



## Clinical trial results:

### A Prospective, Open-Label, Multicenter, Phase 2 Trial to Evaluate the Safety and Efficacy of the Combination of Tirabrutinib (GS-4059) and Idelalisib With and Without Obinutuzumab in Subjects with Chronic Lymphocytic Leukemia

#### Summary

|                          |                 |
|--------------------------|-----------------|
| EudraCT number           | 2015-003909-42  |
| Trial protocol           | DE              |
| Global end of trial date | 14 January 2021 |

#### Results information

|                                |                 |
|--------------------------------|-----------------|
| Result version number          | v1 (current)    |
| This version publication date  | 11 January 2022 |
| First version publication date | 11 January 2022 |

#### Trial information

##### Trial identification

|                       |                |
|-----------------------|----------------|
| Sponsor protocol code | GS-US-401-1958 |
|-----------------------|----------------|

##### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT02968563 |
| WHO universal trial number (UTN)   | -           |

Notes:

#### Sponsors

|                              |                                                                                            |
|------------------------------|--------------------------------------------------------------------------------------------|
| Sponsor organisation name    | Gilead Sciences                                                                            |
| Sponsor organisation address | 333 Lakeside Drive, Foster City, CA, United States, 94404                                  |
| Public contact               | Gilead Clinical Study Information Center, Gilead Sciences, GileadClinicalTrials@gilead.com |
| Scientific contact           | Gilead Clinical Study Information Center, Gilead Sciences, GileadClinicalTrials@gilead.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                       | 14 January 2021 |
| Is this the analysis of the primary completion data? | Yes             |
| Primary completion date                              | 17 June 2019    |
| Global end of trial reached?                         | Yes             |
| Global end of trial date                             | 14 January 2021 |
| Was the trial ended prematurely?                     | No              |

Notes:

## General information about the trial

Main objective of the trial:

The primary objective of this study was to determine the preliminary efficacy of the combination of tirabrutinib and idelalisib with obinutuzumab in adults with relapsed or refractory chronic lymphocytic leukemia (CLL).

The study had a 6 participant per arm safety run-in to evaluate safety prior to the enrollment of subsequent participants. The treatment period was adaptive, with a duration of active treatment up to two years and a total follow-up on study for up to 30 days post end of treatment, or up to Week 25 should a participant discontinue treatment prior to Week 25 for reasons other than disease progression.

Protection of trial subjects:

The protocol and consent/assent forms were submitted by each investigator to a duly constituted Independent Ethics Committee (IEC) or Institutional Review Board (IRB) for review and approval before study initiation. All revisions to the consent/assent forms (if applicable) after initial IEC/IRB approval were submitted by the investigator to the IEC/IRB for review and approval before implementation in accordance with regulatory requirements. This study was conducted in accordance with recognized international scientific and ethical standards, including but not limited to the International Conference on Harmonization guideline for Good Clinical Practice (ICH GCP) and the original principles embodied in the Declaration of Helsinki.

Background therapy: -

Evidence for comparator: -

|                                                           |                  |
|-----------------------------------------------------------|------------------|
| Actual start date of recruitment                          | 13 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 | Germany: 35 |
| Worldwide total number of subjects   | 35          |
| EEA total number of subjects         | 35          |

Notes:

### Subjects enrolled per age group

|                                           |   |
|-------------------------------------------|---|
| In utero                                  | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| 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)                     | 15 |
| From 65 to 84 years                      | 20 |
| 85 years and over                        | 0  |

## Subject disposition

### Recruitment

Recruitment details:

Participants were enrolled at study sites in Germany. The first participant was screened on 13 December 2016. The last study visit occurred on 14 January 2021.

### Pre-assignment

Screening details:

35 participants were screened. Randomization was discontinued after implementation of Protocol Amendment 3; all additional participants were enrolled to Arm: Tirabrutinib + Idelalisib + Obinutuzumab.

### Period 1

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

### Arms

|                              |                           |
|------------------------------|---------------------------|
| Are arms mutually exclusive? | Yes                       |
| <b>Arm title</b>             | Tirabrutinib + Idelalisib |

Arm description:

Tirabrutinib 80 mg (4 x 20 mg tablets/2 x 40 mg tablets/1 x 80 mg tablet) orally once daily + idelalisib 100 mg (1 x 100 mg tablet) orally once daily for up to 104 weeks.

|                                        |                            |
|----------------------------------------|----------------------------|
| Arm type                               | Experimental               |
| Investigational medicinal product name | Idelalisib                 |
| Investigational medicinal product code |                            |
| Other name                             | Zydelig®, GS-1101, CAL-101 |
| Pharmaceutical forms                   | Film-coated tablet         |
| Routes of administration               | Oral use                   |

Dosage and administration details:

100 mg administered once daily

|                                        |                    |
|----------------------------------------|--------------------|
| Investigational medicinal product name | Tirabrutinib       |
| Investigational medicinal product code |                    |
| Other name                             | GS-4059            |
| Pharmaceutical forms                   | Film-coated tablet |
| Routes of administration               | Oral use           |

Dosage and administration details:

80 mg administered once daily

|                  |                                          |
|------------------|------------------------------------------|
| <b>Arm title</b> | Tirabrutinib + Idelalisib + Obinutuzumab |
|------------------|------------------------------------------|

Arm description:

Tirabrutinib 80 mg (4 x 20 mg tablets/ 2 x 40 mg tablets/ 1 x 80 mg tablet) orally once daily + idelalisib 100 mg (1 x 100 mg tablet) orally once daily for up to 104 weeks + obinutuzumab 100 mg on Day 1, 900 mg on Day 1 or 2, and 1000 mg subsequently for up to 8 doses on Day 1 of Weeks 2, 3, 5, and then every 4 weeks through Week 21.

|                                        |                    |
|----------------------------------------|--------------------|
| Arm type                               | Experimental       |
| Investigational medicinal product name | Tirabrutinib       |
| Investigational medicinal product code |                    |
| Other name                             | GS-4059            |
| Pharmaceutical forms                   | Film-coated tablet |
| Routes of administration               | Oral use           |

Dosage and administration details:

80 mg administered once daily

|                                                                               |                                       |
|-------------------------------------------------------------------------------|---------------------------------------|
| Investigational medicinal product name                                        | Obinutuzumab                          |
| Investigational medicinal product code                                        |                                       |
| Other name                                                                    | Gazyvaro®                             |
| Pharmaceutical forms                                                          | Concentrate for solution for infusion |
| Routes of administration                                                      | Intravenous use                       |
| Dosage and administration details:                                            |                                       |
| 100 mg on day 1, 900 mg on day 1 or 2, and 1000 mg administered intravenously |                                       |
| Investigational medicinal product name                                        | Idelalisib                            |
| Investigational medicinal product code                                        |                                       |
| Other name                                                                    | Zydelig®, GS-1101, CAL-101            |
| Pharmaceutical forms                                                          | Film-coated tablet                    |
| Routes of administration                                                      | Oral use                              |
| Dosage and administration details:                                            |                                       |
| 100 mg administered once daily                                                |                                       |

| Number of subjects in period 1 | Tirabrutinib +<br>Idelalisib | Tirabrutinib +<br>Idelalisib +<br>Obinutuzumab |
|--------------------------------|------------------------------|------------------------------------------------|
|                                |                              |                                                |
| Started                        | 5                            | 30                                             |
| Completed                      | 4                            | 22                                             |
| Not completed                  | 1                            | 8                                              |
| Death                          | 1                            | 1                                              |
| Adverse event                  | -                            | 6                                              |
| Lost to follow-up              | -                            | 1                                              |

## Baseline characteristics

### Reporting groups

|                       |                           |
|-----------------------|---------------------------|
| Reporting group title | Tirabrutinib + Idelalisib |
|-----------------------|---------------------------|

Reporting group description:

Tirabrutinib 80 mg (4 x 20 mg tablets/2 x 40 mg tablets/1 x 80 mg tablet) orally once daily + idelalisib 100 mg (1 x 100 mg tablet) orally once daily for up to 104 weeks.

|                       |                                          |
|-----------------------|------------------------------------------|
| Reporting group title | Tirabrutinib + Idelalisib + Obinutuzumab |
|-----------------------|------------------------------------------|

Reporting group description:

Tirabrutinib 80 mg (4 x 20 mg tablets/ 2 x 40 mg tablets/ 1 x 80 mg tablet) orally once daily + idelalisib 100 mg (1 x 100 mg tablet) orally once daily for up to 104 weeks + obinutuzumab 100 mg on Day 1, 900 mg on Day 1 or 2, and 1000 mg subsequently for up to 8 doses on Day 1 of Weeks 2, 3, 5, and then every 4 weeks through Week 21.

| Reporting group values             | Tirabrutinib + Idelalisib | Tirabrutinib + Idelalisib + Obinutuzumab | Total |
|------------------------------------|---------------------------|------------------------------------------|-------|
| Number of subjects                 | 5                         | 30                                       | 35    |
| Age categorical<br>Units: Subjects |                           |                                          |       |

|                                                                                     |             |             |    |
|-------------------------------------------------------------------------------------|-------------|-------------|----|
| Age continuous<br>Units: years<br>arithmetic mean<br>standard deviation             | 62<br>± 4.7 | 65<br>± 9.4 | -  |
| Gender categorical<br>Units: Subjects                                               |             |             |    |
| Female                                                                              | 3           | 10          | 13 |
| Male                                                                                | 2           | 20          | 22 |
| Race                                                                                |             |             |    |
| Not Permitted = local regulators did not allow collection of race information.      |             |             |    |
| Units: Subjects                                                                     |             |             |    |
| White                                                                               | 5           | 29          | 34 |
| Not Permitted                                                                       | 0           | 1           | 1  |
| Ethnicity                                                                           |             |             |    |
| Not Permitted = local regulators did not allow collection of ethnicity information. |             |             |    |
| Units: Subjects                                                                     |             |             |    |
| Not Hispanic or Latino                                                              | 5           | 29          | 34 |
| Not Permitted                                                                       | 0           | 1           | 1  |

## End points

### End points reporting groups

|                                                                                                                                                                                                                                                                                                                                                 |                                          |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------|
| Reporting group title                                                                                                                                                                                                                                                                                                                           | Tirabrutinib + Idelalisib                |
| Reporting group description:                                                                                                                                                                                                                                                                                                                    |                                          |
| Tirabrutinib 80 mg (4 x 20 mg tablets/2 x 40 mg tablets/1 x 80 mg tablet) orally once daily + idelalisib 100 mg (1 x 100 mg tablet) orally once daily for up to 104 weeks.                                                                                                                                                                      |                                          |
| Reporting group title                                                                                                                                                                                                                                                                                                                           | Tirabrutinib + Idelalisib + Obinutuzumab |
| Reporting group description:                                                                                                                                                                                                                                                                                                                    |                                          |
| Tirabrutinib 80 mg (4 x 20 mg tablets/ 2 x 40 mg tablets/ 1 x 80 mg tablet) orally once daily + idelalisib 100 mg (1 x 100 mg tablet) orally once daily for up to 104 weeks + obinutuzumab 100 mg on Day 1, 900 mg on Day 1 or 2, and 1000 mg subsequently for up to 8 doses on Day 1 of Weeks 2, 3, 5, and then every 4 weeks through Week 21. |                                          |

### Primary: Rate of Complete Response/Complete Remission (CR), as Assessed by Investigator Using Modified International Workshop on Chronic Lymphocytic Leukemia (IWCLL) 2008 Criteria at Week 25

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                                                                                                                                                                                                      |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | Rate of Complete Response/Complete Remission (CR), as Assessed by Investigator Using Modified International Workshop on Chronic Lymphocytic Leukemia (IWCLL) 2008 Criteria at Week 25 <sup>[1]</sup> |
| End point description:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                                                                                                                                                                                      |
| Rate of CR per modified IWCLL 2008 criteria at Week 25 was defined as the percentage of participants who achieved CR/complete remission with incomplete recovery of the bone marrow (CRi) at Week 25. CR: meeting following criteria and no disease related symptoms: no lymphadenopathy > 1.5 cm/hepatomegaly/splenomegaly; lymphocytes < 4000/μL; bone marrow sample must be normocellular with 30% lymphocytes and no B-lymphoid nodules; platelets > 100,000/μL; hemoglobin > 11 g/dL; and neutrophils > 1500/μL. CRi: CR criteria (no lymphadenopathy > 1.5 cm/hepatomegaly/splenomegaly; lymphocytes < 4000/μL; bone marrow [hypocellular] with 30% lymphocytes and no B-lymphoid nodules), persistent anemia/thrombocytopenia/neutropenia unrelated to CLL but related to drug toxicity. Analysis Population Description: The Full Analysis Set included all randomized or enrolled participants who received at least 1 dose of any study drug. |                                                                                                                                                                                                      |
| End point type                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | Primary                                                                                                                                                                                              |
| End point timeframe:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                                                                                                                                                                                      |
| Week 25                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |                                                                                                                                                                                                      |

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical comparison was planned or performed.

| End point values                  | Tirabrutinib + Idelalisib | Tirabrutinib + Idelalisib + Obinutuzumab |  |  |
|-----------------------------------|---------------------------|------------------------------------------|--|--|
| Subject group type                | Reporting group           | Reporting group                          |  |  |
| Number of subjects analysed       | 5                         | 30                                       |  |  |
| Units: percentage of participants |                           |                                          |  |  |
| number (confidence interval 90%)  | 0 (0 to 45.1)             | 6.7 (1.2 to 19.5)                        |  |  |

### Statistical analyses

**Secondary: Rate of CR With Bone Marrow Minimal Residual Disease (CR/BM MRD) Negativity, as Assessed by the Investigator Using the Modified IWCLL 2008 Criteria at Week 25**

|                 |                                                                                                                                                                |
|-----------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Rate of CR With Bone Marrow Minimal Residual Disease (CR/BM MRD) Negativity, as Assessed by the Investigator Using the Modified IWCLL 2008 Criteria at Week 25 |
|-----------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------|

## End point description:

Rate of CR/BM MRD at Week 25: percentage of participants who achieved CR/CRi per modified IWCLL 2008 criteria and achieved BM MRD negativity at Week 25. CR: meeting following criteria and no disease related symptoms: no lymphadenopathy > 1.5 cm/hepatomegaly/splenomegaly; lymphocytes < 4000/ $\mu$ L; bone marrow sample must be normocellular with 30% lymphocytes and no B-lymphoid nodules; platelets > 100,000/ $\mu$ L; hemoglobin > 11 g/dL; and neutrophils > 1500/ $\mu$ L. CRi: CR criteria (no lymphadenopathy > 1.5 cm/hepatomegaly/splenomegaly; lymphocytes < 4000/ $\mu$ L; bone marrow [hypocellular] with 30% lymphocytes and no B-lymphoid nodules), persistent anemia/thrombocytopenia/neutropenia unrelated to CLL but related to drug toxicity. MRD response was assessed with four-color-flow cytometry (FACS) and MRD negativity was defined as one CLL cell per 10,000 leukocytes [0.01%], ie,  $<10^{-4}$  and participants were defined as MRD negative if their disease burden was below threshold. Participants in the Full Analysis Set were analyzed.

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

## End point timeframe:

Week 25

| End point values                  | Tirabrutinib + Idelalisib | Tirabrutinib + Idelalisib + Obinutuzumab |  |  |
|-----------------------------------|---------------------------|------------------------------------------|--|--|
| Subject group type                | Reporting group           | Reporting group                          |  |  |
| Number of subjects analysed       | 5                         | 30                                       |  |  |
| Units: percentage of participants |                           |                                          |  |  |
| number (confidence interval 90%)  | 0 (0 to 45.1)             | 0 (0 to 9.5)                             |  |  |

**Statistical analyses**

No statistical analyses for this end point

**Secondary: Rate of CR With Peripheral Minimal Residual Disease (CR/PB MRD) Negativity, as Assessed by the Investigator Using the Modified IWCLL 2008 Criteria at Week 25**

|                 |                                                                                                                                                               |
|-----------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Rate of CR With Peripheral Minimal Residual Disease (CR/PB MRD) Negativity, as Assessed by the Investigator Using the Modified IWCLL 2008 Criteria at Week 25 |
|-----------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------|

## End point description:

Rate of CR/PB MRD at Week 25: percentage of participants who achieved CR/CRi per modified IWCLL 2008 criteria and also achieved PB MRD negativity at Week 25. CR: meeting following criteria and no disease related symptoms: no lymphadenopathy > 1.5 cm/hepatomegaly/splenomegaly; lymphocytes < 4000/ $\mu$ L; bone marrow sample must be normocellular with 30% lymphocytes and no B-lymphoid nodules; platelets > 100,000/ $\mu$ L; hemoglobin > 11 g/dL; and neutrophils > 1500/ $\mu$ L. CRi: CR criteria (no lymphadenopathy > 1.5 cm/hepatomegaly/splenomegaly; lymphocytes < 4000/ $\mu$ L; bone marrow [hypocellular] with 30% lymphocytes and no B-lymphoid nodules), persistent anemia/thrombocytopenia/neutropenia unrelated to CLL but related to drug toxicity. MRD response was assessed with FACS and MRD negativity was defined as one CLL cell per 10,000 leukocytes [0.01%], ie,  $<10^{-4}$  and participants were defined as MRD negative if their disease burden was below this threshold. Participants in the Full Analysis Set were analyzed.



|                      |           |
|----------------------|-----------|
| End point type       | Secondary |
| End point timeframe: |           |
| Week 25              |           |

| End point values                  | Tirabrutinib + Idelalisib | Tirabrutinib + Idelalisib + Obinutuzumab |  |  |
|-----------------------------------|---------------------------|------------------------------------------|--|--|
| Subject group type                | Reporting group           | Reporting group                          |  |  |
| Number of subjects analysed       | 5                         | 30                                       |  |  |
| Units: percentage of participants |                           |                                          |  |  |
| number (confidence interval 90%)  | 0 (0 to 45.1)             | 0 (0 to 9.5)                             |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Overall Response Rate (ORR), as Assessed by the Investigator Using the Modified IWCLL 2008 Criteria at Week 25

|                 |                                                                                                                |
|-----------------|----------------------------------------------------------------------------------------------------------------|
| End point title | Overall Response Rate (ORR), as Assessed by the Investigator Using the Modified IWCLL 2008 Criteria at Week 25 |
|-----------------|----------------------------------------------------------------------------------------------------------------|

End point description:

ORR was assessed based on modified IWCLL 2008 criteria and was defined as percentage of participants achieving a CR, CRi, partial remission (PR; including nodular partial response [nPR]), and PR with lymphocytosis (PR-L). CR and CRi: meeting all the criteria that have been defined in Outcome measures 1, 2 and 3. PR:  $\geq 2$  of these:  $\geq 50\%$  decrease in lymphocytes, lymphadenopathy, size of liver, size of spleen, and  $50\%$  decrease in bone marrow infiltrates; and  $\geq 1$  of these: neutrophils  $> 1500/\mu\text{L}$  or  $\geq 50\%$  increase from Baseline, platelets  $\geq 100,000/\mu\text{L}$  or  $\geq 50\%$  increase from Baseline, hemoglobin  $> 11 \text{ g/dL}$  or  $\geq 50\%$  increase from Baseline. PR-L: meeting PR criteria; however, a lymphocytosis related to treatment may be present. nPR: All criteria for a CR/CRi were fulfilled, but the bone marrow showed lymphoid nodules. Participants in the Full Analysis Set were analyzed.

|                      |           |
|----------------------|-----------|
| End point type       | Secondary |
| End point timeframe: |           |
| Week 25              |           |

| End point values                  | Tirabrutinib + Idelalisib | Tirabrutinib + Idelalisib + Obinutuzumab |  |  |
|-----------------------------------|---------------------------|------------------------------------------|--|--|
| Subject group type                | Reporting group           | Reporting group                          |  |  |
| Number of subjects analysed       | 5                         | 30                                       |  |  |
| Units: percentage of participants |                           |                                          |  |  |
| number (confidence interval 90%)  | 60.0 (18.9 to 92.4)       | 93.3 (80.5 to 98.8)                      |  |  |

## Statistical analyses

No statistical analyses for this end point

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**Secondary: Percentage of Participants Experiencing Any Treatment-Emergent Adverse Events (AEs) and Treatment-Emergent Serious Adverse Events (SAEs)**

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|                 |                                                                                                                                          |
|-----------------|------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Percentage of Participants Experiencing Any Treatment-Emergent Adverse Events (AEs) and Treatment-Emergent Serious Adverse Events (SAEs) |
|-----------------|------------------------------------------------------------------------------------------------------------------------------------------|

End point description:

Treatment-emergent AEs are defined as 1 or both of the following:

- Any AEs with an onset date on or after the study drug start date and no later than 30 days after permanent discontinuation of study drug
- Any AEs leading to discontinuation of study drug

A SAE is defined as an event that, at any dose, resulted in any of the following: death, life-threatening, in-patient hospitalization or prolongation of existing hospitalization, persistent or significant disability/incapacity, a congenital anomaly/birth defect, or a medically important event or reaction.

The Safety Analysis Set included all randomized or enrolled participants who received at least 1 dose of any study drug.

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

End point timeframe:

First dose date up to the last dose date (maximum: 105 weeks) plus 30 days

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| End point values                  | Tirabrutinib +<br>Idelalisib | Tirabrutinib +<br>Idelalisib +<br>Obinutuzumab |  |  |
|-----------------------------------|------------------------------|------------------------------------------------|--|--|
| Subject group type                | Reporting group              | Reporting group                                |  |  |
| Number of subjects analysed       | 5                            | 30                                             |  |  |
| Units: percentage of participants |                              |                                                |  |  |
| number (not applicable)           |                              |                                                |  |  |
| Any Treatment-Emergent AEs        | 100                          | 100                                            |  |  |
| Treatment-Emergent SAEs           | 60.0                         | 46.7                                           |  |  |

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**Statistical analyses**

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No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Adverse Events: First dose date up to last dose date (maximum: 105 weeks) plus 30 days;

All-Cause Mortality: Enrollment up to 31 months

Adverse event reporting additional description:

Adverse Events: The Safety Analysis Set included all randomized or enrolled participants who received at least 1 dose of any study drug.

All-Cause Mortality: The All Enrolled Analysis Set included all participants who received a study participant identification number in the study after screening.

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

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 23.1 |
|--------------------|------|

### Reporting groups

|                       |                           |
|-----------------------|---------------------------|
| Reporting group title | Tirabrutinib + Idelalisib |
|-----------------------|---------------------------|

Reporting group description:

Tirabrutinib 80 mg (4 x 20 mg tablets/2 x 40 mg tablets/1 x 80 mg tablet) orally once daily + idelalisib 100 mg (1 x 100 mg tablet) orally once daily for up to 104 weeks.

|                       |                                          |
|-----------------------|------------------------------------------|
| Reporting group title | Tirabrutinib + Idelalisib + Obinutuzumab |
|-----------------------|------------------------------------------|

Reporting group description:

Tirabrutinib 80 mg (4 x 20 mg tablets/ 2 x 40 mg tablets/ 1 x 80 mg tablet) orally once daily + idelalisib 100 mg (1 x 100 mg tablet) orally once daily for up to 104 weeks + obinutuzumab 100 mg on Day 1, 900 mg on Day 1 or 2, and 1000 mg subsequently for up to 8 doses administered intravenously over 21 weeks.

| Serious adverse events                            | Tirabrutinib + Idelalisib | Tirabrutinib + Idelalisib + Obinutuzumab |  |
|---------------------------------------------------|---------------------------|------------------------------------------|--|
| Total subjects affected by serious adverse events |                           |                                          |  |
| subjects affected / exposed                       | 3 / 5 (60.00%)            | 14 / 30 (46.67%)                         |  |
| number of deaths (all causes)                     | 1                         | 1                                        |  |
| number of deaths resulting from adverse events    |                           |                                          |  |
| Investigations                                    |                           |                                          |  |
| Hepatic enzyme increased                          |                           |                                          |  |
| subjects affected / exposed                       | 0 / 5 (0.00%)             | 1 / 30 (3.33%)                           |  |
| occurrences causally related to treatment / all   | 0 / 0                     | 1 / 1                                    |  |
| deaths causally related to treatment / all        | 0 / 0                     | 0 / 0                                    |  |
| Investigation                                     |                           |                                          |  |
| subjects affected / exposed                       | 0 / 5 (0.00%)             | 1 / 30 (3.33%)                           |  |
| occurrences causally related to treatment / all   | 0 / 0                     | 0 / 1                                    |  |
| deaths causally related to treatment / all        | 0 / 0                     | 0 / 0                                    |  |

|                                                                                                                                                                                                                                         |                                  |                                  |  |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------|----------------------------------|--|
| Neutrophil count decreased<br>subjects affected / exposed<br>occurrences causally related to<br>treatment / all<br>deaths causally related to<br>treatment / all                                                                        | 0 / 5 (0.00%)<br>0 / 0<br>0 / 0  | 1 / 30 (3.33%)<br>1 / 1<br>0 / 0 |  |
| Neoplasms benign, malignant and<br>unspecified (incl cysts and polyps)<br>Acute myeloid leukaemia<br>subjects affected / exposed<br>occurrences causally related to<br>treatment / all<br>deaths causally related to<br>treatment / all | 0 / 5 (0.00%)<br>0 / 0<br>0 / 0  | 1 / 30 (3.33%)<br>0 / 1<br>0 / 0 |  |
| Squamous cell carcinoma<br>subjects affected / exposed<br>occurrences causally related to<br>treatment / all<br>deaths causally related to<br>treatment / all                                                                           | 0 / 5 (0.00%)<br>0 / 0<br>0 / 0  | 1 / 30 (3.33%)<br>1 / 1<br>0 / 0 |  |
| Cardiac disorders<br>Cardiac failure acute<br>subjects affected / exposed<br>occurrences causally related to<br>treatment / all<br>deaths causally related to<br>treatment / all                                                        | 1 / 5 (20.00%)<br>1 / 1<br>1 / 1 | 0 / 30 (0.00%)<br>0 / 0<br>0 / 0 |  |
| Coronary artery stenosis<br>subjects affected / exposed<br>occurrences causally related to<br>treatment / all<br>deaths causally related to<br>treatment / all                                                                          | 0 / 5 (0.00%)<br>0 / 0<br>0 / 0  | 1 / 30 (3.33%)<br>0 / 1<br>0 / 0 |  |
| Nervous system disorders<br>Cerebral infarction<br>subjects affected / exposed<br>occurrences causally related to<br>treatment / all<br>deaths causally related to<br>treatment / all                                                   | 0 / 5 (0.00%)<br>0 / 0<br>0 / 0  | 1 / 30 (3.33%)<br>0 / 1<br>0 / 1 |  |
| Gastrointestinal disorders<br>Colitis<br>subjects affected / exposed<br>occurrences causally related to<br>treatment / all<br>deaths causally related to<br>treatment / all                                                             | 0 / 5 (0.00%)<br>0 / 0<br>0 / 0  | 1 / 30 (3.33%)<br>1 / 1<br>0 / 0 |  |
| Stomatitis                                                                                                                                                                                                                              |                                  |                                  |  |

|                                                 |                |                |  |
|-------------------------------------------------|----------------|----------------|--|
| subjects affected / exposed                     | 0 / 5 (0.00%)  | 1 / 30 (3.33%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Respiratory, thoracic and mediastinal disorders |                |                |  |
| Dyspnoea                                        |                |                |  |
| subjects affected / exposed                     | 0 / 5 (0.00%)  | 1 / 30 (3.33%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Pleural effusion                                |                |                |  |
| subjects affected / exposed                     | 0 / 5 (0.00%)  | 1 / 30 (3.33%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 2          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Skin and subcutaneous tissue disorders          |                |                |  |
| Dermatitis allergic                             |                |                |  |
| subjects affected / exposed                     | 1 / 5 (20.00%) | 0 / 30 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Renal and urinary disorders                     |                |                |  |
| Nephrolithiasis                                 |                |                |  |
| subjects affected / exposed                     | 1 / 5 (20.00%) | 0 / 30 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Ureterolithiasis                                |                |                |  |
| subjects affected / exposed                     | 1 / 5 (20.00%) | 0 / 30 (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                     |                |                |  |
| Atypical pneumonia                              |                |                |  |
| subjects affected / exposed                     | 0 / 5 (0.00%)  | 1 / 30 (3.33%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Cystitis                                        |                |                |  |

|                                                 |               |                |  |
|-------------------------------------------------|---------------|----------------|--|
| subjects affected / exposed                     | 0 / 5 (0.00%) | 1 / 30 (3.33%) |  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 3          |  |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          |  |
| Influenza                                       |               |                |  |
| subjects affected / exposed                     | 0 / 5 (0.00%) | 1 / 30 (3.33%) |  |
| occurrences causally related to treatment / all | 0 / 0         | 1 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          |  |
| Large intestine infection                       |               |                |  |
| subjects affected / exposed                     | 0 / 5 (0.00%) | 1 / 30 (3.33%) |  |
| occurrences causally related to treatment / all | 0 / 0         | 1 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          |  |
| Pneumonia                                       |               |                |  |
| subjects affected / exposed                     | 0 / 5 (0.00%) | 1 / 30 (3.33%) |  |
| occurrences causally related to treatment / all | 0 / 0         | 1 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          |  |
| Metabolism and nutrition disorders              |               |                |  |
| Tumour lysis syndrome                           |               |                |  |
| subjects affected / exposed                     | 0 / 5 (0.00%) | 1 / 30 (3.33%) |  |
| occurrences causally related to treatment / all | 0 / 0         | 1 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0          |  |

Frequency threshold for reporting non-serious adverse events: 5 %

| <b>Non-serious adverse events</b>                     | Tirabrutinib + Idelalisib | Tirabrutinib + Idelalisib + Obinutuzumab |  |
|-------------------------------------------------------|---------------------------|------------------------------------------|--|
| Total subjects affected by non-serious adverse events |                           |                                          |  |
| subjects affected / exposed                           | 5 / 5 (100.00%)           | 29 / 30 (96.67%)                         |  |
| Vascular disorders                                    |                           |                                          |  |
| Haematoma                                             |                           |                                          |  |
| subjects affected / exposed                           | 1 / 5 (20.00%)            | 6 / 30 (20.00%)                          |  |
| occurrences (all)                                     | 1                         | 16                                       |  |
| Hypertension                                          |                           |                                          |  |
| subjects affected / exposed                           | 0 / 5 (0.00%)             | 5 / 30 (16.67%)                          |  |
| occurrences (all)                                     | 0                         | 5                                        |  |
| General disorders and administration site conditions  |                           |                                          |  |

|                                                 |                |                  |  |
|-------------------------------------------------|----------------|------------------|--|
| Fatigue                                         |                |                  |  |
| subjects affected / exposed                     | 1 / 5 (20.00%) | 10 / 30 (33.33%) |  |
| occurrences (all)                               | 1              | 11               |  |
| Pyrexia                                         |                |                  |  |
| subjects affected / exposed                     | 1 / 5 (20.00%) | 7 / 30 (23.33%)  |  |
| occurrences (all)                               | 3              | 7                |  |
| Chills                                          |                |                  |  |
| subjects affected / exposed                     | 1 / 5 (20.00%) | 6 / 30 (20.00%)  |  |
| occurrences (all)                               | 1              | 7                |  |
| Feeling cold                                    |                |                  |  |
| subjects affected / exposed                     | 0 / 5 (0.00%)  | 2 / 30 (6.67%)   |  |
| occurrences (all)                               | 0              | 2                |  |
| Influenza like illness                          |                |                  |  |
| subjects affected / exposed                     | 0 / 5 (0.00%)  | 2 / 30 (6.67%)   |  |
| occurrences (all)                               | 0              | 3                |  |
| Oedema peripheral                               |                |                  |  |
| subjects affected / exposed                     | 0 / 5 (0.00%)  | 2 / 30 (6.67%)   |  |
| occurrences (all)                               | 0              | 2                |  |
| Medical device pain                             |                |                  |  |
| subjects affected / exposed                     | 1 / 5 (20.00%) | 0 / 30 (0.00%)   |  |
| occurrences (all)                               | 1              | 0                |  |
| Respiratory, thoracic and mediastinal disorders |                |                  |  |
| Cough                                           |                |                  |  |
| subjects affected / exposed                     | 0 / 5 (0.00%)  | 8 / 30 (26.67%)  |  |
| occurrences (all)                               | 0              | 12               |  |
| Epistaxis                                       |                |                  |  |
| subjects affected / exposed                     | 0 / 5 (0.00%)  | 4 / 30 (13.33%)  |  |
| occurrences (all)                               | 0              | 6                |  |
| Dysphonia                                       |                |                  |  |
| subjects affected / exposed                     | 0 / 5 (0.00%)  | 2 / 30 (6.67%)   |  |
| occurrences (all)                               | 0              | 2                |  |
| Haemoptysis                                     |                |                  |  |
| subjects affected / exposed                     | 0 / 5 (0.00%)  | 2 / 30 (6.67%)   |  |
| occurrences (all)                               | 0              | 2                |  |
| Nasal mucosal disorder                          |                |                  |  |

|                                                  |                    |                     |  |
|--------------------------------------------------|--------------------|---------------------|--|
| subjects affected / exposed<br>occurrences (all) | 0 / 5 (0.00%)<br>0 | 2 / 30 (6.67%)<br>2 |  |
| Psychiatric disorders                            |                    |                     |  |
| Depression                                       |                    |                     |  |
| subjects affected / exposed                      | 0 / 5 (0.00%)      | 2 / 30 (6.67%)      |  |
| occurrences (all)                                | 0                  | 2                   |  |
| Insomnia                                         |                    |                     |  |
| subjects affected / exposed                      | 1 / 5 (20.00%)     | 1 / 30 (3.33%)      |  |
| occurrences (all)                                | 1                  | 1                   |  |
| Sleep disorder                                   |                    |                     |  |
| subjects affected / exposed                      | 0 / 5 (0.00%)      | 2 / 30 (6.67%)      |  |
| occurrences (all)                                | 0                  | 2                   |  |
| Investigations                                   |                    |                     |  |
| Neutrophil count decreased                       |                    |                     |  |
| subjects affected / exposed                      | 0 / 5 (0.00%)      | 4 / 30 (13.33%)     |  |
| occurrences (all)                                | 0                  | 9                   |  |
| Alanine aminotransferase increased               |                    |                     |  |
| subjects affected / exposed                      | 1 / 5 (20.00%)     | 2 / 30 (6.67%)      |  |
| occurrences (all)                                | 2                  | 4                   |  |
| Aspartate aminotransferase increased             |                    |                     |  |
| subjects affected / exposed                      | 1 / 5 (20.00%)     | 2 / 30 (6.67%)      |  |
| occurrences (all)                                | 2                  | 3                   |  |
| C-reactive protein increased                     |                    |                     |  |
| subjects affected / exposed                      | 0 / 5 (0.00%)      | 3 / 30 (10.00%)     |  |
| occurrences (all)                                | 0                  | 5                   |  |
| Hepatic enzyme increased                         |                    |                     |  |
| subjects affected / exposed                      | 0 / 5 (0.00%)      | 3 / 30 (10.00%)     |  |
| occurrences (all)                                | 0                  | 4                   |  |
| Platelet count decreased                         |                    |                     |  |
| subjects affected / exposed                      | 0 / 5 (0.00%)      | 3 / 30 (10.00%)     |  |
| occurrences (all)                                | 0                  | 3                   |  |
| Gamma-glutamyltransferase increased              |                    |                     |  |
| subjects affected / exposed                      | 0 / 5 (0.00%)      | 2 / 30 (6.67%)      |  |
| occurrences (all)                                | 0                  | 2                   |  |
| Weight decreased                                 |                    |                     |  |



|                                                  |                    |                     |  |
|--------------------------------------------------|--------------------|---------------------|--|
| subjects affected / exposed<br>occurrences (all) | 0 / 5 (0.00%)<br>0 | 2 / 30 (6.67%)<br>2 |  |
| Injury, poisoning and procedural complications   |                    |                     |  |
| Infusion related reaction                        |                    |                     |  |
| subjects affected / exposed                      | 0 / 5 (0.00%)      | 5 / 30 (16.67%)     |  |
| occurrences (all)                                | 0                  | 6                   |  |
| Foot fracture                                    |                    |                     |  |
| subjects affected / exposed                      | 1 / 5 (20.00%)     | 1 / 30 (3.33%)      |  |
| occurrences (all)                                | 1                  | 1                   |  |
| Cardiac disorders                                |                    |                     |  |
| Tachycardia                                      |                    |                     |  |
| subjects affected / exposed                      | 1 / 5 (20.00%)     | 1 / 30 (3.33%)      |  |
| occurrences (all)                                | 1                  | 1                   |  |
| Nervous system disorders                         |                    |                     |  |
| Dizziness                                        |                    |                     |  |
| subjects affected / exposed                      | 2 / 5 (40.00%)     | 3 / 30 (10.00%)     |  |
| occurrences (all)                                | 3                  | 4                   |  |
| Memory impairment                                |                    |                     |  |
| subjects affected / exposed                      | 0 / 5 (0.00%)      | 2 / 30 (6.67%)      |  |
| occurrences (all)                                | 0                  | 2                   |  |
| Headache                                         |                    |                     |  |
| subjects affected / exposed                      | 1 / 5 (20.00%)     | 4 / 30 (13.33%)     |  |
| occurrences (all)                                | 2                  | 6                   |  |
| Restless legs syndrome                           |                    |                     |  |
| subjects affected / exposed                      | 0 / 5 (0.00%)      | 2 / 30 (6.67%)      |  |
| occurrences (all)                                | 0                  | 2                   |  |
| Syncope                                          |                    |                     |  |
| subjects affected / exposed                      | 1 / 5 (20.00%)     | 0 / 30 (0.00%)      |  |
| occurrences (all)                                | 1                  | 0                   |  |
| Blood and lymphatic system disorders             |                    |                     |  |
| Thrombocytopenia                                 |                    |                     |  |
| subjects affected / exposed                      | 0 / 5 (0.00%)      | 8 / 30 (26.67%)     |  |
| occurrences (all)                                | 0                  | 8                   |  |
| Neutropenia                                      |                    |                     |  |
| subjects affected / exposed                      | 0 / 5 (0.00%)      | 11 / 30 (36.67%)    |  |
| occurrences (all)                                | 0                  | 18                  |  |

|                             |                |                  |  |
|-----------------------------|----------------|------------------|--|
| Anaemia                     |                |                  |  |
| subjects affected / exposed | 0 / 5 (0.00%)  | 2 / 30 (6.67%)   |  |
| occurrences (all)           | 0              | 2                |  |
| Leukopenia                  |                |                  |  |
| subjects affected / exposed | 0 / 5 (0.00%)  | 4 / 30 (13.33%)  |  |
| occurrences (all)           | 0              | 5                |  |
| Lymphopenia                 |                |                  |  |
| subjects affected / exposed | 0 / 5 (0.00%)  | 2 / 30 (6.67%)   |  |
| occurrences (all)           | 0              | 3                |  |
| Ear and labyrinth disorders |                |                  |  |
| Vertigo                     |                |                  |  |
| subjects affected / exposed | 0 / 5 (0.00%)  | 6 / 30 (20.00%)  |  |
| occurrences (all)           | 0              | 6                |  |
| Eye disorders               |                |                  |  |
| Vision blurred              |                |                  |  |
| subjects affected / exposed | 1 / 5 (20.00%) | 2 / 30 (6.67%)   |  |
| occurrences (all)           | 1              | 2                |  |
| Visual impairment           |                |                  |  |
| subjects affected / exposed | 0 / 5 (0.00%)  | 2 / 30 (6.67%)   |  |
| occurrences (all)           | 0              | 2                |  |
| Lacrimation increased       |                |                  |  |
| subjects affected / exposed | 1 / 5 (20.00%) | 0 / 30 (0.00%)   |  |
| occurrences (all)           | 1              | 0                |  |
| Gastrointestinal disorders  |                |                  |  |
| Diarrhoea                   |                |                  |  |
| subjects affected / exposed | 2 / 5 (40.00%) | 10 / 30 (33.33%) |  |
| occurrences (all)           | 7              | 17               |  |
| Nausea                      |                |                  |  |
| subjects affected / exposed | 2 / 5 (40.00%) | 7 / 30 (23.33%)  |  |
| occurrences (all)           | 7              | 10               |  |
| Vomiting                    |                |                  |  |
| subjects affected / exposed | 1 / 5 (20.00%) | 4 / 30 (13.33%)  |  |
| occurrences (all)           | 3              | 4                |  |
| Constipation                |                |                  |  |
| subjects affected / exposed | 1 / 5 (20.00%) | 2 / 30 (6.67%)   |  |
| occurrences (all)           | 1              | 3                |  |
| Flatulence                  |                |                  |  |

|                                        |                |                 |  |
|----------------------------------------|----------------|-----------------|--|
| subjects affected / exposed            | 0 / 5 (0.00%)  | 3 / 30 (10.00%) |  |
| occurrences (all)                      | 0              | 4               |  |
| Abdominal distension                   |                |                 |  |
| subjects affected / exposed            | 0 / 5 (0.00%)  | 2 / 30 (6.67%)  |  |
| occurrences (all)                      | 0              | 2               |  |
| Abdominal pain                         |                |                 |  |
| subjects affected / exposed            | 0 / 5 (0.00%)  | 2 / 30 (6.67%)  |  |
| occurrences (all)                      | 0              | 2               |  |
| Abdominal pain upper                   |                |                 |  |
| subjects affected / exposed            | 0 / 5 (0.00%)  | 2 / 30 (6.67%)  |  |
| occurrences (all)                      | 0              | 3               |  |
| Colitis                                |                |                 |  |
| subjects affected / exposed            | 0 / 5 (0.00%)  | 2 / 30 (6.67%)  |  |
| occurrences (all)                      | 0              | 2               |  |
| Gastritis                              |                |                 |  |
| subjects affected / exposed            | 0 / 5 (0.00%)  | 2 / 30 (6.67%)  |  |
| occurrences (all)                      | 0              | 2               |  |
| Diverticulum intestinal                |                |                 |  |
| subjects affected / exposed            | 1 / 5 (20.00%) | 0 / 30 (0.00%)  |  |
| occurrences (all)                      | 1              | 0               |  |
| Skin and subcutaneous tissue disorders |                |                 |  |
| Rash                                   |                |                 |  |
| subjects affected / exposed            | 0 / 5 (0.00%)  | 8 / 30 (26.67%) |  |
| occurrences (all)                      | 0              | 12              |  |
| Rash maculo-papular                    |                |                 |  |
| subjects affected / exposed            | 2 / 5 (40.00%) | 3 / 30 (10.00%) |  |
| occurrences (all)                      | 2              | 4               |  |
| Pruritus                               |                |                 |  |
| subjects affected / exposed            | 0 / 5 (0.00%)  | 4 / 30 (13.33%) |  |
| occurrences (all)                      | 0              | 5               |  |
| Dry skin                               |                |                 |  |
| subjects affected / exposed            | 0 / 5 (0.00%)  | 3 / 30 (10.00%) |  |
| occurrences (all)                      | 0              | 3               |  |
| Ecchymosis                             |                |                 |  |
| subjects affected / exposed            | 0 / 5 (0.00%)  | 3 / 30 (10.00%) |  |
| occurrences (all)                      | 0              | 3               |  |

|                                                                                                                  |                     |                      |  |
|------------------------------------------------------------------------------------------------------------------|---------------------|----------------------|--|
| Night sweats<br>subjects affected / exposed<br>occurrences (all)                                                 | 0 / 5 (0.00%)<br>0  | 3 / 30 (10.00%)<br>3 |  |
| Skin lesion<br>subjects affected / exposed<br>occurrences (all)                                                  | 0 / 5 (0.00%)<br>0  | 3 / 30 (10.00%)<br>3 |  |
| Petechiae<br>subjects affected / exposed<br>occurrences (all)                                                    | 0 / 5 (0.00%)<br>0  | 2 / 30 (6.67%)<br>2  |  |
| Skin exfoliation<br>subjects affected / exposed<br>occurrences (all)                                             | 0 / 5 (0.00%)<br>0  | 2 / 30 (6.67%)<br>4  |  |
| Dermatitis allergic<br>subjects affected / exposed<br>occurrences (all)                                          | 1 / 5 (20.00%)<br>2 | 0 / 30 (0.00%)<br>0  |  |
| Renal and urinary disorders<br>Dysuria<br>subjects affected / exposed<br>occurrences (all)                       | 1 / 5 (20.00%)<br>1 | 1 / 30 (3.33%)<br>1  |  |
| Musculoskeletal and connective tissue disorders<br>Back pain<br>subjects affected / exposed<br>occurrences (all) | 1 / 5 (20.00%)<br>1 | 7 / 30 (23.33%)<br>9 |  |
| Arthralgia<br>subjects affected / exposed<br>occurrences (all)                                                   | 0 / 5 (0.00%)<br>0  | 4 / 30 (13.33%)<br>6 |  |
| Muscle spasms<br>subjects affected / exposed<br>occurrences (all)                                                | 0 / 5 (0.00%)<br>0  | 3 / 30 (10.00%)<br>4 |  |
| Flank pain<br>subjects affected / exposed<br>occurrences (all)                                                   | 1 / 5 (20.00%)<br>1 | 1 / 30 (3.33%)<br>1  |  |
| Myalgia<br>subjects affected / exposed<br>occurrences (all)                                                      | 1 / 5 (20.00%)<br>1 | 1 / 30 (3.33%)<br>1  |  |
| Osteoarthritis                                                                                                   |                     |                      |  |

|                                   |                |                  |  |
|-----------------------------------|----------------|------------------|--|
| subjects affected / exposed       | 0 / 5 (0.00%)  | 2 / 30 (6.67%)   |  |
| occurrences (all)                 | 0              | 2                |  |
| Pain in extremity                 |                |                  |  |
| subjects affected / exposed       | 0 / 5 (0.00%)  | 2 / 30 (6.67%)   |  |
| occurrences (all)                 | 0              | 2                |  |
| Spinal pain                       |                |                  |  |
| subjects affected / exposed       | 0 / 5 (0.00%)  | 2 / 30 (6.67%)   |  |
| occurrences (all)                 | 0              | 2                |  |
| Groin pain                        |                |                  |  |
| subjects affected / exposed       | 1 / 5 (20.00%) | 0 / 30 (0.00%)   |  |
| occurrences (all)                 | 1              | 0                |  |
| Infections and infestations       |                |                  |  |
| Nasopharyngitis                   |                |                  |  |
| subjects affected / exposed       | 0 / 5 (0.00%)  | 10 / 30 (33.33%) |  |
| occurrences (all)                 | 0              | 19               |  |
| Upper respiratory tract infection |                |                  |  |
| subjects affected / exposed       | 2 / 5 (40.00%) | 7 / 30 (23.33%)  |  |
| occurrences (all)                 | 11             | 9                |  |
| Bronchitis                        |                |                  |  |
| subjects affected / exposed       | 0 / 5 (0.00%)  | 6 / 30 (20.00%)  |  |
| occurrences (all)                 | 0              | 8                |  |
| Sinusitis                         |                |                  |  |
| subjects affected / exposed       | 0 / 5 (0.00%)  | 4 / 30 (13.33%)  |  |
| occurrences (all)                 | 0              | 5                |  |
| Influenza                         |                |                  |  |
| subjects affected / exposed       | 1 / 5 (20.00%) | 2 / 30 (6.67%)   |  |
| occurrences (all)                 | 1              | 2                |  |
| Pneumonia                         |                |                  |  |
| subjects affected / exposed       | 0 / 5 (0.00%)  | 3 / 30 (10.00%)  |  |
| occurrences (all)                 | 0              | 4                |  |
| Urinary tract infection           |                |                  |  |
| subjects affected / exposed       | 0 / 5 (0.00%)  | 3 / 30 (10.00%)  |  |
| occurrences (all)                 | 0              | 4                |  |
| Conjunctivitis                    |                |                  |  |
| subjects affected / exposed       | 0 / 5 (0.00%)  | 2 / 30 (6.67%)   |  |
| occurrences (all)                 | 0              | 2                |  |

|                                        |                |                |  |
|----------------------------------------|----------------|----------------|--|
| Cystitis                               |                |                |  |
| subjects affected / exposed            | 0 / 5 (0.00%)  | 2 / 30 (6.67%) |  |
| occurrences (all)                      | 0              | 2              |  |
| Cytomegalovirus infection              |                |                |  |
| subjects affected / exposed            | 0 / 5 (0.00%)  | 2 / 30 (6.67%) |  |
| occurrences (all)                      | 0              | 2              |  |
| Cytomegalovirus infection reactivation |                |                |  |
| subjects affected / exposed            | 0 / 5 (0.00%)  | 2 / 30 (6.67%) |  |
| occurrences (all)                      | 0              | 2              |  |
| Febrile infection                      |                |                |  |
| subjects affected / exposed            | 1 / 5 (20.00%) | 1 / 30 (3.33%) |  |
| occurrences (all)                      | 1              | 1              |  |
| Fungal infection                       |                |                |  |
| subjects affected / exposed            | 0 / 5 (0.00%)  | 2 / 30 (6.67%) |  |
| occurrences (all)                      | 0              | 2              |  |
| Herpes virus infection                 |                |                |  |
| subjects affected / exposed            | 0 / 5 (0.00%)  | 2 / 30 (6.67%) |  |
| occurrences (all)                      | 0              | 7              |  |
| Herpes zoster                          |                |                |  |
| subjects affected / exposed            | 1 / 5 (20.00%) | 0 / 30 (0.00%) |  |
| occurrences (all)                      | 1              | 0              |  |
| Oral pustule                           |                |                |  |
| subjects affected / exposed            | 1 / 5 (20.00%) | 0 / 30 (0.00%) |  |
| occurrences (all)                      | 1              | 0              |  |
| Metabolism and nutrition disorders     |                |                |  |
| Decreased appetite                     |                |                |  |
| subjects affected / exposed            | 0 / 5 (0.00%)  | 2 / 30 (6.67%) |  |
| occurrences (all)                      | 0              | 3              |  |
| Hyperkalaemia                          |                |                |  |
| subjects affected / exposed            | 0 / 5 (0.00%)  | 2 / 30 (6.67%) |  |
| occurrences (all)                      | 0              | 4              |  |
| Hyperuricaemia                         |                |                |  |
| subjects affected / exposed            | 1 / 5 (20.00%) | 0 / 30 (0.00%) |  |
| occurrences (all)                      | 1              | 0              |  |



## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date              | Amendment                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
|-------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 16 August 2016    | <ul style="list-style-type: none"><li>• Update to benefit-risk assessment to include data on adverse events (AEs) that occurred in the idelalisib + obinutuzumab treatment arm of Study GS-US-312-0118</li><li>• Update to dose rationale for the combination treatment</li><li>• Addition of weekly clinic visits and lab monitoring for the first 28 days of treatment</li><li>• Inclusion of statement specifying that results from the safety cohort was provided to BfArM</li><li>• Specification of safety monitoring throughout the duration of the study</li><li>• Clarification that restaging radiologic evaluation was limited to affected areas identified at the time of the screening evaluation</li><li>• Inclusion of statement that imaging assessments are in accordance with European Society for Medical Oncology (ESMO) guidelines</li><li>• Update to instructions for safety reporting to clarify that serious adverse events (SAEs), regardless of cause or relationship, was reported from the time of informed consent throughout the duration of the trial, which is inclusive of the post-treatment period</li></ul>                                                                                                                                                                                                                                                                                    |
| 16 September 2016 | <ul style="list-style-type: none"><li>• Replaced idelalisib 50 mg twice daily (BID) with 100 mg once daily dosing regimen and updated the dose rationale language accordingly</li><li>• Added requirement for evaluation for gastrointestinal events/colitis in alignment with updated idelalisib safety information</li><li>• Revised dose adjustment guidelines and requirements in alignment with updated idelalisib safety information</li></ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| 24 August 2017    | <ul style="list-style-type: none"><li>• Further enrollment into Arm A was discontinued. All additional participants were enrolled to Arm B. A total of approximately 6 participants were enrolled in Arm A and 30 participants in Arm B, thus the total sample size for the study was reduced from 60 participants to approximately 36 participants</li><li>• The requirement for a bone marrow biopsy at Week 25 was limited to participants who otherwise would meet criteria for a CR or complete remission with incomplete bone marrow recovery (CRi). For participants without radiographic evidence of disease at screening, a bone marrow biopsy including aspirate was required at screening. In the presence of systemic disease, the bone marrow result was only critical for assessing a complete remission or progressive disease per International Workshop on Chronic Lymphocytic Leukemia (IWCLL) 2008 guidelines. As bone marrow evaluation in the case of progressive disease was performed only when clinical progression was suspected, the scheduled bone marrow assessment was only necessary to evaluate patients who did not have a radiographically evident change in disease assessment. This change did not preclude investigator assessment of disease response per IWCLL 2008 criteria and should decrease the burden of bone marrow biopsies to the overall cohort of participants enrolled.</li></ul> |
| 15 January 2019   | <ul style="list-style-type: none"><li>• The post treatment follow up period was removed. All subjects completed the study at the End of Treatment visit, or at the Week 25 visit, should treatment have discontinued prior to Week 25</li><li>• Based on ongoing study data that indicate minimal residual disease (MRD) negativity may be achieved post Week 25, additional exploratory endpoints were added to allow for analysis at later time points</li></ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| 19 November 2019  | <ul style="list-style-type: none"><li>• The risk of progressive multifocal leukoencephalopathy was added as discontinuation and dose interruption criteria</li></ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| 28 May 2020       | <ul style="list-style-type: none"><li>• The risk of Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) was added as per Company Core Data Sheet (CCDS), the Idealisib IB edition 21 dated 02-Apr-2020 was updated to reflect this new information</li></ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |



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Notes:

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### **Interruptions (globally)**

Were there any global interruptions to the trial? No

### **Limitations and caveats**

None reported