



Clinical trial results: Dose Optimization Study of Idelalisib in Follicular Lymphoma Summary

| | |
|--------------------------|-------------------|
| EudraCT number | 2015-000366-66 |
| Trial protocol | GB CZ PL ES FR IT |
| Global end of trial date | 27 September 2022 |

Results information

| | |
|--------------------------------|--------------|
| Result version number | v1 |
| This version publication date | 16 July 2023 |
| First version publication date | 16 July 2023 |

Trial information

Trial identification

| | |
|-----------------------|----------------|
| Sponsor protocol code | GS-US-313-1580 |
|-----------------------|----------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02536300 |
| 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 | 27 September 2022 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 27 September 2022 |
| Was the trial ended prematurely? | Yes |

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to establish a safe and effective dosing regimen of idelalisib in participants with relapsed or refractory follicular lymphoma (FL) who have no other therapeutic options.

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 | 14 January 2016 |
| Long term follow-up planned | Yes |
| Long term follow-up rationale | Safety, Efficacy |
| Long term follow-up duration | 5 Years |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | Australia: 2 |
| Country: Number of subjects enrolled | Canada: 1 |
| Country: Number of subjects enrolled | Czechia: 8 |
| Country: Number of subjects enrolled | France: 9 |
| Country: Number of subjects enrolled | Israel: 4 |
| Country: Number of subjects enrolled | Italy: 19 |
| Country: Number of subjects enrolled | Poland: 19 |
| Country: Number of subjects enrolled | Romania: 1 |
| Country: Number of subjects enrolled | Spain: 18 |
| Country: Number of subjects enrolled | United Kingdom: 15 |
| Worldwide total number of subjects | 96 |
| EEA total number of subjects | 74 |

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) | 45 |
| From 65 to 84 years | 48 |
| 85 years and over | 3 |

Subject disposition

Recruitment

Recruitment details:

Participants were enrolled at study sites in Australia, Canada, Europe, Israel, and the United Kingdom.

Pre-assignment

Screening details:

145 participants were screened.

Period 1

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

Blinding implementation details:

Double-blind: Prior to protocol amendment 5; Open-label: Participants enrolled as of protocol amendment 5

Arms

| | |
|------------------------------|-----------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Idelalisib 150 mg BID |

Arm description:

Participants received idelalisib 150 mg tablets, orally, twice daily (BID), continuously for up to maximum 33.5 months.

| | |
|----------------------------------------|----------------------------|
| 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:

Administered 150 mg, BID, continuously.

| | |
|------------------|-----------------------|
| Arm title | Idelalisib 100 mg BID |
|------------------|-----------------------|

Arm description:

Participants received idelalisib 100 mg tablets, orally, BID, continuously for up to maximum 63.6 months.

| | |
|----------------------------------------|----------------------------|
| 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:

Administered 100 mg, BID, continuously.

| | |
|------------------|---------------------------|
| Arm title | Idelalisib 150 mg BID INT |
|------------------|---------------------------|

Arm description:

Participants received idelalisib 150 mg tablets, orally, BID for 21 days and 7 days off-treatment (intermittent [INT] dosing schedule) in each 28-day cycle for up to maximum of 24.6 months.

| | |
|----------|--------------|
| 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:

Administered 150 mg, BID for 21 days and 7 days off-treatment (INT dosing schedule) in each 28-day cycle.

| Number of subjects in period 1 | Idelalisib 150 mg BID | Idelalisib 100 mg BID | Idelalisib 150 mg BID INT |
|------------------------------------------------------|----------------------------------|----------------------------------|--------------------------------------|
| Started | 47 | 27 | 22 |
| Completed | 0 | 0 | 0 |
| Not completed | 47 | 27 | 22 |
| Consent withdrawn by subject | 4 | 2 | - |
| Protocol violation | - | 1 | - |
| Non-compliance With Study Drug | 1 | - | - |
| Death | 7 | - | 5 |
| Investigator's Discretion | 17 | 11 | 2 |
| Progressive Disease | 11 | 7 | 6 |
| Study Terminated by Sponsor | 6 | 4 | 7 |
| Non-study Specific Anti-cancer Therapy Initiation | 1 | 2 | 1 |
| Enrolled but Never Treated | - | - | 1 |

Baseline characteristics

Reporting groups

| | |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------|
| Reporting group title | Idelalisib 150 mg BID |
| Reporting group description: | |
| Participants received idelalisib 150 mg tablets, orally, twice daily (BID), continuously for up to maximum 33.5 months. | |
| Reporting group title | Idelalisib 100 mg BID |
| Reporting group description: | |
| Participants received idelalisib 100 mg tablets, orally, BID, continuously for up to maximum 63.6 months. | |
| Reporting group title | Idelalisib 150 mg BID INT |
| Reporting group description: | |
| Participants received idelalisib 150 mg tablets, orally, BID for 21 days and 7 days off-treatment (intermittent [INT] dosing schedule) in each 28-day cycle for up to maximum of 24.6 months. | |

| Reporting group values | Idelalisib 150 mg BID | Idelalisib 100 mg BID | Idelalisib 150 mg BID INT |
|------------------------------------|-----------------------|-----------------------|---------------------------|
| Number of subjects | 47 | 27 | 22 |
| Age categorical Units: Subjects | | | |

| | | | |
|-------------------------------------------------------------------------|--------------|--------------|--------------|
| Age continuous Units: years arithmetic mean standard deviation | 65 ± 13.0 | 62 ± 13.6 | 63 ± 11.6 |
| Gender categorical Units: Subjects | | | |
| Female | 23 | 13 | 9 |
| Male | 24 | 14 | 13 |
| Race Units: Subjects | | | |
| White | 42 | 25 | 19 |
| Asian | 1 | 0 | 0 |
| Black or African American | 0 | 0 | 1 |
| Unknown or Not Reported | 4 | 1 | 2 |
| Other or More Than One Race | 0 | 1 | 0 |
| Ethnicity Units: Subjects | | | |
| Hispanic or Latino | 1 | 0 | 2 |
| Not Hispanic or Latino | 42 | 26 | 18 |
| Unknown or Not Reported | 4 | 1 | 2 |

| Reporting group values | Total | | |
|------------------------------------|-------|--|--|
| Number of subjects | 96 | | |
| Age categorical Units: Subjects | | | |

| | | | |
|-------------------------------------------------------------------------|----|--|--|
| Age continuous Units: years arithmetic mean standard deviation | - | | |
| Gender categorical Units: Subjects | | | |
| Female | 45 | | |
| Male | 51 | | |
| Race Units: Subjects | | | |
| White | 86 | | |
| Asian | 1 | | |
| Black or African American | 1 | | |
| Unknown or Not Reported | 7 | | |
| Other or More Than One Race | 1 | | |
| Ethnicity Units: Subjects | | | |
| Hispanic or Latino | 3 | | |
| Not Hispanic or Latino | 86 | | |
| Unknown or Not Reported | 7 | | |

End points

End points reporting groups

| | |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------|
| Reporting group title | Idelalisib 150 mg BID |
| Reporting group description: Participants received idelalisib 150 mg tablets, orally, twice daily (BID), continuously for up to maximum 33.5 months. | |
| Reporting group title | Idelalisib 100 mg BID |
| Reporting group description: Participants received idelalisib 100 mg tablets, orally, BID, continuously for up to maximum 63.6 months. | |
| Reporting group title | Idelalisib 150 mg BID INT |
| Reporting group description: Participants received idelalisib 150 mg tablets, orally, BID for 21 days and 7 days off-treatment (intermittent [INT] dosing schedule) in each 28-day cycle for up to maximum of 24.6 months. | |

Primary: Overall Response Rate (ORR)

| | |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------|
| End point title | Overall Response Rate (ORR) ^[1] |
| End point description: ORR=percentage of participants who achieve a partial response (PR)/ complete response (CR).PR criteria: No evidence of new disease,a ≥50% decrease from baseline in sum of products of diameters (SPD) of index lesions,no increase in non-index disease, liver/spleen size and no new liver/spleen enlargement.Persistence of bone marrow involvement in participant who meets other CR criteria based on disappearance of all nodal,extra-nodal masses.CR criteria:No evidence of new disease,regression of all index nodal lesions to normal size (≤1.5 cm in longest dimension (LD) for large nodes and ≤1.0 cm in LD,≤1.0 cm in longest perpendicular dimension (LPD) for small nodes),regression to normal of all nodal non-index disease,disappearance of all detectable extra-nodal index,non-index disease,normal spleen, liver size,no new liver/spleen enlargement,morphologically -ve bone marrow. Intent-to-Treat (ITT) analysis set=all participants who were randomized regardless of whether they received any drug. | |
| End point type | Primary |
| End point timeframe: Randomization up to end of treatment (maximum duration: 73.5 months) | |

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 | Idelalisib 150 mg BID | Idelalisib 100 mg BID | Idelalisib 150 mg BID INT | |
|-----------------------------------|-----------------------|-----------------------|---------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 47 | 27 | 22 | |
| Units: percentage of participants | | | | |
| number (confidence interval 95%) | 38.3 (24.5 to 53.6) | 44.4 (25.5 to 64.7) | 40.9 (20.7 to 63.6) | |

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants With Grade 4 or Higher Treatment-Emergent

Adverse Events (TEAEs)

| | |
|-----------------|--------------------------------------------------------------------------------------------------------|
| End point title | Number of Participants With Grade 4 or Higher Treatment-Emergent Adverse Events (TEAEs) ^[2] |
|-----------------|--------------------------------------------------------------------------------------------------------|

End point description:

TEAEs were defined as 1 or both of any AEs leading to premature discontinuation of study drug, or any AEs with an onset date on or after the study drug start date and no later than the last exposure date after permanent discontinuation of the study drug. TEAEs severity was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 5.0. Grade 1: Mild; Grade 2: Moderate; Grade 3: Severe; Grade 4: Life-threatening; Grade 5: Fatal. Participants were counted at the highest AE grade experienced. Safety analysis set included all participants who received at least 1 dose of study drug.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

First dose date up to 30 days after last dose of study drug (maximum 64.6 months)

Notes:

[2] - 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 | Idelalisib 150 mg BID | Idelalisib 100 mg BID | Idelalisib 150 mg BID INT | |
|-----------------------------|-----------------------|-----------------------|---------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 47 | 27 | 21 | |
| Units: participants | 15 | 12 | 8 | |

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Response Rate (ORR) by Week 24

| | |
|-----------------|----------------------------------------|
| End point title | Overall Response Rate (ORR) by Week 24 |
|-----------------|----------------------------------------|

End point description:

ORR by Week 24 is defined as the percentage of participants who achieve a PR or CR by Week 24. PR criteria: No evidence of new disease, a 50% decrease from baseline in SPD of index lesions, no increase in non-index disease, no increase in liver/spleen size and no new liver/spleen enlargement. CR criteria: No evidence of new disease, regression of all index nodal lesions to normal size (≤ 1.5 cm in LD for large nodes and ≤ 1.0 cm in LD, ≤ 1.0 cm in LPD for small nodes), regression to normal of all nodal non-index disease, disappearance of all detectable extra-nodal index and non-index disease, normal spleen and liver size, no new liver/spleen enlargement, morphologically negative bone marrow. Participants in the ITT analysis set were analysed.

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

End point timeframe:

First dose date up to Week 24

| End point values | Idelalisib 150 mg BID | Idelalisib 100 mg BID | Idelalisib 150 mg BID INT | |
|-----------------------------------|-----------------------|-----------------------|---------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 47 | 27 | 22 | |
| Units: percentage of participants | | | | |
| number (confidence interval 95%) | 36.2 (22.7 to 51.5) | 33.3 (16.5 to 54.0) | 27.3 (10.7 to 50.2) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DOR)

| | |
|-----------------|----------------------------|
| End point title | Duration of Response (DOR) |
|-----------------|----------------------------|

End point description:

DOR: interval from first documentation of CR/PR to earlier of first documentation of disease progression (PD) by independent review committee (IRC)/death from any cause. PR and CR criteria: Please refer the description of endpoint#2 (ORR). PD: New node of >1.5 cm or >1.0 to ≤1.5 cm in LD, >1.0 cm in LPD, new/unequivocal reappearance of resolved extra-nodal lesion, new non-index disease, increase by 50% in SPD of index lesions, LD of individual node/extra-nodal mass. Participants in the ITT analysis set who achieved CR or PR were analysed. 9999=The upper limit of 95% confidence interval (CI) was not estimable as the values were not reached.

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

End point timeframe:

From first documentation of CR or PR until PD or death from any cause (maximum duration: 73.5 months)

| End point values | Idelalisib 150 mg BID | Idelalisib 100 mg BID | Idelalisib 150 mg BID INT | |
|----------------------------------|-----------------------|-----------------------|---------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 18 | 12 | 9 | |
| Units: months | | | | |
| median (confidence interval 95%) | 27.1 (7.7 to 9999) | 18.0 (2.7 to 9999) | 5.7 (0.3 to 9999) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With any TEAE, Grade 3 or Higher TEAEs, Serious TEAEs, Idelalisib-related TEAEs, TEAEs Leading to Interruption or Discontinuation of Idelalisib

| | |
|-----------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Number of Participants With any TEAE, Grade 3 or Higher TEAEs, Serious TEAEs, Idelalisib-related TEAEs, TEAEs Leading to Interruption or Discontinuation of Idelalisib |
|-----------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

End point description:

TEAEs were defined as 1 or both of any AEs leading to premature discontinuation of study drug, or any AEs with an onset date on or after the study drug start date and no later than the last exposure date after permanent discontinuation of the study drug. TEAEs severity was graded according to the NCI CTCAE version 5.0. Grade 1: Mild; Grade 2: Moderate; Grade 3: Severe; Grade 4: Life-threatening; Grade 5: Fatal. Participants are counted at the highest AE grade experienced. Participants in the safety analysis set were analysed.

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

End point timeframe:

First dose date up to 30 days after last dose of study drug (maximum 64.6 months)

| End point values | Idelalisib 150 mg BID | Idelalisib 100 mg BID | Idelalisib 150 mg BID INT | |
|------------------------------------------------|-----------------------|-----------------------|---------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 47 | 27 | 21 | |
| Units: participants | | | | |
| Any TEAE | 45 | 26 | 19 | |
| Grade 3 or Higher TEAEs | 41 | 25 | 12 | |
| Serious TEAEs | 31 | 19 | 11 | |
| Idelalisib-related TEAEs | 38 | 25 | 11 | |
| TEAEs Leading to Interruption of Idelalisib | 32 | 18 | 6 | |
| TEAEs Leading to Discontinuation of Idelalisib | 28 | 13 | 4 | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Clinically Significant Treatment-Emergent Laboratory Abnormalities

| | |
|-----------------|------------------------------------------------------------------------------------------------|
| End point title | Number of Participants With Clinically Significant Treatment-Emergent Laboratory Abnormalities |
|-----------------|------------------------------------------------------------------------------------------------|

End point description:

Treatment-emergent laboratory abnormality was defined as an increase of at least 1 toxicity grade from baseline at any time postbaseline up to and including the date of last study drug dose plus 30 days. Laboratory abnormalities included hematology and serum chemistry parameters. Clinically significant laboratory abnormalities were graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 for severity as Grade 1 (mild), Grade 2 (moderate), Grade 3 (severe), or Grade 4 (life threatening). The number of participants with any post-baseline abnormal laboratory value in Grade 1-4 categories are reported. Participants in the safety analysis set with available data were analysed.

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

End point timeframe:

First dose date up to 30 days after last dose of study drug (maximum 64.6 months)

| End point values | Idelalisib 150 mg BID | Idelalisib 100 mg BID | Idelalisib 150 mg BID INT | |
|-------------------------------------|-----------------------|-----------------------|---------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 47 | 27 | 20 | |
| Units: participants | | | | |
| Hematology: Grade 1 | 7 | 5 | 2 | |
| Hematology: Grade 2 | 12 | 7 | 5 | |
| Hematology: Grade 3 | 15 | 11 | 5 | |
| Hematology: Grade 4 | 6 | 3 | 2 | |
| Serum Chemistry: Grade 1 N=47,27,19 | 9 | 5 | 8 | |

| | | | | |
|-------------------------------------|----|----|---|--|
| Serum Chemistry: Grade 2 N=47,27,19 | 17 | 8 | 4 | |
| Serum Chemistry: Grade 3 N=47,27,19 | 10 | 11 | 6 | |
| Serum Chemistry: Grade 4 N=47,27,19 | 7 | 3 | 1 | |

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-Free Survival (PFS)

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|-----------------|---------------------------------|
| End point title | Progression-Free Survival (PFS) |
|-----------------|---------------------------------|

End point description:

PFS is defined as the interval (in months) from randomization to the earlier of the first documentation of PD by IRC or death from any cause. PD criteria: New node of >1.5 cm or >1.0 cm to ≤1.5 cm in LD, >1.0 cm in LPD, new/unequivocal reappearance of resolved extra-nodal lesion, new non-index disease, increase by 50% in SPD of index lesions, LD of individual node/extra-nodal mass. Participants in the ITT analysis set were analysed.

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

End point timeframe:

Randomization up to PD or death from any cause (maximum duration: 73.5 months)

| End point values | Idelalisib 150 mg BID | Idelalisib 100 mg BID | Idelalisib 150 mg BID INT | |
|----------------------------------|-----------------------|-----------------------|---------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 47 | 27 | 22 | |
| Units: months | | | | |
| median (confidence interval 95%) | 9.8 (5.5 to 28.7) | 19.4 (13.9 to 23.3) | 8.3 (2.9 to 8.7) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS)

| | |
|-----------------|-----------------------|
| End point title | Overall Survival (OS) |
|-----------------|-----------------------|

End point description:

OS is defined as the interval (in months) from randomization to death from any cause. Participants in the ITT analysis set were analysed. 9999=The upper limit of 95% CI was not estimable as the values were not reached. 99999=Median and upper limit of 95% CI were not estimable as the values were not reached.

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

End point timeframe:

Randomization up to death from any cause (maximum duration: 73.5 months)

| End point values | Idelalisib 150 mg BID | Idelalisib 100 mg BID | Idelalisib 150 mg BID INT | |
|----------------------------------|-----------------------|-----------------------|---------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 47 | 27 | 22 | |
| Units: months | | | | |
| median (confidence interval 95%) | 28.7 (14.0 to 9999) | 99999 (23.3 to 99999) | 99999 (13.9 to 99999) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Trough Plasma Concentration of Idelalisib

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|-----------------|-------------------------------------------|
| End point title | Trough Plasma Concentration of Idelalisib |
|-----------------|-------------------------------------------|

End point description:

Pharmacokinetic (PK) analysis set included participants who received at least 1 dose of study drug and had at least 1 sample with detectable drug concentration. Participants in the PK analysis set with available data were analysed. 9999=Mean and Standard Deviation (SD) were not available as the values were below the level of quantitation.

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

End point timeframe:

Predose on Day (D) 1, Weeks (Wk) 2, 4, 6, 8, 10, 12, 16, 20, 24, 32, and 48

| End point values | Idelalisib 150 mg BID | Idelalisib 100 mg BID | Idelalisib 150 mg BID INT | |
|-----------------------------------------|-----------------------|-----------------------|---------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 44 | 27 | 21 | |
| Units: nanograms per millilitre (ng/ml) | | | | |
| arithmetic mean (standard deviation) | | | | |
| D 1 N=43,27,21 | 9999 (± 9999) | 9999 (± 9999) | 9999 (± 9999) | |
| Wk 2 N=44,25,17 | 683.68 (± 514.166) | 382.94 (± 352.842) | 636.35 (± 461.042) | |
| Wk 4 N=38,23,18 | 623.64 (± 466.557) | 447.78 (± 356.971) | 94.14 (± 231.647) | |
| Wk 6 N=34,23,15 | 581.20 (± 470.988) | 361.90 (± 248.996) | 596.80 (± 401.619) | |
| Wk 8 N=32,21,14 | 655.16 (± 498.873) | 430.33 (± 477.877) | 77.66 (± 274.313) | |
| Wk 10 N=25,22,15 | 616.05 (± 370.862) | 356.12 (± 372.557) | 387.40 (± 314.249) | |
| Wk 12 N=27,21,16 | 630.56 (± 664.066) | 389.21 (± 466.104) | 272.44 (± 626.451) | |
| Wk 16 N=26,20,15 | 729.23 (± 832.158) | 730.29 (± 936.798) | 111.67 (± 296.666) | |
| Wk 20 N=22,19,14 | 525.91 (± 411.330) | 745.58 (± 841.105) | 107.34 (± 269.434) | |
| Wk 24 N=19,17,12 | 460.74 (± 321.766) | 728.76 (± 760.391) | 9999 (± 9999) | |
| Wk 32 N=16,11,11 | 446.13 (± 450.821) | 388.58 (± 351.293) | 352.73 (± 875.923) | |
| Wk 48 N=8,8,5 | 706.13 (± 580.022) | 552.13 (± 571.081) | 165.00 (± 368.951) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Peak Plasma Concentration of Idelalisib

| | |
|-----------------|-----------------------------------------|
| End point title | Peak Plasma Concentration of Idelalisib |
|-----------------|-----------------------------------------|

End point description:

Participants in the PK analysis set with available data were analysed.

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

End point timeframe:

1.5 hours postdose on Day (D) 1, Weeks (Wk) 2, 4, 6, 8, 10, 12, 16, 20, 24, 32, and 48

| End point values | Idelalisib 150 mg BID | Idelalisib 100 mg BID | Idelalisib 150 mg BID INT | |
|--------------------------------------|-----------------------|-----------------------|---------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 43 | 27 | 20 | |
| Units: ng/ml | | | | |
| arithmetic mean (standard deviation) | | | | |
| D 1 | 2626.12 (± 1330.290) | 1575.81 (± 803.317) | 2221.35 (± 1621.291) | |
| Wk 2 N=42,24,18 | 2306.12 (± 810.433) | 1520.29 (± 675.089) | 2186.89 (± 1265.850) | |
| Wk 4 N=39,23,17 | 2353.95 (± 930.754) | 1528.48 (± 759.936) | 2608.12 (± 1009.937) | |
| Wk 6 N=30,21,15 | 2433.33 (± 1092.969) | 1682.52 (± 939.455) | 2341.33 (± 948.133) | |
| Wk 8 N=29,20,14 | 2207.59 (± 980.606) | 1649.25 (± 940.683) | 2786.43 (± 1591.408) | |
| Wk 10 N=24,19,15 | 2435.00 (± 1027.469) | 1601.11 (± 804.605) | 2380.00 (± 1118.679) | |
| Wk 12 N=24,19,15 | 2328.13 (± 1141.764) | 1658.89 (± 837.159) | 2316.20 (± 1391.815) | |
| Wk 16 N=23,20,12 | 2634.39 (± 1323.611) | 1756.37 (± 826.784) | 2372.50 (± 1335.420) | |
| Wk 20 N=19,17,13 | 2354.26 (± 1440.587) | 1925.29 (± 776.516) | 2177.69 (± 1417.505) | |
| Wk 24 N=15,17,10 | 2058.47 (± 905.071) | 1914.65 (± 1151.998) | 1906.30 (± 1099.458) | |
| Wk 32 N=14,10,10 | 2009.71 (± 1231.296) | 2028.00 (± 593.236) | 1825.00 (± 947.892) | |
| Wk 48 N=8,9,5 | 2655.13 (± 1348.957) | 1448.33 (± 650.798) | 1312.00 (± 850.894) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Onset of Adverse Events of Interest (AEIs)

| | |
|-----------------|----------------------------------------------------|
| End point title | Time to Onset of Adverse Events of Interest (AEIs) |
|-----------------|----------------------------------------------------|

End point description:

Time to onset of AEIs is defined as the interval (in months) from the start of idelalisib treatment to the first documentation of start of AEI. AEIs included grade ≥ 3 diarrhea/colitis, rash, febrile neutropenia, infection, and any grade of: Pneumonitis, bowel perforation, progressive multifocal leukoencephalopathy (PML), Pneumocystis jirovecii pneumonia (PJP), cytomegalovirus (CMV) infection, and organizing pneumonia.

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

End point timeframe:

First dose date up to 30 days after last dose of study drug (maximum 64.6 months)

| End point values | Idelalisib 150 mg BID | Idelalisib 100 mg BID | Idelalisib 150 mg BID INT | |
|---------------------------------------|-----------------------|-----------------------|---------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 0 ^[3] | 0 ^[4] | 0 ^[5] | |
| Units: months | | | | |
| median (inter-quartile range (Q1-Q3)) | (to) | (to) | (to) | |

Notes:

[3] - AEIs data was not collected for analysis.

[4] - AEIs data was not collected for analysis.

[5] - AEIs data was not collected for analysis.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All-Cause Mortality: Enrollment up to last follow up visit (maximum 73.5 months); Adverse Events: First dose date up to 30 days after last dose of study drug (maximum 64.6 months)

Adverse event reporting additional description:

All-Cause Mortality: All enrolled analysis set included all participants who received a study participant identification number after screening and was used for participant enrollment summary and data listings, unless otherwise specified.

Adverse Events: Safety analysis set included all participants who received at least 1 dose of study drug.

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

Dictionary used

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

| | |
|--------------------|----|
| Dictionary version | 25 |
|--------------------|----|

Reporting groups

| | |
|-----------------------|-----------------------|
| Reporting group title | Idelalisib 150 mg BID |
|-----------------------|-----------------------|

Reporting group description:

Participants received idelalisib 150 mg tablets, orally, BID, continuously for up to maximum 33.5 months.

| | |
|-----------------------|---------------------------|
| Reporting group title | Idelalisib 150 mg BID INT |
|-----------------------|---------------------------|

Reporting group description:

Participants received idelalisib 150 mg tablets, orally, BID for 21 days and 7 days off-treatment (INT dosing schedule) in each 28-day cycle for up to maximum of 24.6 months.

| | |
|-----------------------|-----------------------|
| Reporting group title | Idelalisib 100 mg BID |
|-----------------------|-----------------------|

Reporting group description:

Participants received idelalisib 100 mg tablets, orally, BID, continuously for up to maximum 63.6 months.

| Serious adverse events | Idelalisib 150 mg BID | Idelalisib 150 mg BID INT | Idelalisib 100 mg BID |
|---------------------------------------------------------------------|-----------------------|---------------------------|-----------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 31 / 47 (65.96%) | 11 / 21 (52.38%) | 19 / 27 (70.37%) |
| number of deaths (all causes) | 20 | 6 | 12 |
| number of deaths resulting from adverse events | | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Cancer pain | | | |
| subjects affected / exposed | 1 / 47 (2.13%) | 0 / 21 (0.00%) | 0 / 27 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Acute myeloid leukaemia | | | |
| subjects affected / exposed | 0 / 47 (0.00%) | 0 / 21 (0.00%) | 1 / 27 (3.70%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |

| | | | |
|------------------------------------------------------|----------------|----------------|----------------|
| Vascular disorders | | | |
| Hypotension | | | |
| subjects affected / exposed | 1 / 47 (2.13%) | 0 / 21 (0.00%) | 0 / 27 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General disorders and administration site conditions | | | |
| Generalised oedema | | | |
| subjects affected / exposed | 0 / 47 (0.00%) | 0 / 21 (0.00%) | 1 / 27 (3.70%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pyrexia | | | |
| subjects affected / exposed | 1 / 47 (2.13%) | 1 / 21 (4.76%) | 0 / 27 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Facial pain | | | |
| subjects affected / exposed | 1 / 47 (2.13%) | 0 / 21 (0.00%) | 0 / 27 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Immune system disorders | | | |
| Drug hypersensitivity | | | |
| subjects affected / exposed | 1 / 47 (2.13%) | 0 / 21 (0.00%) | 0 / 27 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Dyspnoea | | | |
| subjects affected / exposed | 1 / 47 (2.13%) | 0 / 21 (0.00%) | 0 / 27 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lung disorder | | | |
| subjects affected / exposed | 0 / 47 (0.00%) | 0 / 21 (0.00%) | 1 / 27 (3.70%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pleural effusion | | | |

| | | | |
|-------------------------------------------------|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 47 (0.00%) | 1 / 21 (4.76%) | 0 / 27 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Pneumonitis | | | |
| subjects affected / exposed | 1 / 47 (2.13%) | 0 / 21 (0.00%) | 0 / 27 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 0 / 47 (0.00%) | 0 / 21 (0.00%) | 1 / 27 (3.70%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| International normalised ratio ~ increased | | | |
| subjects affected / exposed | 0 / 47 (0.00%) | 0 / 21 (0.00%) | 1 / 27 (3.70%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General physical condition abnormal | | | |
| subjects affected / exposed | 1 / 47 (2.13%) | 0 / 21 (0.00%) | 0 / 27 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Klebsiella test positive | | | |
| subjects affected / exposed | 0 / 47 (0.00%) | 0 / 21 (0.00%) | 1 / 27 (3.70%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Injury, poisoning and procedural complications | | | |
| Pelvic fracture | | | |
| subjects affected / exposed | 0 / 47 (0.00%) | 0 / 21 (0.00%) | 1 / 27 (3.70%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Fall | | | |
| subjects affected / exposed | 0 / 47 (0.00%) | 0 / 21 (0.00%) | 1 / 27 (3.70%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|-------------------------------------------------|----------------|----------------|----------------|
| Cardiac disorders | | | |
| Atrial flutter | | | |
| subjects affected / exposed | 1 / 47 (2.13%) | 0 / 21 (0.00%) | 0 / 27 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nervous system disorders | | | |
| Cerebrovascular accident | | | |
| subjects affected / exposed | 1 / 47 (2.13%) | 1 / 21 (4.76%) | 0 / 27 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cerebral ischaemia | | | |
| subjects affected / exposed | 0 / 47 (0.00%) | 1 / 21 (4.76%) | 0 / 27 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood and lymphatic system disorders | | | |
| Thrombocytopenia | | | |
| subjects affected / exposed | 1 / 47 (2.13%) | 0 / 21 (0.00%) | 0 / 27 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Febrile neutropenia | | | |
| subjects affected / exposed | 1 / 47 (2.13%) | 0 / 21 (0.00%) | 2 / 27 (7.41%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 2 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Anaemia | | | |
| subjects affected / exposed | 2 / 47 (4.26%) | 1 / 21 (4.76%) | 0 / 27 (0.00%) |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Eye disorders | | | |
| Visual field defect | | | |
| subjects affected / exposed | 1 / 47 (2.13%) | 0 / 21 (0.00%) | 0 / 27 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Diarrhoea | | | |

| | | | |
|-------------------------------------------------|-----------------|----------------|-----------------|
| subjects affected / exposed | 7 / 47 (14.89%) | 0 / 21 (0.00%) | 6 / 27 (22.22%) |
| occurrences causally related to treatment / all | 7 / 7 | 0 / 0 | 7 / 9 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Colitis | | | |
| subjects affected / exposed | 3 / 47 (6.38%) | 0 / 21 (0.00%) | 0 / 27 (0.00%) |
| occurrences causally related to treatment / all | 4 / 4 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatobiliary disorders | | | |
| Drug-induced liver injury | | | |
| subjects affected / exposed | 1 / 47 (2.13%) | 0 / 21 (0.00%) | 0 / 27 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatotoxicity | | | |
| subjects affected / exposed | 2 / 47 (4.26%) | 0 / 21 (0.00%) | 0 / 27 (0.00%) |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Skin and subcutaneous tissue disorders | | | |
| Rash | | | |
| subjects affected / exposed | 1 / 47 (2.13%) | 1 / 21 (4.76%) | 0 / 27 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Stevens-Johnson syndrome | | | |
| subjects affected / exposed | 1 / 47 (2.13%) | 0 / 21 (0.00%) | 0 / 27 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Rash maculo-papular | | | |
| subjects affected / exposed | 0 / 47 (0.00%) | 0 / 21 (0.00%) | 1 / 27 (3.70%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal and urinary disorders | | | |
| Acute kidney injury | | | |
| subjects affected / exposed | 0 / 47 (0.00%) | 0 / 21 (0.00%) | 4 / 27 (14.81%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 4 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|-------------------------------------------------|----------------|----------------|----------------|
| Haematuria | | | |
| subjects affected / exposed | 1 / 47 (2.13%) | 0 / 21 (0.00%) | 0 / 27 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hydronephrosis | | | |
| subjects affected / exposed | 0 / 47 (0.00%) | 1 / 21 (4.76%) | 0 / 27 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal failure | | | |
| subjects affected / exposed | 1 / 47 (2.13%) | 0 / 21 (0.00%) | 0 / 27 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal impairment | | | |
| subjects affected / exposed | 1 / 47 (2.13%) | 0 / 21 (0.00%) | 0 / 27 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Endocrine disorders | | | |
| Hypercalcaemia of malignancy | | | |
| subjects affected / exposed | 1 / 47 (2.13%) | 0 / 21 (0.00%) | 0 / 27 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Osteonecrosis | | | |
| subjects affected / exposed | 0 / 47 (0.00%) | 0 / 21 (0.00%) | 1 / 27 (3.70%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Mobility decreased | | | |
| subjects affected / exposed | 0 / 47 (0.00%) | 0 / 21 (0.00%) | 1 / 27 (3.70%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Infections and infestations | | | |
| Sepsis | | | |

| | | | |
|-------------------------------------------------|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 47 (0.00%) | 1 / 21 (4.76%) | 1 / 27 (3.70%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Covid-19 pneumonia | | | |
| subjects affected / exposed | 1 / 47 (2.13%) | 1 / 21 (4.76%) | 0 / 27 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Pneumonia | | | |
| subjects affected / exposed | 1 / 47 (2.13%) | 1 / 21 (4.76%) | 2 / 27 (7.41%) |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | 1 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Covid-19 | | | |
| subjects affected / exposed | 1 / 47 (2.13%) | 2 / 21 (9.52%) | 1 / 27 (3.70%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Respiratory tract infection | | | |
| subjects affected / exposed | 1 / 47 (2.13%) | 0 / 21 (0.00%) | 0 / 27 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Abdominal infection | | | |
| subjects affected / exposed | 0 / 47 (0.00%) | 1 / 21 (4.76%) | 0 / 27 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia haemophilus | | | |
| subjects affected / exposed | 1 / 47 (2.13%) | 0 / 21 (0.00%) | 0 / 27 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Aspergillus infection | | | |
| subjects affected / exposed | 1 / 47 (2.13%) | 0 / 21 (0.00%) | 0 / 27 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bronchitis | | | |

| | | | |
|-------------------------------------------------|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 47 (0.00%) | 0 / 21 (0.00%) | 1 / 27 (3.70%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Coronavirus pneumonia | | | |
| subjects affected / exposed | 1 / 47 (2.13%) | 0 / 21 (0.00%) | 0 / 27 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Cytomegalovirus infection | | | |
| subjects affected / exposed | 1 / 47 (2.13%) | 0 / 21 (0.00%) | 0 / 27 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infection | | | |
| subjects affected / exposed | 1 / 47 (2.13%) | 0 / 21 (0.00%) | 0 / 27 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Neutropenic sepsis | | | |
| subjects affected / exposed | 0 / 47 (0.00%) | 1 / 21 (4.76%) | 0 / 27 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| Oesophageal candidiasis | | | |
| subjects affected / exposed | 0 / 47 (0.00%) | 0 / 21 (0.00%) | 1 / 27 (3.70%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia bacterial | | | |
| subjects affected / exposed | 1 / 47 (2.13%) | 0 / 21 (0.00%) | 0 / 27 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Suspected COVID-19 | | | |
| subjects affected / exposed | 0 / 47 (0.00%) | 0 / 21 (0.00%) | 1 / 27 (3.70%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urinary tract infection | | | |

| | | | |
|-------------------------------------------------|----------------|----------------|----------------|
| subjects affected / exposed | 1 / 47 (2.13%) | 0 / 21 (0.00%) | 0 / 27 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metabolism and nutrition disorders | | | |
| Dehydration | | | |
| subjects affected / exposed | 0 / 47 (0.00%) | 0 / 21 (0.00%) | 1 / 27 (3.70%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Decreased appetite | | | |
| subjects affected / exposed | 2 / 47 (4.26%) | 0 / 21 (0.00%) | 0 / 27 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypomagnesaemia | | | |
| subjects affected / exposed | 1 / 47 (2.13%) | 0 / 21 (0.00%) | 0 / 27 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hyperglycaemia | | | |
| subjects affected / exposed | 0 / 47 (0.00%) | 0 / 21 (0.00%) | 1 / 27 (3.70%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

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

| Non-serious adverse events | Idelalisib 150 mg BID | Idelalisib 150 mg BID INT | Idelalisib 100 mg BID |
|-------------------------------------------------------|--------------------------|------------------------------|--------------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 44 / 47 (93.62%) | 16 / 21 (76.19%) | 24 / 27 (88.89%) |
| Investigations | | | |
| Weight decreased | | | |
| subjects affected / exposed | 4 / 47 (8.51%) | 0 / 21 (0.00%) | 3 / 27 (11.11%) |
| occurrences (all) | 4 | 0 | 4 |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 9 / 47 (19.15%) | 0 / 21 (0.00%) | 5 / 27 (18.52%) |
| occurrences (all) | 11 | 0 | 10 |
| Aspartate aminotransferase increased | | | |

| | | | |
|------------------------------------------------------------------------------------------------------------------------|------------------------|----------------------|------------------------|
| subjects affected / exposed occurrences (all) | 8 / 47 (17.02%) 10 | 0 / 21 (0.00%) 0 | 6 / 27 (22.22%) 9 |
| Transaminases increased subjects affected / exposed occurrences (all) | 1 / 47 (2.13%) 1 | 2 / 21 (9.52%) 3 | 0 / 27 (0.00%) 0 |
| Vascular disorders Hypertension subjects affected / exposed occurrences (all) | 5 / 47 (10.64%) 5 | 0 / 21 (0.00%) 0 | 2 / 27 (7.41%) 2 |
| Nervous system disorders Headache subjects affected / exposed occurrences (all) | 3 / 47 (6.38%) 3 | 1 / 21 (4.76%) 1 | 2 / 27 (7.41%) 3 |
| Dizziness subjects affected / exposed occurrences (all) | 0 / 47 (0.00%) 0 | 2 / 21 (9.52%) 2 | 1 / 27 (3.70%) 1 |
| Blood and lymphatic system disorders Thrombocytopenia subjects affected / exposed occurrences (all) | 6 / 47 (12.77%) 7 | 0 / 21 (0.00%) 0 | 3 / 27 (11.11%) 5 |
| Neutropenia subjects affected / exposed occurrences (all) | 12 / 47 (25.53%) 29 | 4 / 21 (19.05%) 9 | 10 / 27 (37.04%) 21 |
| Anaemia subjects affected / exposed occurrences (all) | 10 / 47 (21.28%) 12 | 2 / 21 (9.52%) 4 | 3 / 27 (11.11%) 4 |
| Febrile neutropenia subjects affected / exposed occurrences (all) | 0 / 47 (0.00%) 0 | 0 / 21 (0.00%) 0 | 2 / 27 (7.41%) 2 |
| General disorders and administration site conditions Pyrexia subjects affected / exposed occurrences (all) | 11 / 47 (23.40%) 13 | 3 / 21 (14.29%) 6 | 6 / 27 (22.22%) 6 |
| Asthenia subjects affected / exposed occurrences (all) | 4 / 47 (8.51%) 5 | 3 / 21 (14.29%) 4 | 4 / 27 (14.81%) 6 |

| | | | |
|-----------------------------------------------------------------------|------------------------|----------------------|------------------------|
| Oedema peripheral subjects affected / exposed occurrences (all) | 5 / 47 (10.64%) 5 | 3 / 21 (14.29%) 4 | 2 / 27 (7.41%) 2 |
| Fatigue subjects affected / exposed occurrences (all) | 5 / 47 (10.64%) 5 | 2 / 21 (9.52%) 2 | 2 / 27 (7.41%) 2 |
| Gastrointestinal disorders | | | |
| Diarrhoea subjects affected / exposed occurrences (all) | 19 / 47 (40.43%) 35 | 6 / 21 (28.57%) 9 | 12 / 27 (44.44%) 39 |
| Abdominal pain subjects affected / exposed occurrences (all) | 5 / 47 (10.64%) 5 | 2 / 21 (9.52%) 2 | 2 / 27 (7.41%) 2 |
| Colitis subjects affected / exposed occurrences (all) | 3 / 47 (6.38%) 3 | 0 / 21 (0.00%) 0 | 1 / 27 (3.70%) 1 |
| Nausea subjects affected / exposed occurrences (all) | 5 / 47 (10.64%) 5 | 4 / 21 (19.05%) 5 | 6 / 27 (22.22%) 7 |
| Constipation subjects affected / exposed occurrences (all) | 6 / 47 (12.77%) 6 | 2 / 21 (9.52%) 2 | 4 / 27 (14.81%) 6 |
| Vomiting subjects affected / exposed occurrences (all) | 4 / 47 (8.51%) 4 | 1 / 21 (4.76%) 2 | 5 / 27 (18.52%) 9 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough subjects affected / exposed occurrences (all) | 8 / 47 (17.02%) 8 | 0 / 21 (0.00%) 0 | 4 / 27 (14.81%) 8 |
| Skin and subcutaneous tissue disorders | | | |
| Rash subjects affected / exposed occurrences (all) | 11 / 47 (23.40%) 19 | 6 / 21 (28.57%) 9 | 4 / 27 (14.81%) 8 |
| Hyperhidrosis subjects affected / exposed occurrences (all) | 3 / 47 (6.38%) 4 | 0 / 21 (0.00%) 0 | 0 / 27 (0.00%) 0 |

| | | | |
|-------------------------------------------------|----------------|-----------------|-----------------|
| Psoriasis | | | |
| subjects affected / exposed | 1 / 47 (2.13%) | 0 / 21 (0.00%) | 2 / 27 (7.41%) |
| occurrences (all) | 1 | 0 | 2 |
| Rash papular | | | |
| subjects affected / exposed | 0 / 47 (0.00%) | 2 / 21 (9.52%) | 0 / 27 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Dermatitis allergic | | | |
| subjects affected / exposed | 1 / 47 (2.13%) | 2 / 21 (9.52%) | 1 / 27 (3.70%) |
| occurrences (all) | 1 | 2 | 1 |
| Psychiatric disorders | | | |
| Insomnia | | | |
| subjects affected / exposed | 0 / 47 (0.00%) | 1 / 21 (4.76%) | 2 / 27 (7.41%) |
| occurrences (all) | 0 | 1 | 2 |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain | | | |
| subjects affected / exposed | 4 / 47 (8.51%) | 1 / 21 (4.76%) | 4 / 27 (14.81%) |
| occurrences (all) | 4 | 1 | 5 |
| Muscle spasms | | | |
| subjects affected / exposed | 1 / 47 (2.13%) | 3 / 21 (14.29%) | 0 / 27 (0.00%) |
| occurrences (all) | 1 | 3 | 0 |
| Infections and infestations | | | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 3 / 47 (6.38%) | 0 / 21 (0.00%) | 4 / 27 (14.81%) |
| occurrences (all) | 4 | 0 | 5 |
| Influenza | | | |
| subjects affected / exposed | 3 / 47 (6.38%) | 0 / 21 (0.00%) | 0 / 27 (0.00%) |
| occurrences (all) | 3 | 0 | 0 |
| Respiratory tract infection | | | |
| subjects affected / exposed | 3 / 47 (6.38%) | 1 / 21 (4.76%) | 0 / 27 (0.00%) |
| occurrences (all) | 3 | 1 | 0 |
| Urinary tract infection | | | |
| subjects affected / exposed | 3 / 47 (6.38%) | 2 / 21 (9.52%) | 4 / 27 (14.81%) |
| occurrences (all) | 3 | 2 | 8 |
| Bronchitis | | | |
| subjects affected / exposed | 2 / 47 (4.26%) | 2 / 21 (9.52%) | 1 / 27 (3.70%) |
| occurrences (all) | 3 | 3 | 1 |

| | | | |
|------------------------------------------------------------------------|----------------------|---------------------|---------------------|
| Oral candidiasis subjects affected / exposed occurrences (all) | 4 / 47 (8.51%) 4 | 1 / 21 (4.76%) 2 | 0 / 27 (0.00%) 0 |
| Covid-19 subjects affected / exposed occurrences (all) | 1 / 47 (2.13%) 1 | 2 / 21 (9.52%) 2 | 1 / 27 (3.70%) 1 |
| Metabolism and nutrition disorders | | | |
| Hypokalaemia subjects affected / exposed occurrences (all) | 3 / 47 (6.38%) 3 | 2 / 21 (9.52%) 2 | 2 / 27 (7.41%) 2 |
| Decreased appetite subjects affected / exposed occurrences (all) | 5 / 47 (10.64%) 6 | 1 / 21 (4.76%) 1 | 2 / 27 (7.41%) 2 |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 28 March 2016 | <ul style="list-style-type: none">• Updated the safety information and guidelines for toxicity management to be consistent across idelalisib study protocols, changes included mandated prophylaxis for <i>Pneumocystis jirovecii</i> pneumonia (PJP), Cytomegalovirus (CMV) surveillance, and increased monitoring: CMV testing frequency update (once in 4weeks); Toxicity Management updated to 'Recommendations for Evaluation, Intervention, and Drug Discontinuation for Specific Adverse Events or Conditions'• Target population was modified to align with the European Union (EU) licensed indication of idelalisib. Inclusion criteria modified to require that participants be refractory to and disease progression within 6 months from the last dose of at least two lines of prior therapy; Title and all protocol language modified to include only participants with follicular lymphoma; Removed stratification by FL/Small Lymphocytic Lymphoma (SLL)• Clarified and revised inclusion/exclusion criterion requirements: Modified inclusion criteria to align with Grade 3 neutropenia, thrombocytopenia, and anemia; Removed inclusion criteria due to French central ethics committee (CEC) request• Clarified the section Vital Signs to specify which vital signs will be collected and at which visits• Revised text to allow for the 30-Day Follow-up visit to be conducted via phone (instead of a clinic visit)• Updated language added to Appendix Pregnancy Precautions, Definition for Female of Childbearing Potential, and Contraceptive Requirements to align with the EU guidance for Zydelig contraception language in protocol amendments• Updated language added to Appendix Efficacy Assessments, Nodal Index Lesions to align with Cheson criteria |
| 07 June 2016 | <ul style="list-style-type: none">• Removed screening viral titers• Clarified that around the timing of protocol requires unblinding during study participation |
| 08 September 2016 | Alignment with Urgent Safety Measures to define the recommended versus required actions related to dose modifications for adverse events related to idelalisib. |
| 25 September 2017 | Organizing pneumonia (OP) emerged as a potential safety signal during Gilead routine signal detection monitoring. This risk was included in the Investigator's Brochure (IB). All idelalisib protocols with ongoing participants were amended to add OP as a potential risk. |
| 13 March 2019 | <p>Amended to fulfill a new post marketing requirement (PMR) 2180-10, to verify the clinical benefit of Zydelig, including defined efficacy and safety endpoints and an alternative, non-continuous dosing regimen proposed by Food and Drug Administration (FDA), as follows:</p> <ul style="list-style-type: none">• Conduct a trial establishing a safe and effective dosing regimen of idelalisib in patients with relapsed or refractory FL who have no other therapeutic options and require treatment. Include a dosing-regimen arm of 28-day cycles with 21 days on-treatment and 7 days off-treatment• The primary efficacy endpoint should be ORR. There should be sufficient follow-up to provide a credible assessment of DOR. A dosing regimen of idelalisib was considered to be effective in relapsed/refractory FL if the ORR is greater than 50% with a DOR of at least 6 months• The primary safety endpoint should be incidence of grade 4 and 5 TEAE. A dosing regimen of idelalisib was considered safe in this patient population if the rate of grade 4 and 5 TEAE is less than 30%• In addition, enrollment to Arm B was closed. This decision was based on preliminary data suggesting that Arm B appears unlikely to meet the PMR objective of achieving an ORR $\geq 50\%$, and there was insufficient exposure to the 100mg twice daily dosing regimen to evaluate intermediate and long term safety |

| | |
|---------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 18 March 2021 | <ul style="list-style-type: none"> • Unblinded the remaining blinded participants on the study for data analysis and the study design was made open label and all subsequent participants moved into Arm A and all participants enlisted into newly created Arm C were enrolled in an unblinded manner. However, there were participants remaining on the study who had been originally blinded across Arm A and Arm B • Included appendix Pandemic Risk Assessment and Mitigation Plan, which summarized potential risks associated with participants being unable to attend study visits due to an ongoing pandemic and mitigation plans • Exclusion criteria was updated to clarify that participants who received antiviral prophylaxis specifically for CMV should be excluded. • Include drug reactions with eosinophilia and systemic symptoms (DRESS) and progressive multifocal leukoencephalopathy (PML) as specific adverse events to align with the current version of the IB • Added a section outlining coronavirus disease 2019 (COVID-19) vaccination guidelines whilst a participant is on study drug |
|---------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

| Date | Interruption | Restart date |
|-------------------|-------------------------------------------------------------------------------|--------------|
| 27 September 2022 | Gilead has made the decision to close the study due to enrollment challenges. | - |

Notes:

Limitations and caveats

None reported