | 9999 (9999 to 9999)    |  |  |

Notes:

[2] - 9999 = Not Estimable due to insufficient number of events

[3] - 9999 = Not Estimable due to insufficient number of events

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of participants achieving either CR or VGPR in as assessed by the investigator

|                 |                                                                                           |
|-----------------|-------------------------------------------------------------------------------------------|
| End point title | Percentage of participants achieving either CR or VGPR in as assessed by the investigator |
|-----------------|-------------------------------------------------------------------------------------------|

End point description:

Percentage of participants with CR, defined as normal serum immunoglobulin M (IgM) levels, disappearance of monoclonal protein by immunofixation, and negative cryoglobulinemia if cryoglobulinemia was positive at Baseline, or VGPR, defined as  $\geq 90\%$  reduction in serum IgM level from baseline or normal serum IgM values. ITT Analysis set

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Up to approximately 5 years and 5 months

| End point values                  | Arm A:<br>Ibrutinib | Arm B:<br>Zanubrutinib |  |  |
|-----------------------------------|---------------------|------------------------|--|--|
| Subject group type                | Reporting group     | Reporting group        |  |  |
| Number of subjects analysed       | 99                  | 101                    |  |  |
| Units: Percentage of Participants |                     |                        |  |  |
| number (confidence interval 95%)  | 25.3 (17.1 to 35.0) | 38.2 (28.8 to 48.4)    |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: DOR in as assessed by the Investigator

|                 |                                        |
|-----------------|----------------------------------------|
| End point title | DOR in as assessed by the Investigator |
|-----------------|----------------------------------------|

End point description:

DOR is defined as the time from first determination of response (CR, VGPR or PR) until first documentation of progression or death, whichever comes first. ITT Analysis Set

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Up to approximately 5 years and 5 months

| End point values                 | Arm A:<br>Ibrutinib | Arm B:<br>Zanubrutinib |  |  |
|----------------------------------|---------------------|------------------------|--|--|
| Subject group type               | Reporting group     | Reporting group        |  |  |
| Number of subjects analysed      | 99 <sup>[4]</sup>   | 102 <sup>[5]</sup>     |  |  |
| Units: Months                    |                     |                        |  |  |
| median (confidence interval 95%) | 9999 (53.5 to 9999) | 9999 (9999 to 9999)    |  |  |

Notes:

[4] - 9999 = Not Estimable due to insufficient number of events

[5] - 9999 = Not Estimable due to insufficient number of events

## Statistical analyses

No statistical analyses for this end point

### Secondary: Progression Free Survival (PFS) as assessed by the Investigator

|                 |                                                                 |
|-----------------|-----------------------------------------------------------------|
| End point title | Progression Free Survival (PFS) as assessed by the Investigator |
|-----------------|-----------------------------------------------------------------|

End point description:

PFS as assessed by the Investigator, defined as time from randomization to the first documentation of progression (per modified IWWM criteria) or death, whichever occurs first. ITT Analysis Set

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Up to approximately 5 years and 5 months

| End point values                 | Arm A:<br>Ibrutinib | Arm B:<br>Zanubrutinib |  |  |
|----------------------------------|---------------------|------------------------|--|--|
| Subject group type               | Reporting group     | Reporting group        |  |  |
| Number of subjects analysed      | 99 <sup>[6]</sup>   | 102 <sup>[7]</sup>     |  |  |
| Units: Months                    |                     |                        |  |  |
| median (confidence interval 95%) | 9999 (54.4 to 9999) | 9999 (9999 to 9999)    |  |  |

Notes:

[6] - 9999 = Not Estimable due to insufficient number of events

[7] - 9999 = Not Estimable due to insufficient number of events

## Statistical analyses

No statistical analyses for this end point

### Secondary: Progression Free Survival (PFS) as assessed by the IRC

|                 |                                                        |
|-----------------|--------------------------------------------------------|
| End point title | Progression Free Survival (PFS) as assessed by the IRC |
|-----------------|--------------------------------------------------------|

End point description:

PFS as assessed by the IRC, defined as time from randomization to the first documentation of progression (per modified IWWM criteria) or death, whichever occurs first. ITT Analysis Set

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:  
Up to approximately 2 years and 7 months

| End point values                 | Arm A:<br>Ibrutinib | Arm B:<br>Zanubrutinib |  |  |
|----------------------------------|---------------------|------------------------|--|--|
| Subject group type               | Reporting group     | Reporting group        |  |  |
| Number of subjects analysed      | 99 <sup>[8]</sup>   | 102 <sup>[9]</sup>     |  |  |
| Units: Months                    |                     |                        |  |  |
| median (confidence interval 95%) | 9999 (9999 to 9999) | 9999 (9999 to 9999)    |  |  |

Notes:

[8] - 9999 = Not Estimable due to insufficient number of events

[9] - 9999 = Not Estimable due to insufficient number of events

### Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of participants with Resolution of all Treatment-precipitating Symptoms

|                 |                                                                                    |
|-----------------|------------------------------------------------------------------------------------|
| End point title | Percentage of participants with Resolution of all Treatment-precipitating Symptoms |
|-----------------|------------------------------------------------------------------------------------|

End point description:

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Up to approximately 5 years and 5 months

| End point values                  | Arm A:<br>Ibrutinib | Arm B:<br>Zanubrutinib |  |  |
|-----------------------------------|---------------------|------------------------|--|--|
| Subject group type                | Reporting group     | Reporting group        |  |  |
| Number of subjects analysed       | 99                  | 102                    |  |  |
| Units: Percentage of Participants |                     |                        |  |  |
| number (not applicable)           | 78.6                | 79.2                   |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of participants with an anti-Lymphoma effect

|                 |                                                         |
|-----------------|---------------------------------------------------------|
| End point title | Percentage of participants with an anti-Lymphoma effect |
|-----------------|---------------------------------------------------------|

End point description:

ITT Analysis Set

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:  
Up to approximately 5 years and 5 months

| End point values                  | Arm A:<br>Ibrutinib | Arm B:<br>Zanubrutinib |  |  |
|-----------------------------------|---------------------|------------------------|--|--|
| Subject group type                | Reporting group     | Reporting group        |  |  |
| Number of subjects analysed       | 99                  | 102                    |  |  |
| Units: Percentage of Participants |                     |                        |  |  |
| number (not applicable)           | 84.2                | 78.8                   |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Number of Participants with Treatment-Emergent adverse Events (TEAEs) and Serious Adverse Events (SAEs)

|                 |                                                                                                         |
|-----------------|---------------------------------------------------------------------------------------------------------|
| End point title | Number of Participants with Treatment-Emergent adverse Events (TEAEs) and Serious Adverse Events (SAEs) |
|-----------------|---------------------------------------------------------------------------------------------------------|

End point description:

Safety Analysis Set includes all participants who received any dose of zanubrutinib or ibrutinib

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Up to approximately 5 years and 5 months

| End point values                  | Arm A:<br>Ibrutinib | Arm B:<br>Zanubrutinib |  |  |
|-----------------------------------|---------------------|------------------------|--|--|
| Subject group type                | Reporting group     | Reporting group        |  |  |
| Number of subjects analysed       | 98                  | 101                    |  |  |
| Units: Percentage of Participants |                     |                        |  |  |
| number (not applicable)           |                     |                        |  |  |
| Participants with At Least 1 TEAE | 98                  | 101                    |  |  |
| Participants with SAEs            | 50                  | 59                     |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: DOR as Assessed by IRC: Event -Free Rate

|                 |                                          |
|-----------------|------------------------------------------|
| End point title | DOR as Assessed by IRC: Event -Free Rate |
|-----------------|------------------------------------------|

End point description:

Estimated percentage of participants who were event-free based on Kaplan-Meier method.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

12 and 18 months from the date of randomization (up to approximately 2 years and 7 months)

| End point values                  | Arm A:<br>Ibrutinib | Arm B:<br>Zanubrutinib |  |  |
|-----------------------------------|---------------------|------------------------|--|--|
| Subject group type                | Reporting group     | Reporting group        |  |  |
| Number of subjects analysed       | 99                  | 102                    |  |  |
| Units: Percentage of Participants |                     |                        |  |  |
| number (confidence interval 95%)  |                     |                        |  |  |
| 12 Months                         | 87.9 (77.0 to 93.8) | 94.4 (85.8 to 97.9)    |  |  |
| 18 Months                         | 87.9 (77.0 to 93.8) | 85.2 (71.7 to 92.6)    |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: DOR as Assessed by the Investigator: Event-Free Rate

End point title DOR as Assessed by the Investigator: Event-Free Rate

End point description:

Estimated percentage of participants who were event-free based on Kaplan-Meier method.

End point type Secondary

End point timeframe:

24, 36 and 48 months from the date of randomization (up to approximately 5 years and 5 months)

| End point values                  | Arm A:<br>Ibrutinib | Arm B:<br>Zanubrutinib |  |  |
|-----------------------------------|---------------------|------------------------|--|--|
| Subject group type                | Reporting group     | Reporting group        |  |  |
| Number of subjects analysed       | 99                  | 102                    |  |  |
| Units: Percentage of Participants |                     |                        |  |  |
| number (confidence interval 95%)  |                     |                        |  |  |
| 24 Months                         | 87.7 (77.8 to 93.4) | 89.7 (80.4 to 94.7)    |  |  |
| 36 Months                         | 77.5 (65.9 to 85.6) | 81.1 (70.1 to 88.4)    |  |  |
| 48 Months                         | 73.9 (61.6 to 82.8) | 81.1 (70.1 to 88.4)    |  |  |

### Statistical analyses

No statistical analyses for this end point

**Secondary: PFS as Assessed by IRC: Event-Free Rate**

|                                                                                            |                                         |
|--------------------------------------------------------------------------------------------|-----------------------------------------|
| End point title                                                                            | PFS as Assessed by IRC: Event-Free Rate |
| End point description:                                                                     |                                         |
| Estimated percentage of participants who were event-free based on Kaplan-Meier method      |                                         |
| End point type                                                                             | Secondary                               |
| End point timeframe:                                                                       |                                         |
| 12 and 18 months from the date of randomization (up to approximately 2 years and 7 months) |                                         |

| End point values                  | Arm A:<br>Ibrutinib | Arm B:<br>Zanubrutinib |  |  |
|-----------------------------------|---------------------|------------------------|--|--|
| Subject group type                | Reporting group     | Reporting group        |  |  |
| Number of subjects analysed       | 99                  | 102                    |  |  |
| Units: Percentage of Participants |                     |                        |  |  |
| number (confidence interval 95%)  |                     |                        |  |  |
| 12 Months                         | 87.2 (78.6 to 92.5) | 89.7 (81.7 to 94.3)    |  |  |
| 18 Months                         | 83.8 (74.5 to 89.9) | 85.0 (75.2 to 91.2)    |  |  |

**Statistical analyses**

No statistical analyses for this end point

**Secondary: PFS as Assessed by the Investigator: Event-Free Rate**

|                                                                                                |                                                      |
|------------------------------------------------------------------------------------------------|------------------------------------------------------|
| End point title                                                                                | PFS as Assessed by the Investigator: Event-Free Rate |
| End point description:                                                                         |                                                      |
| Percentage of participants who were event-free based on Kaplan-Meier method.                   |                                                      |
| End point type                                                                                 | Secondary                                            |
| End point timeframe:                                                                           |                                                      |
| 24, 36 and 48 months from the date of randomization (up to approximately 5 years and 5 months) |                                                      |

| End point values                  | Arm A:<br>Ibrutinib | Arm B:<br>Zanubrutinib |  |  |
|-----------------------------------|---------------------|------------------------|--|--|
| Subject group type                | Reporting group     | Reporting group        |  |  |
| Number of subjects analysed       | 99                  | 102                    |  |  |
| Units: Percentage of Participants |                     |                        |  |  |
| number (confidence interval 95%)  |                     |                        |  |  |
| 24 Months                         | 80.6 (70.9 to 87.3) | 88.5 (80.2 to 93.5)    |  |  |
| 36 Months                         | 74.8 (64.5 to 82.5) | 78.3 (68.4 to 85.5)    |  |  |
| 48 Months                         | 67.3 (56.3 to 76.1) | 78.3 (68.4 to 85.5)    |  |  |

## **Statistical analyses**

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No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Up to Approximately 5 years 5 months

|                 |            |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

### Dictionary used

|                 |        |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

|                    |    |
|--------------------|----|
| Dictionary version | 22 |
|--------------------|----|

### Reporting groups

|                       |           |
|-----------------------|-----------|
| Reporting group title | Ibrutinib |
|-----------------------|-----------|

Reporting group description:

Ibrutinib

|                       |              |
|-----------------------|--------------|
| Reporting group title | Zanubrutinib |
|-----------------------|--------------|

Reporting group description:

Zanubrutinib

| Serious adverse events                                              | Ibrutinib        | Zanubrutinib      |  |
|---------------------------------------------------------------------|------------------|-------------------|--|
| Total subjects affected by serious adverse events                   |                  |                   |  |
| subjects affected / exposed                                         | 50 / 98 (51.02%) | 59 / 101 (58.42%) |  |
| number of deaths (all causes)                                       | 18               | 14                |  |
| number of deaths resulting from adverse events                      | 7                | 3                 |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                  |                   |  |
| Basal cell carcinoma                                                |                  |                   |  |
| subjects affected / exposed                                         | 0 / 98 (0.00%)   | 2 / 101 (1.98%)   |  |
| occurrences causally related to treatment / all                     | 0 / 0            | 0 / 2             |  |
| deaths causally related to treatment / all                          | 0 / 0            | 0 / 0             |  |
| Bladder transitional cell carcinoma                                 |                  |                   |  |
| subjects affected / exposed                                         | 3 / 98 (3.06%)   | 0 / 101 (0.00%)   |  |
| occurrences causally related to treatment / all                     | 0 / 3            | 0 / 0             |  |
| deaths causally related to treatment / all                          | 0 / 0            | 0 / 0             |  |
| Breast cancer                                                       |                  |                   |  |
| subjects affected / exposed                                         | 0 / 98 (0.00%)   | 1 / 101 (0.99%)   |  |
| occurrences causally related to treatment / all                     | 0 / 0            | 0 / 1             |  |
| deaths causally related to treatment / all                          | 0 / 0            | 0 / 0             |  |
| Lymphoma transformation                                             |                  |                   |  |

|                                                      |                |                 |  |
|------------------------------------------------------|----------------|-----------------|--|
| subjects affected / exposed                          | 0 / 98 (0.00%) | 1 / 101 (0.99%) |  |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0           |  |
| Endometrial adenocarcinoma                           |                |                 |  |
| subjects affected / exposed                          | 0 / 98 (0.00%) | 1 / 101 (0.99%) |  |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0           |  |
| Tumour haemorrhage                                   |                |                 |  |
| subjects affected / exposed                          | 0 / 98 (0.00%) | 1 / 101 (0.99%) |  |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0           |  |
| Nodular melanoma                                     |                |                 |  |
| subjects affected / exposed                          | 0 / 98 (0.00%) | 1 / 101 (0.99%) |  |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0           |  |
| Myelodysplastic syndrome                             |                |                 |  |
| subjects affected / exposed                          | 0 / 98 (0.00%) | 1 / 101 (0.99%) |  |
| occurrences causally related to treatment / all      | 0 / 0          | 1 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0           |  |
| Metastatic malignant melanoma                        |                |                 |  |
| subjects affected / exposed                          | 0 / 98 (0.00%) | 1 / 101 (0.99%) |  |
| occurrences causally related to treatment / all      | 0 / 0          | 1 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0          | 1 / 1           |  |
| Vascular disorders                                   |                |                 |  |
| Peripheral vascular disorder                         |                |                 |  |
| subjects affected / exposed                          | 0 / 98 (0.00%) | 1 / 101 (0.99%) |  |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0           |  |
| General disorders and administration site conditions |                |                 |  |
| Death                                                |                |                 |  |
| subjects affected / exposed                          | 2 / 98 (2.04%) | 0 / 101 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 2          | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 2          | 0 / 0           |  |

|                                                 |                |                 |  |
|-------------------------------------------------|----------------|-----------------|--|
| Adverse drug reaction                           |                |                 |  |
| subjects affected / exposed                     | 0 / 98 (0.00%) | 1 / 101 (0.99%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Pyrexia                                         |                |                 |  |
| subjects affected / exposed                     | 3 / 98 (3.06%) | 4 / 101 (3.96%) |  |
| occurrences causally related to treatment / all | 1 / 3          | 1 / 4           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Oedema peripheral                               |                |                 |  |
| subjects affected / exposed                     | 1 / 98 (1.02%) | 0 / 101 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Drug withdrawal syndrome                        |                |                 |  |
| subjects affected / exposed                     | 0 / 98 (0.00%) | 1 / 101 (0.99%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Immune system disorders                         |                |                 |  |
| Amyloidosis                                     |                |                 |  |
| subjects affected / exposed                     | 1 / 98 (1.02%) | 0 / 101 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Reproductive system and breast disorders        |                |                 |  |
| Vaginal prolapse                                |                |                 |  |
| subjects affected / exposed                     | 0 / 98 (0.00%) | 1 / 101 (0.99%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Prostatitis                                     |                |                 |  |
| subjects affected / exposed                     | 1 / 98 (1.02%) | 0 / 101 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Respiratory, thoracic and mediastinal disorders |                |                 |  |
| Acute pulmonary oedema                          |                |                 |  |

|                                                 |                |                 |  |
|-------------------------------------------------|----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 98 (1.02%) | 0 / 101 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Pleural effusion                                |                |                 |  |
| subjects affected / exposed                     | 2 / 98 (2.04%) | 2 / 101 (1.98%) |  |
| occurrences causally related to treatment / all | 1 / 3          | 0 / 6           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Laryngeal oedema                                |                |                 |  |
| subjects affected / exposed                     | 1 / 98 (1.02%) | 0 / 101 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Interstitial lung disease                       |                |                 |  |
| subjects affected / exposed                     | 0 / 98 (0.00%) | 2 / 101 (1.98%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Haemothorax                                     |                |                 |  |
| subjects affected / exposed                     | 0 / 98 (0.00%) | 1 / 101 (0.99%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Acute respiratory failure                       |                |                 |  |
| subjects affected / exposed                     | 0 / 98 (0.00%) | 1 / 101 (0.99%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Pneumonia aspiration                            |                |                 |  |
| subjects affected / exposed                     | 0 / 98 (0.00%) | 1 / 101 (0.99%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Respiratory disorder                            |                |                 |  |
| subjects affected / exposed                     | 1 / 98 (1.02%) | 0 / 101 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Respiratory failure                             |                |                 |  |

|                                                 |                |                 |  |
|-------------------------------------------------|----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 98 (0.00%) | 1 / 101 (0.99%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Psychiatric disorders                           |                |                 |  |
| Anxiety                                         |                |                 |  |
| subjects affected / exposed                     | 1 / 98 (1.02%) | 0 / 101 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 3          | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Investigations                                  |                |                 |  |
| Interferon gamma release assay positive         |                |                 |  |
| subjects affected / exposed                     | 0 / 98 (0.00%) | 1 / 101 (0.99%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Injury, poisoning and procedural complications  |                |                 |  |
| Ankle fracture                                  |                |                 |  |
| subjects affected / exposed                     | 0 / 98 (0.00%) | 1 / 101 (0.99%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Fall                                            |                |                 |  |
| subjects affected / exposed                     | 1 / 98 (1.02%) | 2 / 101 (1.98%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Contusion                                       |                |                 |  |
| subjects affected / exposed                     | 1 / 98 (1.02%) | 0 / 101 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Femoral neck fracture                           |                |                 |  |
| subjects affected / exposed                     | 1 / 98 (1.02%) | 0 / 101 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Femur fracture                                  |                |                 |  |

|                                                 |                |                 |  |
|-------------------------------------------------|----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 98 (1.02%) | 1 / 101 (0.99%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Head injury                                     |                |                 |  |
| subjects affected / exposed                     | 0 / 98 (0.00%) | 1 / 101 (0.99%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Lumbar vertebral fracture                       |                |                 |  |
| subjects affected / exposed                     | 1 / 98 (1.02%) | 1 / 101 (0.99%) |  |
| occurrences causally related to treatment / all | 0 / 2          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Periorbital haematoma                           |                |                 |  |
| subjects affected / exposed                     | 0 / 98 (0.00%) | 1 / 101 (0.99%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Post procedural complication                    |                |                 |  |
| subjects affected / exposed                     | 0 / 98 (0.00%) | 1 / 101 (0.99%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Post procedural haemorrhage                     |                |                 |  |
| subjects affected / exposed                     | 1 / 98 (1.02%) | 0 / 101 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1          | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Stress fracture                                 |                |                 |  |
| subjects affected / exposed                     | 1 / 98 (1.02%) | 0 / 101 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Spinal compression fracture                     |                |                 |  |
| subjects affected / exposed                     | 0 / 98 (0.00%) | 1 / 101 (0.99%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Subdural haematoma                              |                |                 |  |

|                                                 |                |                 |  |
|-------------------------------------------------|----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 98 (1.02%) | 1 / 101 (0.99%) |  |
| occurrences causally related to treatment / all | 1 / 1          | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 1 / 1           |  |
| Subdural haemorrhage                            |                |                 |  |
| subjects affected / exposed                     | 0 / 98 (0.00%) | 1 / 101 (0.99%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Thoracic vertebral fracture                     |                |                 |  |
| subjects affected / exposed                     | 0 / 98 (0.00%) | 1 / 101 (0.99%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Traumatic intracranial haemorrhage              |                |                 |  |
| subjects affected / exposed                     | 0 / 98 (0.00%) | 1 / 101 (0.99%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Cardiac disorders                               |                |                 |  |
| Acute left ventricular failure                  |                |                 |  |
| subjects affected / exposed                     | 0 / 98 (0.00%) | 1 / 101 (0.99%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Acute myocardial infarction                     |                |                 |  |
| subjects affected / exposed                     | 3 / 98 (3.06%) | 2 / 101 (1.98%) |  |
| occurrences causally related to treatment / all | 1 / 3          | 1 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Aortic valve incompetence                       |                |                 |  |
| subjects affected / exposed                     | 0 / 98 (0.00%) | 1 / 101 (0.99%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Angina pectoris                                 |                |                 |  |
| subjects affected / exposed                     | 1 / 98 (1.02%) | 0 / 101 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1          | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Aortic valve stenosis                           |                |                 |  |

|                                                 |                |                 |  |
|-------------------------------------------------|----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 98 (0.00%) | 1 / 101 (0.99%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Atrial fibrillation                             |                |                 |  |
| subjects affected / exposed                     | 5 / 98 (5.10%) | 2 / 101 (1.98%) |  |
| occurrences causally related to treatment / all | 4 / 5          | 2 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Atrial flutter                                  |                |                 |  |
| subjects affected / exposed                     | 2 / 98 (2.04%) | 0 / 101 (0.00%) |  |
| occurrences causally related to treatment / all | 3 / 3          | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Atrioventricular block second degree            |                |                 |  |
| subjects affected / exposed                     | 0 / 98 (0.00%) | 1 / 101 (0.99%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Atrioventricular block complete                 |                |                 |  |
| subjects affected / exposed                     | 0 / 98 (0.00%) | 1 / 101 (0.99%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Cardiac failure acute                           |                |                 |  |
| subjects affected / exposed                     | 1 / 98 (1.02%) | 0 / 101 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1          | 0 / 0           |  |
| Cardiac failure                                 |                |                 |  |
| subjects affected / exposed                     | 0 / 98 (0.00%) | 1 / 101 (0.99%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Cardiac failure congestive                      |                |                 |  |
| subjects affected / exposed                     | 0 / 98 (0.00%) | 1 / 101 (0.99%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Cardiac tamponade                               |                |                 |  |

|                                                 |                |                 |  |
|-------------------------------------------------|----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 98 (0.00%) | 1 / 101 (0.99%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Cardiomegaly                                    |                |                 |  |
| subjects affected / exposed                     | 0 / 98 (0.00%) | 1 / 101 (0.99%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 1 / 1           |  |
| Coronary artery disease                         |                |                 |  |
| subjects affected / exposed                     | 1 / 98 (1.02%) | 0 / 101 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Mitral valve incompetence                       |                |                 |  |
| subjects affected / exposed                     | 0 / 98 (0.00%) | 1 / 101 (0.99%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Pericardial haemorrhage                         |                |                 |  |
| subjects affected / exposed                     | 1 / 98 (1.02%) | 0 / 101 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1          | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Pericarditis                                    |                |                 |  |
| subjects affected / exposed                     | 3 / 98 (3.06%) | 0 / 101 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 3          | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Sinus node dysfunction                          |                |                 |  |
| subjects affected / exposed                     | 0 / 98 (0.00%) | 1 / 101 (0.99%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Nervous system disorders                        |                |                 |  |
| Cerebrovascular accident                        |                |                 |  |
| subjects affected / exposed                     | 1 / 98 (1.02%) | 1 / 101 (0.99%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Headache                                        |                |                 |  |

|                                                 |                |                 |  |
|-------------------------------------------------|----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 98 (0.00%) | 1 / 101 (0.99%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Lethargy                                        |                |                 |  |
| subjects affected / exposed                     | 1 / 98 (1.02%) | 0 / 101 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Loss of consciousness                           |                |                 |  |
| subjects affected / exposed                     | 2 / 98 (2.04%) | 0 / 101 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2          | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Dizziness                                       |                |                 |  |
| subjects affected / exposed                     | 0 / 98 (0.00%) | 1 / 101 (0.99%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Syncope                                         |                |                 |  |
| subjects affected / exposed                     | 3 / 98 (3.06%) | 3 / 101 (2.97%) |  |
| occurrences causally related to treatment / all | 1 / 3          | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Subarachnoid haemorrhage                        |                |                 |  |
| subjects affected / exposed                     | 1 / 98 (1.02%) | 0 / 101 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Blood and lymphatic system disorders            |                |                 |  |
| Anaemia                                         |                |                 |  |
| subjects affected / exposed                     | 1 / 98 (1.02%) | 2 / 101 (1.98%) |  |
| occurrences causally related to treatment / all | 1 / 1          | 1 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Febrile neutropenia                             |                |                 |  |
| subjects affected / exposed                     | 0 / 98 (0.00%) | 3 / 101 (2.97%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 3 / 4           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Haemorrhagic disorder                           |                |                 |  |

|                                                 |                |                 |  |
|-------------------------------------------------|----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 98 (1.02%) | 0 / 101 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1          | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Haemolytic anaemia                              |                |                 |  |
| subjects affected / exposed                     | 1 / 98 (1.02%) | 0 / 101 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1          | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Thrombocytopenia                                |                |                 |  |
| subjects affected / exposed                     | 0 / 98 (0.00%) | 2 / 101 (1.98%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Neutropenia                                     |                |                 |  |
| subjects affected / exposed                     | 0 / 98 (0.00%) | 3 / 101 (2.97%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 3 / 4           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Hyperviscosity syndrome                         |                |                 |  |
| subjects affected / exposed                     | 1 / 98 (1.02%) | 0 / 101 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Eye disorders                                   |                |                 |  |
| Diplopia                                        |                |                 |  |
| subjects affected / exposed                     | 0 / 98 (0.00%) | 1 / 101 (0.99%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Eye haemorrhage                                 |                |                 |  |
| subjects affected / exposed                     | 0 / 98 (0.00%) | 1 / 101 (0.99%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Gastrointestinal disorders                      |                |                 |  |
| Anal inflammation                               |                |                 |  |
| subjects affected / exposed                     | 0 / 98 (0.00%) | 1 / 101 (0.99%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Gastric haemorrhage                             |                |                 |  |

|                                                 |                |                 |  |
|-------------------------------------------------|----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 98 (0.00%) | 1 / 101 (0.99%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Dysphagia                                       |                |                 |  |
| subjects affected / exposed                     | 0 / 98 (0.00%) | 1 / 101 (0.99%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Colitis                                         |                |                 |  |
| subjects affected / exposed                     | 1 / 98 (1.02%) | 0 / 101 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1          | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Melaena                                         |                |                 |  |
| subjects affected / exposed                     | 1 / 98 (1.02%) | 0 / 101 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1          | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Oral blood blister                              |                |                 |  |
| subjects affected / exposed                     | 1 / 98 (1.02%) | 0 / 101 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Pancreatic disorder                             |                |                 |  |
| subjects affected / exposed                     | 0 / 98 (0.00%) | 1 / 101 (0.99%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Vomiting                                        |                |                 |  |
| subjects affected / exposed                     | 0 / 98 (0.00%) | 1 / 101 (0.99%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Upper gastrointestinal haemorrhage              |                |                 |  |
| subjects affected / exposed                     | 1 / 98 (1.02%) | 0 / 101 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1          | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Hepatobiliary disorders                         |                |                 |  |
| Cholecystitis                                   |                |                 |  |

|                                                 |                |                 |  |
|-------------------------------------------------|----------------|-----------------|--|
| subjects affected / exposed                     | 2 / 98 (2.04%) | 0 / 101 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2          | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Drug-induced liver injury                       |                |                 |  |
| subjects affected / exposed                     | 1 / 98 (1.02%) | 1 / 101 (0.99%) |  |
| occurrences causally related to treatment / all | 1 / 1          | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Renal and urinary disorders                     |                |                 |  |
| Chronic kidney disease                          |                |                 |  |
| subjects affected / exposed                     | 1 / 98 (1.02%) | 1 / 101 (0.99%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Acute kidney injury                             |                |                 |  |
| subjects affected / exposed                     | 1 / 98 (1.02%) | 1 / 101 (0.99%) |  |
| occurrences causally related to treatment / all | 1 / 1          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Urinary bladder haemorrhage                     |                |                 |  |
| subjects affected / exposed                     | 1 / 98 (1.02%) | 0 / 101 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2          | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Haematuria                                      |                |                 |  |
| subjects affected / exposed                     | 2 / 98 (2.04%) | 1 / 101 (0.99%) |  |
| occurrences causally related to treatment / all | 2 / 2          | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Musculoskeletal and connective tissue disorders |                |                 |  |
| Neck pain                                       |                |                 |  |
| subjects affected / exposed                     | 0 / 98 (0.00%) | 1 / 101 (0.99%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Osteoarthritis                                  |                |                 |  |
| subjects affected / exposed                     | 0 / 98 (0.00%) | 1 / 101 (0.99%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |

|                                                 |                |                 |  |
|-------------------------------------------------|----------------|-----------------|--|
| Spinal stenosis                                 |                |                 |  |
| subjects affected / exposed                     | 1 / 98 (1.02%) | 0 / 101 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Infections and infestations                     |                |                 |  |
| Bacterial sepsis                                |                |                 |  |
| subjects affected / exposed                     | 1 / 98 (1.02%) | 0 / 101 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1          | 0 / 0           |  |
| Brain abscess                                   |                |                 |  |
| subjects affected / exposed                     | 1 / 98 (1.02%) | 0 / 101 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| COVID-19                                        |                |                 |  |
| subjects affected / exposed                     | 2 / 98 (2.04%) | 1 / 101 (0.99%) |  |
| occurrences causally related to treatment / all | 0 / 2          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Arthritis bacterial                             |                |                 |  |
| subjects affected / exposed                     | 0 / 98 (0.00%) | 1 / 101 (0.99%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Cryptococcal fungaemia                          |                |                 |  |
| subjects affected / exposed                     | 0 / 98 (0.00%) | 1 / 101 (0.99%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Device related infection                        |                |                 |  |
| subjects affected / exposed                     | 1 / 98 (1.02%) | 0 / 101 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| COVID-19 pneumonia                              |                |                 |  |
| subjects affected / exposed                     | 2 / 98 (2.04%) | 2 / 101 (1.98%) |  |
| occurrences causally related to treatment / all | 0 / 2          | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Cellulitis                                      |                |                 |  |

|                                                 |                |                 |  |
|-------------------------------------------------|----------------|-----------------|--|
| subjects affected / exposed                     | 2 / 98 (2.04%) | 0 / 101 (0.00%) |  |
| occurrences causally related to treatment / all | 2 / 4          | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Clostridium difficile infection                 |                |                 |  |
| subjects affected / exposed                     | 1 / 98 (1.02%) | 0 / 101 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Gastroenteritis rotavirus                       |                |                 |  |
| subjects affected / exposed                     | 0 / 98 (0.00%) | 1 / 101 (0.99%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Escherichia sepsis                              |                |                 |  |
| subjects affected / exposed                     | 0 / 98 (0.00%) | 1 / 101 (0.99%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Diverticulitis                                  |                |                 |  |
| subjects affected / exposed                     | 0 / 98 (0.00%) | 1 / 101 (0.99%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 6           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Endocarditis bacterial                          |                |                 |  |
| subjects affected / exposed                     | 0 / 98 (0.00%) | 1 / 101 (0.99%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Gastrointestinal infection                      |                |                 |  |
| subjects affected / exposed                     | 1 / 98 (1.02%) | 0 / 101 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Neurocryptococcosis                             |                |                 |  |
| subjects affected / exposed                     | 1 / 98 (1.02%) | 0 / 101 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1          | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Neutropenic sepsis                              |                |                 |  |

|                                                 |                  |                 |  |
|-------------------------------------------------|------------------|-----------------|--|
| subjects affected / exposed                     | 0 / 98 (0.00%)   | 1 / 101 (0.99%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Herpes zoster                                   |                  |                 |  |
| subjects affected / exposed                     | 1 / 98 (1.02%)   | 1 / 101 (0.99%) |  |
| occurrences causally related to treatment / all | 1 / 1            | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Influenza                                       |                  |                 |  |
| subjects affected / exposed                     | 1 / 98 (1.02%)   | 3 / 101 (2.97%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 2 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Lower respiratory tract infection               |                  |                 |  |
| subjects affected / exposed                     | 0 / 98 (0.00%)   | 2 / 101 (1.98%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 1 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Osteomyelitis                                   |                  |                 |  |
| subjects affected / exposed                     | 0 / 98 (0.00%)   | 1 / 101 (0.99%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Paronychia                                      |                  |                 |  |
| subjects affected / exposed                     | 1 / 98 (1.02%)   | 1 / 101 (0.99%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Pneumonia                                       |                  |                 |  |
| subjects affected / exposed                     | 14 / 98 (14.29%) | 2 / 101 (1.98%) |  |
| occurrences causally related to treatment / all | 6 / 15           | 0 / 4           |  |
| deaths causally related to treatment / all      | 1 / 2            | 0 / 0           |  |
| Pneumonia viral                                 |                  |                 |  |
| subjects affected / exposed                     | 1 / 98 (1.02%)   | 0 / 101 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Post procedural sepsis                          |                  |                 |  |

|                                                 |                |                 |  |
|-------------------------------------------------|----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 98 (1.02%) | 0 / 101 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Post-acute COVID-19 syndrome                    |                |                 |  |
| subjects affected / exposed                     | 0 / 98 (0.00%) | 1 / 101 (0.99%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Postoperative abscess                           |                |                 |  |
| subjects affected / exposed                     | 0 / 98 (0.00%) | 1 / 101 (0.99%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Pulmonary tuberculosis                          |                |                 |  |
| subjects affected / exposed                     | 0 / 98 (0.00%) | 1 / 101 (0.99%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Pyelonephritis                                  |                |                 |  |
| subjects affected / exposed                     | 1 / 98 (1.02%) | 0 / 101 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Septic shock                                    |                |                 |  |
| subjects affected / exposed                     | 1 / 98 (1.02%) | 0 / 101 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Sepsis                                          |                |                 |  |
| subjects affected / exposed                     | 4 / 98 (4.08%) | 3 / 101 (2.97%) |  |
| occurrences causally related to treatment / all | 1 / 4          | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 1          | 0 / 0           |  |
| Soft tissue infection                           |                |                 |  |
| subjects affected / exposed                     | 0 / 98 (0.00%) | 1 / 101 (0.99%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Streptococcal bacteraemia                       |                |                 |  |

|                                                 |                |                 |  |
|-------------------------------------------------|----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 98 (1.02%) | 0 / 101 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1          | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Streptococcal endocarditis                      |                |                 |  |
| subjects affected / exposed                     | 0 / 98 (0.00%) | 1 / 101 (0.99%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Streptococcal sepsis                            |                |                 |  |
| subjects affected / exposed                     | 1 / 98 (1.02%) | 1 / 101 (0.99%) |  |
| occurrences causally related to treatment / all | 1 / 1          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Upper respiratory tract infection               |                |                 |  |
| subjects affected / exposed                     | 2 / 98 (2.04%) | 0 / 101 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 2          | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Urinary tract infection                         |                |                 |  |
| subjects affected / exposed                     | 2 / 98 (2.04%) | 0 / 101 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2          | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Urinary tract infection bacterial               |                |                 |  |
| subjects affected / exposed                     | 0 / 98 (0.00%) | 1 / 101 (0.99%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Urosepsis                                       |                |                 |  |
| subjects affected / exposed                     | 1 / 98 (1.02%) | 0 / 101 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2          | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Wound infection staphylococcal                  |                |                 |  |
| subjects affected / exposed                     | 1 / 98 (1.02%) | 0 / 101 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1          | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Viral infection                                 |                |                 |  |

|                                                 |                |                 |  |
|-------------------------------------------------|----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 98 (1.02%) | 0 / 101 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| <b>Metabolism and nutrition disorders</b>       |                |                 |  |
| <b>Hypokalaemia</b>                             |                |                 |  |
| subjects affected / exposed                     | 0 / 98 (0.00%) | 1 / 101 (0.99%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| <b>Malnutrition</b>                             |                |                 |  |
| subjects affected / exposed                     | 0 / 98 (0.00%) | 1 / 101 (0.99%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| <b>Hyponatraemia</b>                            |                |                 |  |
| subjects affected / exposed                     | 0 / 98 (0.00%) | 1 / 101 (0.99%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |

Frequency threshold for reporting non-serious adverse events: 3 %

| <b>Non-serious adverse events</b>                                          | <b>Ibrutinib</b> | <b>Zanubrutinib</b> |  |
|----------------------------------------------------------------------------|------------------|---------------------|--|
| <b>Total subjects affected by non-serious adverse events</b>               |                  |                     |  |
| subjects affected / exposed                                                | 96 / 98 (97.96%) | 99 / 101 (98.02%)   |  |
| <b>Neoplasms benign, malignant and unspecified (incl cysts and polyps)</b> |                  |                     |  |
| <b>Basal cell carcinoma</b>                                                |                  |                     |  |
| subjects affected / exposed                                                | 5 / 98 (5.10%)   | 4 / 101 (3.96%)     |  |
| occurrences (all)                                                          | 5                | 4                   |  |
| <b>Seborrhoeic keratosis</b>                                               |                  |                     |  |
| subjects affected / exposed                                                | 3 / 98 (3.06%)   | 0 / 101 (0.00%)     |  |
| occurrences (all)                                                          | 3                | 0                   |  |
| <b>Squamous cell carcinoma of skin</b>                                     |                  |                     |  |
| subjects affected / exposed                                                | 5 / 98 (5.10%)   | 3 / 101 (2.97%)     |  |
| occurrences (all)                                                          | 6                | 3                   |  |
| <b>Bladder transitional cell carcinoma</b>                                 |                  |                     |  |

|                                                         |                     |                      |  |
|---------------------------------------------------------|---------------------|----------------------|--|
| subjects affected / exposed<br>occurrences (all)        | 3 / 98 (3.06%)<br>4 | 0 / 101 (0.00%)<br>0 |  |
| Vascular disorders                                      |                     |                      |  |
| Haematoma                                               |                     |                      |  |
| subjects affected / exposed                             | 9 / 98 (9.18%)      | 5 / 101 (4.95%)      |  |
| occurrences (all)                                       | 11                  | 7                    |  |
| Hypertension                                            |                     |                      |  |
| subjects affected / exposed                             | 24 / 98 (24.49%)    | 16 / 101 (15.84%)    |  |
| occurrences (all)                                       | 46                  | 20                   |  |
| Hypotension                                             |                     |                      |  |
| subjects affected / exposed                             | 2 / 98 (2.04%)      | 4 / 101 (3.96%)      |  |
| occurrences (all)                                       | 3                   | 4                    |  |
| General disorders and administration<br>site conditions |                     |                      |  |
| Fatigue                                                 |                     |                      |  |
| subjects affected / exposed                             | 19 / 98 (19.39%)    | 26 / 101 (25.74%)    |  |
| occurrences (all)                                       | 25                  | 49                   |  |
| Drug withdrawal syndrome                                |                     |                      |  |
| subjects affected / exposed                             | 2 / 98 (2.04%)      | 4 / 101 (3.96%)      |  |
| occurrences (all)                                       | 3                   | 4                    |  |
| Chills                                                  |                     |                      |  |
| subjects affected / exposed                             | 4 / 98 (4.08%)      | 3 / 101 (2.97%)      |  |
| occurrences (all)                                       | 5                   | 3                    |  |
| Chest pain                                              |                     |                      |  |
| subjects affected / exposed                             | 5 / 98 (5.10%)      | 4 / 101 (3.96%)      |  |
| occurrences (all)                                       | 5                   | 4                    |  |
| Asthenia                                                |                     |                      |  |
| subjects affected / exposed                             | 6 / 98 (6.12%)      | 9 / 101 (8.91%)      |  |
| occurrences (all)                                       | 9                   | 14                   |  |
| Pyrexia                                                 |                     |                      |  |
| subjects affected / exposed                             | 12 / 98 (12.24%)    | 16 / 101 (15.84%)    |  |
| occurrences (all)                                       | 21                  | 30                   |  |
| Peripheral swelling                                     |                     |                      |  |
| subjects affected / exposed                             | 12 / 98 (12.24%)    | 5 / 101 (4.95%)      |  |
| occurrences (all)                                       | 12                  | 6                    |  |
| Oedema peripheral                                       |                     |                      |  |

|                                                                                                                              |                        |                         |  |
|------------------------------------------------------------------------------------------------------------------------------|------------------------|-------------------------|--|
| subjects affected / exposed<br>occurrences (all)                                                                             | 22 / 98 (22.45%)<br>38 | 19 / 101 (18.81%)<br>29 |  |
| Malaise<br>subjects affected / exposed<br>occurrences (all)                                                                  | 3 / 98 (3.06%)<br>3    | 1 / 101 (0.99%)<br>1    |  |
| Influenza like illness<br>subjects affected / exposed<br>occurrences (all)                                                   | 5 / 98 (5.10%)<br>7    | 6 / 101 (5.94%)<br>9    |  |
| Gait disturbance<br>subjects affected / exposed<br>occurrences (all)                                                         | 0 / 98 (0.00%)<br>0    | 4 / 101 (3.96%)<br>4    |  |
| Immune system disorders<br>Seasonal allergy<br>subjects affected / exposed<br>occurrences (all)                              | 2 / 98 (2.04%)<br>2    | 4 / 101 (3.96%)<br>4    |  |
| Reproductive system and breast disorders<br>Benign prostatic hyperplasia<br>subjects affected / exposed<br>occurrences (all) | 3 / 98 (3.06%)<br>3    | 1 / 101 (0.99%)<br>1    |  |
| Respiratory, thoracic and mediastinal disorders<br>Cough<br>subjects affected / exposed<br>occurrences (all)                 | 20 / 98 (20.41%)<br>29 | 20 / 101 (19.80%)<br>36 |  |
| Epistaxis<br>subjects affected / exposed<br>occurrences (all)                                                                | 21 / 98 (21.43%)<br>35 | 18 / 101 (17.82%)<br>21 |  |
| Dyspnoea<br>subjects affected / exposed<br>occurrences (all)                                                                 | 9 / 98 (9.18%)<br>11   | 17 / 101 (16.83%)<br>22 |  |
| Oropharyngeal pain<br>subjects affected / exposed<br>occurrences (all)                                                       | 10 / 98 (10.20%)<br>11 | 4 / 101 (3.96%)<br>5    |  |
| Nasal congestion<br>subjects affected / exposed<br>occurrences (all)                                                         | 3 / 98 (3.06%)<br>6    | 2 / 101 (1.98%)<br>2    |  |
| Dyspnoea exertional                                                                                                          |                        |                         |  |

|                                                                                                          |                      |                       |  |
|----------------------------------------------------------------------------------------------------------|----------------------|-----------------------|--|
| subjects affected / exposed<br>occurrences (all)                                                         | 3 / 98 (3.06%)<br>3  | 2 / 101 (1.98%)<br>2  |  |
| Wheezing<br>subjects affected / exposed<br>occurrences (all)                                             | 1 / 98 (1.02%)<br>1  | 4 / 101 (3.96%)<br>4  |  |
| Productive cough<br>subjects affected / exposed<br>occurrences (all)                                     | 4 / 98 (4.08%)<br>4  | 6 / 101 (5.94%)<br>7  |  |
| Pneumonitis<br>subjects affected / exposed<br>occurrences (all)                                          | 3 / 98 (3.06%)<br>3  | 1 / 101 (0.99%)<br>1  |  |
| Rhinorrhoea<br>subjects affected / exposed<br>occurrences (all)                                          | 5 / 98 (5.10%)<br>5  | 2 / 101 (1.98%)<br>2  |  |
| Psychiatric disorders<br>Depression<br>subjects affected / exposed<br>occurrences (all)                  | 4 / 98 (4.08%)<br>4  | 3 / 101 (2.97%)<br>4  |  |
| Insomnia<br>subjects affected / exposed<br>occurrences (all)                                             | 9 / 98 (9.18%)<br>10 | 3 / 101 (2.97%)<br>4  |  |
| Anxiety<br>subjects affected / exposed<br>occurrences (all)                                              | 7 / 98 (7.14%)<br>7  | 5 / 101 (4.95%)<br>5  |  |
| Investigations<br>Alanine aminotransferase increased<br>subjects affected / exposed<br>occurrences (all) | 3 / 98 (3.06%)<br>5  | 2 / 101 (1.98%)<br>2  |  |
| Blood alkaline phosphatase increased<br>subjects affected / exposed<br>occurrences (all)                 | 4 / 98 (4.08%)<br>4  | 0 / 101 (0.00%)<br>0  |  |
| Neutrophil count decreased<br>subjects affected / exposed<br>occurrences (all)                           | 4 / 98 (4.08%)<br>9  | 8 / 101 (7.92%)<br>33 |  |
| Gamma-glutamyltransferase increased                                                                      |                      |                       |  |

|                                                  |                     |                      |  |
|--------------------------------------------------|---------------------|----------------------|--|
| subjects affected / exposed<br>occurrences (all) | 3 / 98 (3.06%)<br>6 | 2 / 101 (1.98%)<br>2 |  |
| Injury, poisoning and procedural complications   |                     |                      |  |
| Contusion                                        |                     |                      |  |
| subjects affected / exposed                      | 27 / 98 (27.55%)    | 19 / 101 (18.81%)    |  |
| occurrences (all)                                | 59                  | 38                   |  |
| Fall                                             |                     |                      |  |
| subjects affected / exposed                      | 10 / 98 (10.20%)    | 9 / 101 (8.91%)      |  |
| occurrences (all)                                | 12                  | 17                   |  |
| Joint injury                                     |                     |                      |  |
| subjects affected / exposed                      | 4 / 98 (4.08%)      | 1 / 101 (0.99%)      |  |
| occurrences (all)                                | 5                   | 1                    |  |
| Limb injury                                      |                     |                      |  |
| subjects affected / exposed                      | 5 / 98 (5.10%)      | 5 / 101 (4.95%)      |  |
| occurrences (all)                                | 7                   | 5                    |  |
| Procedural pain                                  |                     |                      |  |
| subjects affected / exposed                      | 0 / 98 (0.00%)      | 4 / 101 (3.96%)      |  |
| occurrences (all)                                | 0                   | 5                    |  |
| Skin laceration                                  |                     |                      |  |
| subjects affected / exposed                      | 8 / 98 (8.16%)      | 5 / 101 (4.95%)      |  |
| occurrences (all)                                | 13                  | 5                    |  |
| Cardiac disorders                                |                     |                      |  |
| Atrial fibrillation                              |                     |                      |  |
| subjects affected / exposed                      | 18 / 98 (18.37%)    | 7 / 101 (6.93%)      |  |
| occurrences (all)                                | 24                  | 8                    |  |
| Angina pectoris                                  |                     |                      |  |
| subjects affected / exposed                      | 4 / 98 (4.08%)      | 4 / 101 (3.96%)      |  |
| occurrences (all)                                | 4                   | 4                    |  |
| Sinus bradycardia                                |                     |                      |  |
| subjects affected / exposed                      | 3 / 98 (3.06%)      | 6 / 101 (5.94%)      |  |
| occurrences (all)                                | 3                   | 6                    |  |
| Bradycardia                                      |                     |                      |  |
| subjects affected / exposed                      | 3 / 98 (3.06%)      | 1 / 101 (0.99%)      |  |
| occurrences (all)                                | 4                   | 1                    |  |
| Atrial flutter                                   |                     |                      |  |

|                                      |                  |                   |  |
|--------------------------------------|------------------|-------------------|--|
| subjects affected / exposed          | 4 / 98 (4.08%)   | 1 / 101 (0.99%)   |  |
| occurrences (all)                    | 4                | 1                 |  |
| Palpitations                         |                  |                   |  |
| subjects affected / exposed          | 10 / 98 (10.20%) | 6 / 101 (5.94%)   |  |
| occurrences (all)                    | 15               | 8                 |  |
| Nervous system disorders             |                  |                   |  |
| Dizziness                            |                  |                   |  |
| subjects affected / exposed          | 14 / 98 (14.29%) | 15 / 101 (14.85%) |  |
| occurrences (all)                    | 16               | 29                |  |
| Headache                             |                  |                   |  |
| subjects affected / exposed          | 15 / 98 (15.31%) | 17 / 101 (16.83%) |  |
| occurrences (all)                    | 20               | 20                |  |
| Neuralgia                            |                  |                   |  |
| subjects affected / exposed          | 3 / 98 (3.06%)   | 0 / 101 (0.00%)   |  |
| occurrences (all)                    | 3                | 0                 |  |
| Paraesthesia                         |                  |                   |  |
| subjects affected / exposed          | 8 / 98 (8.16%)   | 4 / 101 (3.96%)   |  |
| occurrences (all)                    | 10               | 6                 |  |
| Syncope                              |                  |                   |  |
| subjects affected / exposed          | 6 / 98 (6.12%)   | 3 / 101 (2.97%)   |  |
| occurrences (all)                    | 7                | 5                 |  |
| Sciatica                             |                  |                   |  |
| subjects affected / exposed          | 3 / 98 (3.06%)   | 1 / 101 (0.99%)   |  |
| occurrences (all)                    | 4                | 1                 |  |
| Peripheral sensory neuropathy        |                  |                   |  |
| subjects affected / exposed          | 5 / 98 (5.10%)   | 8 / 101 (7.92%)   |  |
| occurrences (all)                    | 6                | 10                |  |
| Blood and lymphatic system disorders |                  |                   |  |
| Anaemia                              |                  |                   |  |
| subjects affected / exposed          | 22 / 98 (22.45%) | 18 / 101 (17.82%) |  |
| occurrences (all)                    | 48               | 57                |  |
| Thrombocytopenia                     |                  |                   |  |
| subjects affected / exposed          | 16 / 98 (16.33%) | 15 / 101 (14.85%) |  |
| occurrences (all)                    | 47               | 61                |  |
| Neutropenia                          |                  |                   |  |

|                                                                                  |                        |                         |  |
|----------------------------------------------------------------------------------|------------------------|-------------------------|--|
| subjects affected / exposed<br>occurrences (all)                                 | 16 / 98 (16.33%)<br>51 | 29 / 101 (28.71%)<br>87 |  |
| Lymphadenopathy<br>subjects affected / exposed<br>occurrences (all)              | 1 / 98 (1.02%)<br>1    | 4 / 101 (3.96%)<br>4    |  |
| Increased tendency to bruise<br>subjects affected / exposed<br>occurrences (all) | 5 / 98 (5.10%)<br>6    | 3 / 101 (2.97%)<br>3    |  |
| Ear and labyrinth disorders                                                      |                        |                         |  |
| Vertigo<br>subjects affected / exposed<br>occurrences (all)                      | 4 / 98 (4.08%)<br>4    | 3 / 101 (2.97%)<br>3    |  |
| Tinnitus<br>subjects affected / exposed<br>occurrences (all)                     | 3 / 98 (3.06%)<br>4    | 6 / 101 (5.94%)<br>6    |  |
| Eye disorders                                                                    |                        |                         |  |
| Vision blurred<br>subjects affected / exposed<br>occurrences (all)               | 6 / 98 (6.12%)<br>7    | 3 / 101 (2.97%)<br>3    |  |
| Retinal haemorrhage<br>subjects affected / exposed<br>occurrences (all)          | 4 / 98 (4.08%)<br>8    | 0 / 101 (0.00%)<br>0    |  |
| Ocular hyperaemia<br>subjects affected / exposed<br>occurrences (all)            | 3 / 98 (3.06%)<br>3    | 1 / 101 (0.99%)<br>1    |  |
| Dry eye<br>subjects affected / exposed<br>occurrences (all)                      | 3 / 98 (3.06%)<br>3    | 2 / 101 (1.98%)<br>2    |  |
| Cataract<br>subjects affected / exposed<br>occurrences (all)                     | 6 / 98 (6.12%)<br>7    | 3 / 101 (2.97%)<br>4    |  |
| Conjunctival haemorrhage<br>subjects affected / exposed<br>occurrences (all)     | 6 / 98 (6.12%)<br>10   | 5 / 101 (4.95%)<br>9    |  |
| Gastrointestinal disorders                                                       |                        |                         |  |

|                                  |                  |                   |
|----------------------------------|------------------|-------------------|
| Abdominal discomfort             |                  |                   |
| subjects affected / exposed      | 5 / 98 (5.10%)   | 1 / 101 (0.99%)   |
| occurrences (all)                | 5                | 1                 |
| Abdominal distension             |                  |                   |
| subjects affected / exposed      | 3 / 98 (3.06%)   | 2 / 101 (1.98%)   |
| occurrences (all)                | 3                | 2                 |
| Abdominal pain                   |                  |                   |
| subjects affected / exposed      | 6 / 98 (6.12%)   | 4 / 101 (3.96%)   |
| occurrences (all)                | 9                | 5                 |
| Abdominal pain upper             |                  |                   |
| subjects affected / exposed      | 6 / 98 (6.12%)   | 4 / 101 (3.96%)   |
| occurrences (all)                | 7                | 4                 |
| Constipation                     |                  |                   |
| subjects affected / exposed      | 12 / 98 (12.24%) | 20 / 101 (19.80%) |
| occurrences (all)                | 18               | 25                |
| Diarrhoea                        |                  |                   |
| subjects affected / exposed      | 36 / 98 (36.73%) | 23 / 101 (22.77%) |
| occurrences (all)                | 62               | 38                |
| Gingival bleeding                |                  |                   |
| subjects affected / exposed      | 5 / 98 (5.10%)   | 2 / 101 (1.98%)   |
| occurrences (all)                | 6                | 2                 |
| Gastrooesophageal reflux disease |                  |                   |
| subjects affected / exposed      | 5 / 98 (5.10%)   | 4 / 101 (3.96%)   |
| occurrences (all)                | 5                | 4                 |
| Dysphagia                        |                  |                   |
| subjects affected / exposed      | 3 / 98 (3.06%)   | 3 / 101 (2.97%)   |
| occurrences (all)                | 4                | 4                 |
| Dyspepsia                        |                  |                   |
| subjects affected / exposed      | 7 / 98 (7.14%)   | 6 / 101 (5.94%)   |
| occurrences (all)                | 7                | 7                 |
| Dry mouth                        |                  |                   |
| subjects affected / exposed      | 4 / 98 (4.08%)   | 5 / 101 (4.95%)   |
| occurrences (all)                | 4                | 5                 |
| Haemorrhoids                     |                  |                   |
| subjects affected / exposed      | 4 / 98 (4.08%)   | 2 / 101 (1.98%)   |
| occurrences (all)                | 5                | 2                 |

|                                                                        |                        |                         |  |
|------------------------------------------------------------------------|------------------------|-------------------------|--|
| Inguinal hernia<br>subjects affected / exposed<br>occurrences (all)    | 3 / 98 (3.06%)<br>3    | 1 / 101 (0.99%)<br>1    |  |
| Mouth ulceration<br>subjects affected / exposed<br>occurrences (all)   | 5 / 98 (5.10%)<br>9    | 2 / 101 (1.98%)<br>2    |  |
| Nausea<br>subjects affected / exposed<br>occurrences (all)             | 15 / 98 (15.31%)<br>22 | 19 / 101 (18.81%)<br>25 |  |
| Rectal haemorrhage<br>subjects affected / exposed<br>occurrences (all) | 2 / 98 (2.04%)<br>3    | 5 / 101 (4.95%)<br>5    |  |
| Stomatitis<br>subjects affected / exposed<br>occurrences (all)         | 5 / 98 (5.10%)<br>7    | 4 / 101 (3.96%)<br>4    |  |
| Vomiting<br>subjects affected / exposed<br>occurrences (all)           | 15 / 98 (15.31%)<br>20 | 14 / 101 (13.86%)<br>27 |  |
| Skin and subcutaneous tissue disorders                                 |                        |                         |  |
| Dry skin<br>subjects affected / exposed<br>occurrences (all)           | 7 / 98 (7.14%)<br>12   | 2 / 101 (1.98%)<br>5    |  |
| Dermatitis<br>subjects affected / exposed<br>occurrences (all)         | 5 / 98 (5.10%)<br>6    | 1 / 101 (0.99%)<br>1    |  |
| Actinic keratosis<br>subjects affected / exposed<br>occurrences (all)  | 5 / 98 (5.10%)<br>6    | 3 / 101 (2.97%)<br>3    |  |
| Onychoclasia<br>subjects affected / exposed<br>occurrences (all)       | 10 / 98 (10.20%)<br>10 | 1 / 101 (0.99%)<br>1    |  |
| Petechiae<br>subjects affected / exposed<br>occurrences (all)          | 5 / 98 (5.10%)<br>6    | 7 / 101 (6.93%)<br>8    |  |
| Nail disorder                                                          |                        |                         |  |

|                             |                  |                   |
|-----------------------------|------------------|-------------------|
| subjects affected / exposed | 3 / 98 (3.06%)   | 1 / 101 (0.99%)   |
| occurrences (all)           | 3                | 1                 |
| Erythema                    |                  |                   |
| subjects affected / exposed | 3 / 98 (3.06%)   | 5 / 101 (4.95%)   |
| occurrences (all)           | 3                | 5                 |
| Ecchymosis                  |                  |                   |
| subjects affected / exposed | 4 / 98 (4.08%)   | 1 / 101 (0.99%)   |
| occurrences (all)           | 6                | 1                 |
| Rash                        |                  |                   |
| subjects affected / exposed | 19 / 98 (19.39%) | 19 / 101 (18.81%) |
| occurrences (all)           | 25               | 25                |
| Rash maculo-papular         |                  |                   |
| subjects affected / exposed | 2 / 98 (2.04%)   | 4 / 101 (3.96%)   |
| occurrences (all)           | 2                | 6                 |
| Pruritus                    |                  |                   |
| subjects affected / exposed | 6 / 98 (6.12%)   | 15 / 101 (14.85%) |
| occurrences (all)           | 10               | 20                |
| Rash erythematous           |                  |                   |
| subjects affected / exposed | 1 / 98 (1.02%)   | 5 / 101 (4.95%)   |
| occurrences (all)           | 1                | 6                 |
| Purpura                     |                  |                   |
| subjects affected / exposed | 6 / 98 (6.12%)   | 4 / 101 (3.96%)   |
| occurrences (all)           | 9                | 4                 |
| Psoriasis                   |                  |                   |
| subjects affected / exposed | 3 / 98 (3.06%)   | 0 / 101 (0.00%)   |
| occurrences (all)           | 3                | 0                 |
| Skin toxicity               |                  |                   |
| subjects affected / exposed | 3 / 98 (3.06%)   | 1 / 101 (0.99%)   |
| occurrences (all)           | 3                | 1                 |
| Skin lesion                 |                  |                   |
| subjects affected / exposed | 3 / 98 (3.06%)   | 6 / 101 (5.94%)   |
| occurrences (all)           | 3                | 9                 |
| Skin fissures               |                  |                   |
| subjects affected / exposed | 3 / 98 (3.06%)   | 1 / 101 (0.99%)   |
| occurrences (all)           | 4                | 2                 |
| Rosacea                     |                  |                   |

|                                                                                |                        |                         |  |
|--------------------------------------------------------------------------------|------------------------|-------------------------|--|
| subjects affected / exposed<br>occurrences (all)                               | 5 / 98 (5.10%)<br>5    | 2 / 101 (1.98%)<br>2    |  |
| Skin ulcer<br>subjects affected / exposed<br>occurrences (all)                 | 4 / 98 (4.08%)<br>4    | 3 / 101 (2.97%)<br>3    |  |
| Renal and urinary disorders                                                    |                        |                         |  |
| Acute kidney injury<br>subjects affected / exposed<br>occurrences (all)        | 3 / 98 (3.06%)<br>4    | 1 / 101 (0.99%)<br>1    |  |
| Urinary retention<br>subjects affected / exposed<br>occurrences (all)          | 0 / 98 (0.00%)<br>0    | 4 / 101 (3.96%)<br>6    |  |
| Haematuria<br>subjects affected / exposed<br>occurrences (all)                 | 13 / 98 (13.27%)<br>17 | 11 / 101 (10.89%)<br>13 |  |
| Dysuria<br>subjects affected / exposed<br>occurrences (all)                    | 3 / 98 (3.06%)<br>3    | 0 / 101 (0.00%)<br>0    |  |
| Pollakiuria<br>subjects affected / exposed<br>occurrences (all)                | 3 / 98 (3.06%)<br>3    | 1 / 101 (0.99%)<br>1    |  |
| Musculoskeletal and connective tissue disorders                                |                        |                         |  |
| Muscular weakness<br>subjects affected / exposed<br>occurrences (all)          | 1 / 98 (1.02%)<br>1    | 4 / 101 (3.96%)<br>4    |  |
| Musculoskeletal chest pain<br>subjects affected / exposed<br>occurrences (all) | 3 / 98 (3.06%)<br>4    | 3 / 101 (2.97%)<br>4    |  |
| Arthralgia<br>subjects affected / exposed<br>occurrences (all)                 | 24 / 98 (24.49%)<br>50 | 24 / 101 (23.76%)<br>42 |  |
| Back pain<br>subjects affected / exposed<br>occurrences (all)                  | 18 / 98 (18.37%)<br>23 | 18 / 101 (17.82%)<br>31 |  |
| Joint swelling                                                                 |                        |                         |  |

|                             |                  |                   |  |
|-----------------------------|------------------|-------------------|--|
| subjects affected / exposed | 4 / 98 (4.08%)   | 4 / 101 (3.96%)   |  |
| occurrences (all)           | 5                | 5                 |  |
| Muscle spasms               |                  |                   |  |
| subjects affected / exposed | 28 / 98 (28.57%) | 12 / 101 (11.88%) |  |
| occurrences (all)           | 43               | 15                |  |
| Myalgia                     |                  |                   |  |
| subjects affected / exposed | 3 / 98 (3.06%)   | 7 / 101 (6.93%)   |  |
| occurrences (all)           | 4                | 9                 |  |
| Neck pain                   |                  |                   |  |
| subjects affected / exposed | 6 / 98 (6.12%)   | 3 / 101 (2.97%)   |  |
| occurrences (all)           | 6                | 3                 |  |
| Osteoarthritis              |                  |                   |  |
| subjects affected / exposed | 3 / 98 (3.06%)   | 2 / 101 (1.98%)   |  |
| occurrences (all)           | 3                | 2                 |  |
| Rotator cuff syndrome       |                  |                   |  |
| subjects affected / exposed | 3 / 98 (3.06%)   | 3 / 101 (2.97%)   |  |
| occurrences (all)           | 3                | 3                 |  |
| Pain in extremity           |                  |                   |  |
| subjects affected / exposed | 10 / 98 (10.20%) | 15 / 101 (14.85%) |  |
| occurrences (all)           | 12               | 21                |  |
| Osteoporosis                |                  |                   |  |
| subjects affected / exposed | 3 / 98 (3.06%)   | 1 / 101 (0.99%)   |  |
| occurrences (all)           | 3                | 1                 |  |
| Infections and infestations |                  |                   |  |
| Cellulitis                  |                  |                   |  |
| subjects affected / exposed | 7 / 98 (7.14%)   | 6 / 101 (5.94%)   |  |
| occurrences (all)           | 18               | 10                |  |
| COVID-19                    |                  |                   |  |
| subjects affected / exposed | 5 / 98 (5.10%)   | 9 / 101 (8.91%)   |  |
| occurrences (all)           | 5                | 10                |  |
| Bronchitis                  |                  |                   |  |
| subjects affected / exposed | 4 / 98 (4.08%)   | 4 / 101 (3.96%)   |  |
| occurrences (all)           | 4                | 4                 |  |
| Ear infection               |                  |                   |  |
| subjects affected / exposed | 3 / 98 (3.06%)   | 2 / 101 (1.98%)   |  |
| occurrences (all)           | 3                | 2                 |  |

|                                   |                  |                   |
|-----------------------------------|------------------|-------------------|
| Cystitis                          |                  |                   |
| subjects affected / exposed       | 3 / 98 (3.06%)   | 0 / 101 (0.00%)   |
| occurrences (all)                 | 3                | 0                 |
| Folliculitis                      |                  |                   |
| subjects affected / exposed       | 5 / 98 (5.10%)   | 2 / 101 (1.98%)   |
| occurrences (all)                 | 6                | 2                 |
| Conjunctivitis                    |                  |                   |
| subjects affected / exposed       | 7 / 98 (7.14%)   | 2 / 101 (1.98%)   |
| occurrences (all)                 | 7                | 3                 |
| Furuncle                          |                  |                   |
| subjects affected / exposed       | 4 / 98 (4.08%)   | 0 / 101 (0.00%)   |
| occurrences (all)                 | 7                | 0                 |
| Localised infection               |                  |                   |
| subjects affected / exposed       | 11 / 98 (11.22%) | 2 / 101 (1.98%)   |
| occurrences (all)                 | 15               | 2                 |
| Laryngitis                        |                  |                   |
| subjects affected / exposed       | 3 / 98 (3.06%)   | 0 / 101 (0.00%)   |
| occurrences (all)                 | 3                | 0                 |
| Gastroenteritis                   |                  |                   |
| subjects affected / exposed       | 5 / 98 (5.10%)   | 6 / 101 (5.94%)   |
| occurrences (all)                 | 6                | 7                 |
| Herpes zoster                     |                  |                   |
| subjects affected / exposed       | 4 / 98 (4.08%)   | 5 / 101 (4.95%)   |
| occurrences (all)                 | 4                | 5                 |
| Lower respiratory tract infection |                  |                   |
| subjects affected / exposed       | 10 / 98 (10.20%) | 8 / 101 (7.92%)   |
| occurrences (all)                 | 15               | 13                |
| Nail infection                    |                  |                   |
| subjects affected / exposed       | 6 / 98 (6.12%)   | 0 / 101 (0.00%)   |
| occurrences (all)                 | 11               | 0                 |
| Nasopharyngitis                   |                  |                   |
| subjects affected / exposed       | 9 / 98 (9.18%)   | 14 / 101 (13.86%) |
| occurrences (all)                 | 10               | 21                |
| Onychomycosis                     |                  |                   |
| subjects affected / exposed       | 5 / 98 (5.10%)   | 1 / 101 (0.99%)   |
| occurrences (all)                 | 5                | 1                 |

|                                    |                  |                   |  |
|------------------------------------|------------------|-------------------|--|
| Oral herpes                        |                  |                   |  |
| subjects affected / exposed        | 5 / 98 (5.10%)   | 1 / 101 (0.99%)   |  |
| occurrences (all)                  | 7                | 1                 |  |
| Paronychia                         |                  |                   |  |
| subjects affected / exposed        | 3 / 98 (3.06%)   | 2 / 101 (1.98%)   |  |
| occurrences (all)                  | 4                | 2                 |  |
| Pneumonia                          |                  |                   |  |
| subjects affected / exposed        | 9 / 98 (9.18%)   | 3 / 101 (2.97%)   |  |
| occurrences (all)                  | 9                | 3                 |  |
| Respiratory tract infection        |                  |                   |  |
| subjects affected / exposed        | 3 / 98 (3.06%)   | 8 / 101 (7.92%)   |  |
| occurrences (all)                  | 4                | 10                |  |
| Rhinitis                           |                  |                   |  |
| subjects affected / exposed        | 7 / 98 (7.14%)   | 7 / 101 (6.93%)   |  |
| occurrences (all)                  | 8                | 12                |  |
| Sinusitis                          |                  |                   |  |
| subjects affected / exposed        | 10 / 98 (10.20%) | 6 / 101 (5.94%)   |  |
| occurrences (all)                  | 11               | 9                 |  |
| Skin infection                     |                  |                   |  |
| subjects affected / exposed        | 7 / 98 (7.14%)   | 3 / 101 (2.97%)   |  |
| occurrences (all)                  | 16               | 4                 |  |
| Tooth infection                    |                  |                   |  |
| subjects affected / exposed        | 5 / 98 (5.10%)   | 3 / 101 (2.97%)   |  |
| occurrences (all)                  | 9                | 3                 |  |
| Upper respiratory tract infection  |                  |                   |  |
| subjects affected / exposed        | 31 / 98 (31.63%) | 33 / 101 (32.67%) |  |
| occurrences (all)                  | 55               | 49                |  |
| Urinary tract infection            |                  |                   |  |
| subjects affected / exposed        | 17 / 98 (17.35%) | 16 / 101 (15.84%) |  |
| occurrences (all)                  | 38               | 25                |  |
| Wound infection                    |                  |                   |  |
| subjects affected / exposed        | 3 / 98 (3.06%)   | 0 / 101 (0.00%)   |  |
| occurrences (all)                  | 3                | 0                 |  |
| Metabolism and nutrition disorders |                  |                   |  |
| Decreased appetite                 |                  |                   |  |

|                             |                |                 |
|-----------------------------|----------------|-----------------|
| subjects affected / exposed | 4 / 98 (4.08%) | 4 / 101 (3.96%) |
| occurrences (all)           | 6              | 4               |
| Gout                        |                |                 |
| subjects affected / exposed | 5 / 98 (5.10%) | 3 / 101 (2.97%) |
| occurrences (all)           | 6              | 3               |
| Hyperglycaemia              |                |                 |
| subjects affected / exposed | 4 / 98 (4.08%) | 3 / 101 (2.97%) |
| occurrences (all)           | 10             | 4               |
| Vitamin D deficiency        |                |                 |
| subjects affected / exposed | 2 / 98 (2.04%) | 5 / 101 (4.95%) |
| occurrences (all)           | 2              | 5               |
| Iron deficiency             |                |                 |
| subjects affected / exposed | 7 / 98 (7.14%) | 7 / 101 (6.93%) |
| occurrences (all)           | 7              | 8               |
| Hyponatraemia               |                |                 |
| subjects affected / exposed | 1 / 98 (1.02%) | 4 / 101 (3.96%) |
| occurrences (all)           | 1              | 4               |
| Hypokalaemia                |                |                 |
| subjects affected / exposed | 6 / 98 (6.12%) | 3 / 101 (2.97%) |
| occurrences (all)           | 6              | 14              |
| Hypoalbuminaemia            |                |                 |
| subjects affected / exposed | 3 / 98 (3.06%) | 1 / 101 (0.99%) |
| occurrences (all)           | 5              | 1               |
| Hyperuricaemia              |                |                 |
| subjects affected / exposed | 9 / 98 (9.18%) | 4 / 101 (3.96%) |
| occurrences (all)           | 14             | 7               |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date             | Amendment                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
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| 01 November 2016 | <ul style="list-style-type: none"><li>• Updated background with new zanubrutinib trial results and data on role of MYD88 mutation in responsiveness of WM to BTK inhibitors</li><li>• Changed the primary objective to the proportion of patients who achieved CR/VGPR, based on the clarification of the primary study hypothesis that stemmed from the updated zanubrutinib data</li><li>• Added major response rate and VGPR/CR (by investigator assessment) as secondary endpoints</li><li>• Added antitumor activity and safety of zanubrutinib in MYD88WT WM patients as an exploratory endpoint</li><li>• Added quality of life and medical resource utilization as exploratory endpoints</li><li>• Identified patients with MYD88MUT WM as the primary population for randomization and study analyses (Cohort 1)</li><li>• Revised sample size consideration</li><li>• Added language describing sequential analysis approach to the primary and secondary endpoints</li><li>• Identified treatment cohorts based on MYD88 mutational status: Cohort 1 (MYD88MUT) and newly added Cohort 2 (MYD88WT)</li><li>• Added the inclusion criterion to clarify that treatment-naïve patients were considered inappropriate candidates for intensive therapy</li><li>• Added the inclusion criterion to require measurable disease, in accordance with the response rate primary objective</li><li>• Added clarification for efficacy assessments in the occasion of study drug holding and plasmapheresis</li></ul> |
| 08 May 2017      | <ul style="list-style-type: none"><li>• study rationale, benefit/risk assessment, and dose justification</li><li>• Updated the timing of response assessments to every 4 weeks (each cycle)</li><li>Increased the screening phase to up to 35 days before randomization</li><li>• Added EQ-5D to quality-of-life assessments</li><li>• Updated the timing of bone marrow assessment for the presence of WM</li><li>• Clarified the study population by providing definitions for relapsed/refractory</li><li>• Clarified that up to 20% of patients may have been treatment naïve</li><li>• Updated the eligibility criteria to clarify that patients may have had relapsed/refractory or treatment-naïve WM considered by their treating physician to be inappropriate for standard chemoimmunotherapy regimens</li><li>• Clarified blinding of the Independent Review Committee and DMC</li><li>• Clarified dose modification to allow for study drug to be held for up to 2 consecutive cycles and that more than 1 drug hold was allowed over the course of the study</li><li>• Removed the ECHO/MUGA from screening and exclusion criteria</li><li>• Added the requirement for confirmation of disease transformation by biopsy</li><li>• Added adverse events of special interest</li><li>• Updated pregnancy and contraception language</li></ul>                                                                                                                                                              |

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| 02 February 2018 | <ul style="list-style-type: none"> <li>• Updated the total number of patients to approximately 210. Cohort 1 included approximately 150 patients with relapsed/refractory disease and 38 treatment-naïve MYD88MUT patients. Cohort 2 included approximately 22 MYD88WT patients.</li> <li>• Revised the statistical analysis methods for analyzing relapsed/refractory MYD88MUT patients</li> <li>• Changed the timing of the interim analysis to 6 months after the first 50 patients with relapsed/refractory disease were randomized to Cohort 1</li> <li>• Updated the sample size considerations to have the power to test the primary endpoint in the Cohort 1 Relapsed/Refractory Analysis Set</li> <li>• Changed the timing of the primary analysis from 9 months to 12 months</li> <li>• Added an assessment of impact of plasmapheresis on zanubrutinib PK as a new exploratory objective and endpoint</li> <li>• Revised the zanubrutinib and ibrutinib guidelines for dose modification, reduction, and discontinuation</li> <li>• Added ventricular arrhythmia as an adverse event of special interest</li> </ul> <p>Revised the definition of treatment-emergent adverse event to be consistent with other protocols</p> <ul style="list-style-type: none"> <li>• Clarified that evaluation of extramedullary disease included evaluation of splenomegaly rather than organomegaly</li> <li>• Clarified that infection prophylaxis was per institutional standards</li> <li>• Clarified when corticosteroid usage was prohibited</li> <li>• Added that all treatment-related serious adverse events were to be followed until resolution or stabilization</li> <li>• Revised the efficacy follow-up to continue even though a patient may have started a new anticancer therapy after the last dose of study drug</li> <li>• Added that patients who continued to benefit from zanubrutinib after disease progression may have remained on study upon discussion with the medical monitor or designee</li> <li>• Added back ECHO/MUGA assessments at screening and when clinically indicated</li> </ul> |
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| 21 September 2018 | <ul style="list-style-type: none"> <li>• Clarified for patients with mild hepatic impairment (Child-Pugh Class A) and moderate hepatic impairment (Child-Pugh Class B) to refer to the local prescribing guidelines for specific instructions on ibrutinib dose modifications</li> <li>• Removed the QT/QTc prolonging drug guidance</li> <li>• Removed the adverse events of special interest list, including protocol definitions and associated expedited reporting requirements</li> <li>• Updated Phase 1 first-in-human study data</li> <li>• Clarified the maximum number of repetitions of a failed screening test to be 1 time</li> <li>• Updated the overdose reporting guidance</li> <li>• Added guidance about the potential for opportunistic infections in patients with hematologic malignancies, particularly for those having received prior lymphodepleting chemotherapy or prolonged corticosteroid exposure</li> <li>• Added that patients who remained on the study after disease progression continued to follow the required assessments during the treatment phase</li> <li>• Clarified that the serum IgM value at Cycle 1 Day 1 served as the baseline for all assessments except for patients who had undergone plasmapheresis</li> <li>• Clarified that assessments were performed in the same laboratory using the same methodology throughout the study</li> <li>• Clarified that patients with new disease symptoms documented objective evidence of disease progression according to the disease-specific response criteria</li> <li>• Clarified that as part of the tumor assessment, the physical examination was also to be included the evaluation of the presence and degree of enlarged lymph nodes and splenomegaly</li> <li>• Clarified that ECGs were to be performed in triplicate at each timepoint assessment</li> <li>• Clarified the sample collection practices for cryoglobulin, serum immunoglobulins, and immunofixation for patients with cryoglobulinemia at screening</li> <li>• Clarified that the clinical significance of a laboratory test abnormality was at the judgment of the investigator</li> </ul> |
| 26 August 2019    | <ul style="list-style-type: none"> <li>• Clarified that capsules or other dose forms and strengths were allowed for ibrutinib</li> <li>• Clarified that a barrier method of contraception must have also been used if hormonal contraceptives were used</li> <li>• Added section on dose modifications for zanubrutinib when coadministered with strong/moderate CYP3A inhibitors/inducers</li> <li>• Clarified medications to be used with caution</li> <li>• Clarified use of efficacy criteria with and without consideration of extramedullary disease</li> <li>• Clarified instructions for post-baseline CT scans</li> <li>• Updated lists of moderate and strong CYP3A inhibitors and inducers</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

None reported