



Clinical trial results:

A Modular Phase I/II, Open-label, Multicentre Study to Assess AZD4573 in Novel Combinations with Anti-cancer Agents in Patients with Advanced Haematological Malignancies

Summary

| | |
|--------------------------|----------------|
| EudraCT number | 2020-001642-18 |
| Trial protocol | IE ES FR IT |
| Global end of trial date | |

Results information

| | |
|--------------------------------|--------------|
| Result version number | v1 (current) |
| This version publication date | 14 May 2025 |
| First version publication date | 14 May 2025 |

Trial information

Trial identification

| | |
|-----------------------|-------------|
| Sponsor protocol code | D8230C00002 |
|-----------------------|-------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT04630756 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | AstraZeneca AB |
| Sponsor organisation address | Södertälje, Södertälje, Sweden, 15185 |
| Public contact | Global Clinical Lead, AstraZeneca, +1 877-240-9479, information.center@astrazeneca.com |
| Scientific contact | Global Clinical Lead, AstraZeneca, +1 877-240-9479, information.center@astrazeneca.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 | Interim |
| Date of interim/final analysis | 31 December 2024 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 31 December 2024 |
| Global end of trial reached? | No |

Notes:

General information about the trial

Main objective of the trial:

To assess AZD4573 in novel combinations with anti-cancer agents in patients with advanced haematological malignancies.

Protection of trial subjects:

This study was performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with ICH/GCP, applicable regulatory requirements and the AstraZeneca policy on Bioethics.

Background therapy: -

Evidence for comparator: -

| | |
|---|------------------|
| Actual start date of recruitment | 17 February 2021 |
| Long term follow-up planned | Yes |
| Long term follow-up rationale | Safety |
| Long term follow-up duration | 30 Months |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|-----------------------|
| Country: Number of subjects enrolled | Australia: 7 |
| Country: Number of subjects enrolled | France: 4 |
| Country: Number of subjects enrolled | Ireland: 2 |
| Country: Number of subjects enrolled | Korea, Republic of: 5 |
| Country: Number of subjects enrolled | Poland: 3 |
| Country: Number of subjects enrolled | Spain: 1 |
| Country: Number of subjects enrolled | United Kingdom: 1 |
| Country: Number of subjects enrolled | United States: 17 |
| Worldwide total number of subjects | 40 |
| EEA total number of subjects | 10 |

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 | 0 |

| | |
|---------------------------|----|
| months) | |
| Children (2-11 years) | 0 |
| Adolescents (12-17 years) | 0 |
| Adults (18-64 years) | 27 |
| From 65 to 84 years | 13 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

This study was conducted from 17 February 2021 to 08 September 2023. Module 1 was conducted at 17 study centers in 10 countries. Module 2 was conducted at 2 sites in the United States.

Pre-assignment

Screening details:

The screening period was 30 days for both parts of the study. Informed Consent Form was signed prior to screening procedures. All study assessments were performed as per the schedule of assessment. Participants who met the eligibility criteria were randomized to study intervention in addition to receiving background local standard of care therapy.

Period 1

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

Arms

| | |
|------------------------------|--|
| Are arms mutually exclusive? | Yes |
| Arm title | Module 1 Part A: AZD4573 9 mg + 100g acalabrutinib BID |

Arm description:

Participants received AZD4573 9 mg as Intravenous (IV) infusion once weekly with acalabrutinib 100 mg twice daily.

| | |
|--|---------------------------------------|
| Arm type | Active comparator |
| Investigational medicinal product name | AZD4573 |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Concentrate for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Participants received AZD4573 9 mg as Intravenous (IV) infusion once weekly with acalabrutinib 100 mg twice daily.

| | |
|--|---------------|
| Investigational medicinal product name | Acalabrutinib |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

Participants received AZD4573 9 mg as Intravenous (IV) infusion once weekly with acalabrutinib 100 mg twice daily.

| | |
|------------------|---|
| Arm title | Module 1 Part B: AZD4573 12 mg + 100g acalabrutinib BID |
|------------------|---|

Arm description:

Participants received AZD4573 dose expansion to RP2D 12 mg as IV infusion once weekly with acalabrutinib 100 mg twice daily.

| | |
|--|-------------------|
| Arm type | Active comparator |
| Investigational medicinal product name | Acalabrutinib |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

Participants received AZD4573 dose expansion to RP2D 12 mg as IV infusion once weekly with acalabrutinib 100 mg twice daily.

| | |
|--|---------------------------------------|
| Investigational medicinal product name | AZD4573 |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Concentrate for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Participants received AZD4573 dose expansion to RP2D 12 mg as IV infusion once weekly with acalabrutinib 100 mg twice daily.

| | |
|------------------|--|
| Arm title | Module 2 Period 1 + 2: AZD4573 12 mg monotherapy + combination |
|------------------|--|

Arm description:

Participants received AZD4573 12 mg monotherapy until progression and thereafter received a combination regimen of AZD4573 12 mg once weekly and acalabrutinib 100 mg twice daily.

| | |
|--|-------------------|
| Arm type | Active comparator |
| Investigational medicinal product name | Acalabrutinib |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

Participants received AZD4573 12 mg monotherapy until progression and thereafter received a combination regimen of AZD4573 12 mg once weekly and acalabrutinib 100 mg twice daily.

| | |
|--|---------------------------------------|
| Investigational medicinal product name | AZD4573 |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Concentrate for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Participants received AZD4573 12 mg monotherapy until progression and thereafter received a combination regimen of AZD4573 12 mg once weekly and acalabrutinib 100 mg twice daily.

| Number of subjects in period 1 | Module 1 Part A: AZD4573 9 mg + 100g acalabrutinib BID | Module 1 Part B: AZD4573 12 mg + 100g acalabrutinib BID | Module 2 Period 1 + 2: AZD4573 12 mg monotherapy + combination |
|--|---|--|---|
| Started | 9 | 28 | 3 |
| Completed | 8 | 28 | 3 |
| Not completed | 1 | 0 | 0 |
| Ongoing subjects in Post Trial Access Program | 1 | - | - |

Baseline characteristics

Reporting groups

| | |
|--|--|
| Reporting group title | Module 1 Part A: AZD4573 9 mg + 100g acalabrutinib BID |
| Reporting group description: Participants received AZD4573 9 mg as Intravenous (IV) infusion once weekly with acalabrutinib 100 mg twice daily. | |
| Reporting group title | Module 1 Part B: AZD4573 12 mg + 100g acalabrutinib BID |
| Reporting group description: Participants received AZD4573 dose expansion to RP2D 12 mg as IV infusion once weekly with acalabrutinib 100 mg twice daily. | |
| Reporting group title | Module 2 Period 1 + 2: AZD4573 12 mg monotherapy + combination |
| Reporting group description: Participants received AZD4573 12 mg monotherapy until progression and thereafter received a combination regimen of AZD4573 12 mg once weekly and acalabrutinib 100 mg twice daily. | |

| Reporting group values | Module 1 Part A: AZD4573 9 mg + 100g acalabrutinib BID | Module 1 Part B: AZD4573 12 mg + 100g acalabrutinib BID | Module 2 Period 1 + 2: AZD4573 12 mg monotherapy + combination |
|---|---|--|---|
| Number of subjects | 9 | 28 | 3 |
| Age Categorical Units: Participants | | | |
| In utero | 0 | 0 | 0 |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | 0 |
| Newborns (0-27 days) | 0 | 0 | 0 |
| Infants and toddlers (28 days-23 months) | 0 | 0 | 0 |
| Children (2-11 years) | 0 | 0 | 0 |
| Adolescents (12-17 years) | 0 | 0 | 0 |
| Adults (18-64 years) | 7 | 17 | 3 |
| From 65-84 years | 2 | 11 | 0 |
| 85 years and over | 0 | 0 | 0 |
| Age Continuous Units: years | | | |
| arithmetic mean | 51.2 | 61.7 | 59.7 |
| standard deviation | ± 18.72 | ± 9.52 | ± 2.63 |
| Gender Categorical Units: Participants | | | |
| Female | 4 | 10 | 0 |
| Male | 5 | 18 | 3 |
| Race/Ethnicity Units: Subjects | | | |
| Asian | 2 | 8 | 0 |
| White | 6 | 17 | 2 |
| Not Reported | 1 | 1 | 0 |
| Missing | 0 | 2 | 0 |
| Other | 0 | 0 | 1 |

| | | | |
|-------------------------------|-------|--|--|
| Reporting group values | Total | | |
|-------------------------------|-------|--|--|

| | | | |
|---|----|--|--|
| Number of subjects | 40 | | |
| Age Categorical | | | |
| Units: Participants | | | |
| In utero | 0 | | |
| Preterm newborn infants (gestational age < 37 wks) | 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) | 27 | | |
| From 65-84 years | 13 | | |
| 85 years and over | 0 | | |
| Age Continuous | | | |
| Units: years | | | |
| arithmetic mean | | | |
| standard deviation | - | | |
| Gender Categorical | | | |
| Units: Participants | | | |
| Female | 14 | | |
| Male | 26 | | |
| Race/Ethnicity | | | |
| Units: Subjects | | | |
| Asian | 10 | | |
| White | 25 | | |
| Not Reported | 2 | | |
| Missing | 2 | | |
| Other | 1 | | |

End points

End points reporting groups

| | |
|--|--|
| Reporting group title | Module 1 Part A: AZD4573 9 mg + 100g acalabrutinib BID |
| Reporting group description: Participants received AZD4573 9 mg as Intravenous (IV) infusion once weekly with acalabrutinib 100 mg twice daily. | |
| Reporting group title | Module 1 Part B: AZD4573 12 mg + 100g acalabrutinib BID |
| Reporting group description: Participants received AZD4573 dose expansion to RP2D 12 mg as IV infusion once weekly with acalabrutinib 100 mg twice daily. | |
| Reporting group title | Module 2 Period 1 + 2: AZD4573 12 mg monotherapy + combination |
| Reporting group description: Participants received AZD4573 12 mg monotherapy until progression and thereafter received a combination regimen of AZD4573 12 mg once weekly and acalabrutinib 100 mg twice daily. | |

Primary: Module 1: Number of participants with adverse events

| | |
|--|--|
| End point title | Module 1: Number of participants with adverse events ^{[1][2]} |
| End point description: The safety and tolerability of AZD4573 in combination with acalabrutinib was assessed in the safety analysis set. The safety analysis set included all participants who received any amount of AZD4573 and/or acalabrutinib. | |
| End point type | Primary |
| End point timeframe: From Screening (Day -30 to Day -1) until disease progression or survival until death (approximately 2.5 years) | |

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: The endpoint title is specific to the arms which are presented only. Participants in Module 2: Periods 1 and 2 were not assessed for this outcome measure. Hence, only the arms which are referenced in the title are presented per outcome measure.

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: The endpoint title is specific to the arms which are presented only. Participants in Module 2: Periods 1 and 2 were not assessed for this outcome measure. Hence, only the arms which are referenced in the title are presented per outcome measure.

| End point values | Module 1 Part A: AZD4573 9 mg + 100g acalabrutinib BID | Module 1 Part B: AZD4573 12 mg + 100g acalabrutinib BID | | |
|---------------------------------|--|---|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 9 | 28 | | |
| Units: Participants | | | | |
| Any adverse event (AE) | 9 | 28 | | |
| Any serious adverse event (SAE) | 4 | 16 | | |

Statistical analyses

No statistical analyses for this end point

Primary: Module 1: Overall response rate (ORR) of AZD4573 in combination with acalabrutinib

| | |
|-----------------|--|
| End point title | Module 1: Overall response rate (ORR) of AZD4573 in combination with acalabrutinib ^{[3][4]} |
|-----------------|--|

End point description:

Objective response rate (ORR), defined as the proportion of participants who have a tumour response (complete response [CR] and partial response [PR]) was assessed in the response evaluable analysis set. The response evaluable analysis set included participants dosed with AZD4573 or acalabrutinib with a baseline tumour assessment.

Here, 999.999 indicates that the value was not calculated due to an insufficient number of participants with events.

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

End point timeframe:

From Screening (Day -30 to Day -1) until disease progression or survival until death (approximately 2.5 years)

Notes:

[3] - 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: The endpoint title is specific to the arms which are presented only. Participants in Module 2: Periods 1 and 2 were not assessed for this outcome measure. Hence, only the arms which are referenced in the title are presented per outcome measure.

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: The endpoint title is specific to the arms which are presented only. Participants in Module 2: Periods 1 and 2 were not assessed for this outcome measure. Hence, only the arms which are referenced in the title are presented per outcome measure.

| End point values | Module 1 Part A: AZD4573 9 mg + 100g acalabrutinib BID | Module 1 Part B: AZD4573 12 mg + 100g acalabrutinib BID | | |
|---|--|---|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 9 | 28 | | |
| Units: Percentage of participants with response | | | | |
| number (confidence interval 95%) | 44.4 (13.7 to 78.8) | 50.0 (30.6 to 69.4) | | |

Statistical analyses

No statistical analyses for this end point

Primary: Module 2: Number of participants with adverse events

| | |
|-----------------|--|
| End point title | Module 2: Number of participants with adverse events ^{[5][6]} |
|-----------------|--|

End point description:

Assessed safety and confirmed the RP2D of AZD4573 monotherapy in MCL participants and assessed the safety and tolerability of AZD4573 in combination with acalabrutinib in participants administered AZD4573 monotherapy in the safety analysis set. The safety analysis set included all participants who received any amount of AZD4573 and/or acalabrutinib.

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

End point timeframe:

From Screening (Day -30 to Day -1) until disease progression or survival until death (approximately 2.5 years)

Notes:

[5] - 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: The endpoint title is specific to the arms which are presented only. Participants in Module 2: Periods 1 and 2 were not assessed for this outcome measure. Hence, only the arms which are referenced in the title are presented per outcome measure.

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: The endpoint title is specific to the arms which are presented only. Participants in Module 2: Periods 1 and 2 were not assessed for this outcome measure. Hence, only the arms which are referenced in the title are presented per outcome measure.

| | | | | |
|-------------------------------|---|--|--|--|
| End point values | Module 2 Period 1 + 2: AZD4573 12 mg monotherapy + combination | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 3 | | | |
| Units: Number of Participants | | | | |
| Any AE | 3 | | | |
| Any SAE | 1 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Module 1: Complete response (CR) rate

| | |
|-----------------|--|
| End point title | Module 1: Complete response (CR) rate ^[7] |
|-----------------|--|

End point description:

CR, defined as no detectable evidence of tumor, according to the revised response criteria for malignant lymphoma, was assessed in the response evaluable analysis set. The response evaluable analysis set included participants dosed with AZD4573 or acalabrutinib with a baseline tumour assessment.

Here, 999.999 indicates that the value was not calculated due to an insufficient number of participants with events.

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

End point timeframe:

From Screening (Day -30 to Day -1) until disease progression or survival until death (approximately 2.5 years)

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: The endpoint title is specific to the arms which are presented only. Participants in Module 2: Periods 1 and 2 were not assessed for this outcome measure. Hence, only the arms which are referenced in the title are presented per outcome measure.

| | | | | |
|---|--|---|--|--|
| End point values | Module 1 Part A: AZD4573 9 mg + 100g acalabrutinib BID | Module 1 Part B: AZD4573 12 mg + 100g acalabrutinib BID | | |
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 9 | 28 | | |
| Units: Percentage of participants with response | | | | |
| number (confidence interval 95%) | 11.1 (0.3 to | 21.4 (8.3 to | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Module 1: Cmax of AZD4573

End point title | Module 1: Cmax of AZD4573^[8]

End point description:

Maximum concentration that a drug achieves in a specified compartment or test area of the body after the drug has been administered (Cmax) was measured in the pharmacokinetic analysis set. The pharmacokinetic analysis set included all dosed patients with reportable plasma concentrations and no important adverse events or protocol deviations that may impact PK.

Here, 999.999 indicates that the value was not calculated due to an insufficient number of participants analyzed.

End point type | Secondary

End point timeframe:

Cycle 1 (5 weeks in total) on Day 1 of Week 1, 2 and 3, and Cycle 2 (3 weeks in total) on Day 1 of Week 1

Notes:

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: The endpoint title is specific to the arms which are presented only. Participants in Module 2: Periods 1 and 2 were not assessed for this outcome measure. Hence, only the arms which are referenced in the title are presented per outcome measure.

| End point values | Module 1 Part A: AZD4573 9 mg + 100g acalabrutinib BID | Module 1 Part B: AZD4573 12 mg + 100g acalabrutinib BID | | |
|---|--|---|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 9 | 12 | | |
| Units: nanograms per milliliter (ng/mL) | | | | |
| geometric mean (geometric coefficient of variation) | | | | |
| Cycle 1 Week 1 Day 1 (n=9, 12) | 164.2 (± 469.0) | 112.6 (± 70.20) | | |
| Cycle 1 Week 2 Day 1 (n=6, 11) | 235.7 (± 359.3) | 185.3 (± 50.61) | | |
| Cycle 1 Week 3 Day 1 (n=8, 11) | 337.8 (± 194.3) | 270.8 (± 38.61) | | |
| Cycle 2 Week 1 Day 1 (n=6, 9) | 643.1 (± 578.0) | 294.6 (± 48.83) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Module 1: Progression free survival (PFS)

| | |
|-----------------|--|
| End point title | Module 1: Progression free survival (PFS) ^[9] |
|-----------------|--|

End point description:

PFS, defined as the time from first dose date to documented disease progression, or death from any cause, whichever occurs first, was measured in the full analysis set. The full analysis set included all participants who received any amount of study intervention.
Here, 999.999 indicates that the value was not calculated due to an insufficient number of participants with events.

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

End point timeframe:

From Screening (Day -30 to Day -1) until disease progression or survival until death (approximately 2.5 years)

Notes:

[9] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: The endpoint title is specific to the arms which are presented only. Participants in Module 2: Periods 1 and 2 were not assessed for this outcome measure. Hence, only the arms which are referenced in the title are presented per outcome measure.

| End point values | Module 1 Part A: AZD4573 9 mg + 100g acalabrutinib BID | Module 1 Part B: AZD4573 12 mg + 100g acalabrutinib BID | | |
|----------------------------------|--|---|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 9 | 28 | | |
| Units: Months | | | | |
| median (confidence interval 95%) | 2.1 (0.30 to 6.44) | 2.8 (1.91 to 3.98) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Module 1: Overall survival (OS)

| | |
|-----------------|---|
| End point title | Module 1: Overall survival (OS) ^[10] |
|-----------------|---|

End point description:

OS, defined as the time from first dose until the date of death from any cause, was measured in the full analysis set. The full analysis set included all participants who received any amount of study intervention.
Here, 999.999 indicates that the value was not calculated due to an insufficient number of participants with events.

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

End point timeframe:

From Screening (Day -30 to Day -1) until disease progression or survival until death (approximately 2.5 years)

Notes:

[10] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: The endpoint title is specific to the arms which are presented only. Participants in Module 2: Periods 1 and 2 were not assessed for this outcome measure. Hence, only the arms which are referenced in the title are presented per outcome measure.

| | | | | |
|----------------------------------|--|---|--|--|
| End point values | Module 1 Part A: AZD4573 9 mg + 100g acalabrutinib BID | Module 1 Part B: AZD4573 12 mg + 100g acalabrutinib BID | | |
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 9 | 28 | | |
| Units: Months | | | | |
| median (confidence interval 95%) | 999.999 (3.52 to 999.999) | 8.8 (3.91 to 999.999) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Module 1: Duration of response (DoR)

| | |
|-----------------|--|
| End point title | Module 1: Duration of response (DoR) ^[11] |
|-----------------|--|

End point description:

DoR, defined as the time from the first objective response of CR or PR to the time of documented disease progression or death due to any cause, whichever occurs first, was measured in the response evaluable analysis set. The response evaluable analysis set included participants dosed with AZD4573 or acalabrutinib with a baseline tumour assessment.

Here, 999.999 indicates that the value was not calculated due to an insufficient number of participants with events.

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

End point timeframe:

From Screening (Day -30 to Day -1) until disease progression or survival until death (approximately 2.5 years)

Notes:

[11] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: The endpoint title is specific to the arms which are presented only. Participants in Module 2: Periods 1 and 2 were not assessed for this outcome measure. Hence, only the arms which are referenced in the title are presented per outcome measure.

| | | | | |
|----------------------------------|--|---|--|--|
| End point values | Module 1 Part A: AZD4573 9 mg + 100g acalabrutinib BID | Module 1 Part B: AZD4573 12 mg + 100g acalabrutinib BID | | |
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 9 | 28 | | |
| Units: Months | | | | |
| median (confidence interval 95%) | 4.4 (4.1 to 999.999) | 3.3 (1.2 to 6.2) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Module 1: Cmax of acalabrutinib

| | |
|-----------------|---|
| End point title | Module 1: Cmax of acalabrutinib ^[12] |
|-----------------|---|

End point description:

Maximum concentration that a drug achieves in a specified compartment or test area of the body after the drug has been administered (C_{max}) was measured in the pharmacokinetic analysis set. The pharmacokinetic analysis set included all dosed patients with reportable plasma concentrations and no important adverse events or protocol deviations that may impact PK.

Here, 999.999 indicates that the value was not calculated due to an insufficient number of participants analyzed.

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

End point timeframe:

Cycle 1 (5 weeks in total) on Day 1 of Week 1, 2 and 3, and Cycle 2 (3 weeks in total) on Day 1 of Week 1

Notes:

[12] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: The endpoint title is specific to the arms which are presented only. Participants in Module 2: Periods 1 and 2 were not assessed for this outcome measure. Hence, only the arms which are referenced in the title are presented per outcome measure.

| End point values | Module 1 Part A: AZD4573 9 mg + 100g acalabrutinib BID | Module 1 Part B: AZD4573 12 mg + 100g acalabrutinib BID | | |
|---|--|---|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 7 | 12 | | |
| Units: nanograms per milliliter (ng/mL) | | | | |
| geometric mean (geometric coefficient of variation) | | | | |
| Cycle 1 Week 1 Day 1 (n=6, 11) | 219.9 (± 66.94) | 306.1 (± 76.06) | | |
| Cycle 1 Week 2 Day 1 (n=6, 10) | 209.8 (± 45.79) | 322.7 (± 95.53) | | |
| Cycle 1 Week 3 Day 1 (n=7, 10) | 232.1 (± 74.77) | 274.2 (± 78.98) | | |
| Cycle 2 Week 1 Day 1 (n=5, 8) | 217.5 (± 100.8) | 256.7 (± 67.75) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Module 1: C_{max} of ACP-5862

| | |
|-----------------|--|
| End point title | Module 1: C _{max} of ACP-5862 ^[13] |
|-----------------|--|

End point description:

Maximum concentration that a drug achieves in a specified compartment or test area of the body after the drug has been administered (C_{max}) was measured in the pharmacokinetic analysis set. The pharmacokinetic analysis set included all dosed patients with reportable plasma concentrations and no important adverse events or protocol deviations that may impact PK.

Here, 999.999 indicates that the value was not calculated due to an insufficient number of participants analyzed.

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

End point timeframe:

Cycle 1 (5 weeks in total) on Day 1 of Week 1, 2 and 3, and Cycle 2 (3 weeks in total) on Day 1 of Week 1

Notes:

[13] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: The endpoint title is specific to the arms which are presented only. Participants in Module 2: Periods 1 and 2 were not assessed for this outcome measure. Hence, only the arms which are referenced in the title are presented per outcome measure.

| End point values | Module 1 Part A: AZD4573 9 mg + 100g acalabrutinib BID | Module 1 Part B: AZD4573 12 mg + 100g acalabrutinib BID | | |
|---|--|---|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 7 | 11 | | |
| Units: nanograms per milliliter (ng/mL) | | | | |
| geometric mean (geometric coefficient of variation) | | | | |
| Cycle 1 Week 1 Day 1 (n=6, 11) | 199.2 (± 129.3) | 250.2 (± 78.12) | | |
| Cycle 1 Week 2 Day 1 (n=6, 10) | 382.1 (± 51.58) | 288.0 (± 63.26) | | |
| Cycle 1 Week 3 Day 1 (n=7, 10) | 320.8 (± 35.92) | 282.9 (± 55.76) | | |
| Cycle 2 Week 1 Day 1 (n=5, 8) | 304.6 (± 79.28) | 251.8 (± 45.54) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Module 1: AUClast of acalabrutinib

End point title | Module 1: AUClast of acalabrutinib^[14]

End point description:

The area under the plasma concentration time curve from zero to the time of the last measurable concentration (AUClast) was measured in the pharmacokinetic analysis set. The pharmacokinetic analysis set included all dosed patients with reportable plasma concentrations and no important adverse events or protocol deviations that may impact PK.

Here, 999.999 indicates that the value was not calculated due to an insufficient number of participants analyzed.

End point type | Secondary

End point timeframe:

Cycle 1 (5 weeks in total) on Day 1 of Week 1, 2 and 3, and Cycle 2 (3 weeks in total) on Day 1 of Week 1

Notes:

[14] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: The endpoint title is specific to the arms which are presented only. Participants in Module 2: Periods 1 and 2 were not assessed for this outcome measure. Hence, only the arms which are referenced in the title are presented per outcome measure.

| End point values | Module 1 Part A: AZD4573 9 mg + 100g acalabrutinib BID | Module 1 Part B: AZD4573 12 mg + 100g acalabrutinib BID | | |
|---|--|---|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 7 | 11 | | |
| Units: time*nanogram per milliliter (h*ng/mL) | | | | |
| geometric mean (geometric coefficient of variation) | | | | |
| Cycle 1 Week 1 Day 1 (n=6, 11) | 493.9 (± 58.91) | 631.4 (± 69.98) | | |
| Cycle 1 Week 2 Day 1 (n=6, 10) | 520.9 (± 46.04) | 638.2 (± 81.66) | | |
| Cycle 1 Week 3 Day 1 (n=7, 10) | 475.9 (± 45.57) | 570.7 (± 67.75) | | |
| Cycle 2 Week 1 Day 1 (n=5, 8) | 481.8 (± 58.39) | 424.5 (± 162.8) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Module 1: AUClast of AZD4573

| | |
|---|--|
| End point title | Module 1: AUClast of AZD4573 ^[15] |
| End point description: | |
| <p>The area under the plasma concentration time curve from zero to the time of the last measurable concentration (AUClast) was measured in the pharmacokinetic analysis set. The pharmacokinetic analysis set included all dosed patients with reportable plasma concentrations and no important adverse events or protocol deviations that may impact PK.</p> <p>Here, 999.999 indicates that the value was not calculated due to an insufficient number of participants analyzed.</p> | |
| End point type | Secondary |
| End point timeframe: | |
| Cycle 1 (5 weeks in total) on Day 1 of Week 1, 2 and 3, and Cycle 2 (3 weeks in total) on Day 1 of Week 1 | |

Notes:

[15] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: The endpoint title is specific to the arms which are presented only. Participants in Module 2: Periods 1 and 2 were not assessed for this outcome measure. Hence, only the arms which are referenced in the title are presented per outcome measure.

| End point values | Module 1 Part A: AZD4573 9 mg + 100g acalabrutinib BID | Module 1 Part B: AZD4573 12 mg + 100g acalabrutinib BID | | |
|---|--|---|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 8 | 12 | | |
| Units: time*nanogram per milliliter (h*ng/mL) | | | | |
| geometric mean (geometric coefficient of variation) | | | | |

| | | | | |
|--------------------------------|-----------------|-----------------|--|--|
| Cycle 1 Week 1 Day 1 (n=6, 12) | 532.9 (± 164.5) | 561.3 (± 60.83) | | |
| Cycle 1 Week 2 Day 1 (n=6, 11) | 845.3 (± 134.8) | 929.0 (± 55.85) | | |
| Cycle 1 Week 3 Day 1 (n=8, 11) | 1273 (± 127.7) | 1697 (± 62.55) | | |
| Cycle 2 Week 1 Day 1 (n=6, 9) | 1939 (± 330.9) | 1439 (± 90.63) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Module 1: AUClast of ACP-5862

| | |
|-----------------|---|
| End point title | Module 1: AUClast of ACP-5862 ^[16] |
|-----------------|---|

End point description:

The area under the plasma concentration time curve from zero to the time of the last measurable concentration (AUClast) was measured in the pharmacokinetic analysis set. The pharmacokinetic analysis set included all dosed patients with reportable plasma concentrations and no important adverse events or protocol deviations that may impact PK.

Here, 999.999 indicates that the value was not calculated due to an insufficient number of participants analyzed.

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

End point timeframe:

Cycle 1 (5 weeks in total) on Day 1 of Week 1, 2 and 3, and Cycle 2 (3 weeks in total) on Day 1 of Week 1

Notes:

[16] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: The endpoint title is specific to the arms which are presented only. Participants in Module 2: Periods 1 and 2 were not assessed for this outcome measure. Hence, only the arms which are referenced in the title are presented per outcome measure.

| End point values | Module 1 Part A: AZD4573 9 mg + 100g acalabrutinib BID | Module 1 Part B: AZD4573 12 mg + 100g acalabrutinib BID | | |
|---|--|---|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 7 | 11 | | |
| Units: time*nanogram per milliliter (h*ng/mL) | | | | |
| geometric mean (geometric coefficient of variation) | | | | |
| Cycle 1 Week 1 Day 1 (n=6, 11) | 673.9 (± 93.89) | 870.8 (± 68.73) | | |
| Cycle 1 Week 2 Day 1 (n=6, 10) | 1173 (± 48.03) | 1135 (± 54.95) | | |
| Cycle 1 Week 3 Day 1 (n=7, 10) | 1204 (± 36.24) | 1093 (± 54.50) | | |
| Cycle 2 Week 1 Day 1 (n=5, 8) | 941.9 (± 102.5) | 849.3 (± 60.56) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Module 1: AUCinf of AZD4573

End point title | Module 1: AUCinf of AZD4573^[17]

End point description:

The area under the plasma concentration time curve from zero extrapolated to infinity (AUCinf) was measured in the pharmacokinetic analysis set. The pharmacokinetic analysis set included all dosed patients with reportable plasma concentrations and no important adverse events or protocol deviations that may impact PK.

Here, 999.999 indicates that the value was not calculated due to an insufficient number of participants analyzed.

End point type | Secondary

End point timeframe:

Cycle 1 (5 weeks in total) on Day 1 of Week 1, 2 and 3, and Cycle 2 (3 weeks in total) on Day 1 of Week 1

Notes:

[17] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: The endpoint title is specific to the arms which are presented only. Participants in Module 2: Periods 1 and 2 were not assessed for this outcome measure. Hence, only the arms which are referenced in the title are presented per outcome measure.

| End point values | Module 1 Part A: AZD4573 9 mg + 100g acalabrutinib BID | Module 1 Part B: AZD4573 12 mg + 100g acalabrutinib BID | | |
|---|--|---|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 5 | 9 | | |
| Units: h*ng/mL | | | | |
| geometric mean (geometric coefficient of variation) | | | | |
| Cycle 1 Week 1 Day 1 (n=1, 4) | 999.999 (± 999.999) | 640.5 (± 15.33) | | |
| Cycle 1 Week 2 Day 1 (n=4, 6) | 1188 (± 160.1) | 847.4 (± 68.22) | | |
| Cycle 1 Week 3 Day 1 (n=5, 9) | 1588 (± 169.6) | 1736 (± 67.09) | | |
| Cycle 2 Week 1 Day 1 (n=4, 5) | 4672 (± 162.9) | 1853 (± 29.55) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Module 1: AUCinf of acalabrutinib

End point title | Module 1: AUCinf of acalabrutinib^[18]

End point description:

The area under the plasma concentration time curve from zero extrapolated to infinity (AUCinf) was measured in the pharmacokinetic analysis set. The pharmacokinetic analysis set included all dosed patients with reportable plasma concentrations and no important adverse events or protocol deviations that may impact PK.

Here, 999.999 indicates that the value was not calculated due to an insufficient number of participants analyzed.

End point type | Secondary

End point timeframe:

Cycle 1 (5 weeks in total) on Day 1 of Week 1, 2 and 3, and Cycle 2 (3 weeks in total) on Day 1 of Week 1

Notes:

[18] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: The endpoint title is specific to the arms which are presented only. Participants in Module 2: Periods 1 and 2 were not assessed for this outcome measure. Hence, only the arms which are referenced in the title are presented per outcome measure.

| End point values | Module 1 Part A: AZD4573 9 mg + 100g acalabrutinib BID | Module 1 Part B: AZD4573 12 mg + 100g acalabrutinib BID | | |
|---|--|---|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 3 | 5 | | |
| Units: h*ng/mL | | | | |
| geometric mean (geometric coefficient of variation) | | | | |
| Cycle 1 Week 1 Day 1 (n=3, 5) | 600.1 (± 34.99) | 501.3 (± 58.03) | | |
| Cycle 1 Week 2 Day 1 (n=0, 0) | 999.999 (± 999.999) | 999.999 (± 999.999) | | |
| Cycle 1 Week 3 Day 1 (n=0, 0) | 999.999 (± 999.999) | 999.999 (± 999.999) | | |
| Cycle 2 Week 1 Day 1 (n=0, 0) | 999.999 (± 999.999) | 999.999 (± 999.999) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Module 1: AUCinf of ACP-5862

End point title | Module 1: AUCinf of ACP-5862^[19]

End point description:

The area under the plasma concentration time curve from zero extrapolated to infinity (AUCinf) was measured in the pharmacokinetic analysis set. The pharmacokinetic analysis set included all dosed patients with reportable plasma concentrations and no important adverse events or protocol deviations that may impact PK.

Here, 999.999 indicates that the value was not calculated due to an insufficient number of participants analyzed.

End point type | Secondary

End point timeframe:

Cycle 1 (5 weeks in total) on Day 1 of Week 1, 2 and 3, and Cycle 2 (3 weeks in total) on Day 1 of Week 1

Notes:

[19] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: The endpoint title is specific to the arms which are presented only. Participants in Module 2: Periods 1 and 2 were not assessed for this outcome measure. Hence, only the arms which are referenced in the title are presented per outcome measure.

| End point values | Module 1 Part A: AZD4573 9 mg + 100g acalabrutinib BID | Module 1 Part B: AZD4573 12 mg + 100g acalabrutinib BID | | |
|---|--|---|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 2 | 4 | | |
| Units: h*ng/mL | | | | |
| geometric mean (geometric coefficient of variation) | | | | |
| Cycle 1 Week 1 Day 1 (n=2, 4) | 999.999 (± 999.999) | 935.2 (± 38.81) | | |
| Cycle 1 Week 2 Day 1 (n=0, 0) | 999.999 (± 999.999) | 999.999 (± 999.999) | | |
| Cycle 1 Week 3 Day 1 (n=0, 0) | 999.999 (± 999.999) | 999.999 (± 999.999) | | |
| Cycle 2 Week 1 Day 1 (n=0, 0) | 999.999 (± 999.999) | 999.999 (± 999.999) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Module 1: tmax of AZD4573

| | |
|------------------------|---|
| End point title | Module 1: tmax of AZD4573 ^[20] |
| End point description: | The time to reach peak or maximum observed concentration following drug administration (tmax) was measured in the pharmacokinetic analysis set. The pharmacokinetic analysis set included all dosed patients with reportable plasma concentrations and no important adverse events or protocol deviations that may impact PK. |
| End point type | Secondary |
| End point timeframe: | Cycle 1 (5 weeks in total) on Day 1 of Week 1, 2 and 3, and Cycle 2 (3 weeks in total) on Day 1 of Week 1 |

Notes:

[20] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: The endpoint title is specific to the arms which are presented only. Participants in Module 2: Periods 1 and 2 were not assessed for this outcome measure. Hence, only the arms which are referenced in the title are presented per outcome measure.

| End point values | Module 1 Part A: AZD4573 9 mg + 100g acalabrutinib BID | Module 1 Part B: AZD4573 12 mg + 100g acalabrutinib BID | | |
|--------------------------------|--|---|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 8 | 12 | | |
| Units: Hours (h) | | | | |
| median (full range (min-max)) | | | | |
| Cycle 1 Week 1 Day 1 (n=6, 12) | 1.992 (0.750 to 4.17) | 2.083 (1.00 to 10.5) | | |
| Cycle 1 Week 2 Day 1 (n=6, 11) | 1.892 (1.00 to 3.00) | 2.033 (1.05 to 2.15) | | |
| Cycle 1 Week 3 Day 1 (n=8, 11) | 2.192 (0.933 to 3.32) | 2.000 (1.03 to 2.15) | | |

| | | | | |
|-------------------------------|----------------------|----------------------|--|--|
| Cycle 2 Week 1 Day 1 (n=6, 9) | 2.067 (1.00 to 2.22) | 2.083 (1.85 to 3.63) | | |
|-------------------------------|----------------------|----------------------|--|--|

Statistical analyses

No statistical analyses for this end point

Secondary: Module 1: tmax of acalabrutinib

| | |
|-----------------|---|
| End point title | Module 1: tmax of acalabrutinib ^[21] |
|-----------------|---|

End point description:

The time to reach peak or maximum observed concentration following drug administration (tmax) was measured in the pharmacokinetic analysis set. The pharmacokinetic analysis set included all dosed patients with reportable plasma concentrations and no important adverse events or protocol deviations that may impact PK.

Here, 999.999 indicates that the value was not calculated due to an insufficient number of participants analyzed.

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

End point timeframe:

Cycle 1 (5 weeks in total) on Day 1 of Week 1, 2 and 3, and Cycle 2 (3 weeks in total) on Day 1 of Week 1

Notes:

[21] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: The endpoint title is specific to the arms which are presented only. Participants in Module 2: Periods 1 and 2 were not assessed for this outcome measure. Hence, only the arms which are referenced in the title are presented per outcome measure.

| End point values | Module 1 Part A: AZD4573 9 mg + 100g acalabrutinib BID | Module 1 Part B: AZD4573 12 mg + 100g acalabrutinib BID | | |
|--------------------------------|--|---|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 7 | 11 | | |
| Units: Hours (h) | | | | |
| median (full range (min-max)) | | | | |
| Cycle 1 Week 1 Day 1 (n=6, 11) | 1.242 (1.02 to 3.80) | 1.117 (0.933 to 2.65) | | |
| Cycle 1 Week 2 Day 1 (n=6, 9) | 2.017 (1.00 to 4.52) | 1.133 (0.950 to 11.6) | | |
| Cycle 1 Week 3 Day 1 (n=7, 10) | 1.233 (1.00 to 3.17) | 1.433 (0.850 to 4.00) | | |
| Cycle 2 Week 1 Day 1 (n=5, 7) | 1.933 (1.03 to 5.75) | 1.200 (0.833 to 2.25) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Module 1: tmax of ACP-5862

| | |
|-----------------|--|
| End point title | Module 1: tmax of ACP-5862 ^[22] |
|-----------------|--|

End point description:

The time to reach peak or maximum observed concentration following drug administration (tmax) was measured in the pharmacokinetic analysis set. The pharmacokinetic analysis set included all dosed patients with reportable plasma concentrations and no important adverse events or protocol deviations that may impact PK.

Here, 999.999 indicates that the value was not calculated due to an insufficient number of participants analyzed.

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

End point timeframe:

Cycle 1 (5 weeks in total) on Day 1 of Week 1, 2 and 3, and Cycle 2 (3 weeks in total) on Day 1 of Week 1

Notes:

[22] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: The endpoint title is specific to the arms which are presented only. Participants in Module 2: Periods 1 and 2 were not assessed for this outcome measure. Hence, only the arms which are referenced in the title are presented per outcome measure.

| End point values | Module 1 Part A: AZD4573 9 mg + 100g acalabrutinib BID | Module 1 Part B: AZD4573 12 mg + 100g acalabrutinib BID | | |
|--------------------------------|--|---|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 7 | 11 | | |
| Units: Hours (h) | | | | |
| median (full range (min-max)) | | | | |
| Cycle 1 Week 1 Day 1 (n=6, 11) | 3.067 (1.02 to 7.00) | 1.117 (0.933 to 7.08) | | |
| Cycle 1 Week 2 Day 1 (n=6, 9) | 2.075 (1.08 to 7.52) | 2.117 (1.05 to 11.6) | | |
| Cycle 1 Week 3 Day 1 (n=7, 10) | 1.233 (1.00 to 4.58) | 1.892 (0.850 to 4.00) | | |
| Cycle 2 Week 1 Day 1 (n=5, 7) | 2.167 (2.05 to 8.92) | 2.117 (0.917 to 4.13) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Module 1: t1/2 of AZD4573

| | |
|-----------------|---|
| End point title | Module 1: t1/2 of AZD4573 ^[23] |
|-----------------|---|

End point description:

The time taken for half the initial dose of drug administered to be eliminated from the body (t1/2) was measured in the pharmacokinetic analysis set. The pharmacokinetic analysis set included all dosed patients with reportable plasma concentrations and no important adverse events or protocol deviations that may impact PK.

Here, 999.999 indicates that the value was not calculated due to an insufficient number of participants analyzed.

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

End point timeframe:

Cycle 1 (5 weeks in total) on Day 1 of Week 1, 2 and 3, and Cycle 2 (3 weeks in total) on Day 1 of Week 1

Notes:

[23] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: The endpoint title is specific to the arms which are presented only. Participants in Module 2: Periods 1 and 2 were not assessed for this outcome measure. Hence, only the arms which are referenced in the title are presented per outcome measure.

| End point values | Module 1 Part A: AZD4573 9 mg + 100g acalabrutinib BID | Module 1 Part B: AZD4573 12 mg + 100g acalabrutinib BID | | |
|---|--|---|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 5 | 10 | | |
| Units: Hours (h) | | | | |
| geometric mean (geometric coefficient of variation) | | | | |
| Cycle 1 Week 1 Day 1 (n=1, 5) | 999.999 (± 999.999) | 3.692 (± 37.98) | | |
| Cycle 1 Week 2 Day 1 (n=4, 7) | 3.364 (± 43.80) | 5.407 (± 73.47) | | |
| Cycle 1 Week 3 Day 1 (n=5, 10) | 4.465 (± 42.28) | 6.177 (± 30.16) | | |
| Cycle 2 Week 1 Day 1 (n=4, 5) | 6.508 (± 30.61) | 5.808 (± 25.52) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Module 1: t1/2 of ACP-5862

| | |
|------------------------|--|
| End point title | Module 1: t1/2 of ACP-5862 ^[24] |
| End point description: | The time taken for half the initial dose of drug administered to be eliminated from the body (t1/2) was measured in the pharmacokinetic analysis set. The pharmacokinetic analysis set included all dosed patients with reportable plasma concentrations and no important adverse events or protocol deviations that may impact PK. Here, 999.999 indicates that the value was not calculated due to an insufficient number of participants analyzed. |
| End point type | Secondary |
| End point timeframe: | Cycle 1 (5 weeks in total) on Day 1 of Week 1, 2 and 3, and Cycle 2 (3 weeks in total) on Day 1 of Week 1 |

Notes:

[24] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: The endpoint title is specific to the arms which are presented only. Participants in Module 2: Periods 1 and 2 were not assessed for this outcome measure. Hence, only the arms which are referenced in the title are presented per outcome measure.

| End point values | Module 1 Part A: AZD4573 9 mg + 100g acalabrutinib BID | Module 1 Part B: AZD4573 12 mg + 100g acalabrutinib BID | | |
|---|--|---|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 5 | 6 | | |
| Units: Hours (h) | | | | |
| geometric mean (geometric coefficient of variation) | | | | |
| Cycle 1 Week 1 Day 1 (n=2, 5) | 999.999 (± 999.999) | 2.568 (± 33.27) | | |
| Cycle 1 Week 2 Day 1 (n=2, 4) | 999.999 (± 999.999) | 3.021 (± 47.65) | | |
| Cycle 1 Week 3 Day 1 (n=5, 6) | 2.650 (± 34.68) | 3.557 (± 38.06) | | |
| Cycle 2 Week 1 Day 1 (n=0, 2) | 999.999 (± 999.999) | 999.999 (± 999.999) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Module 1: t1/2 of acalabrutinib

| | |
|-----------------|---|
| End point title | Module 1: t1/2 of acalabrutinib ^[25] |
|-----------------|---|

End point description:

The time taken for half the initial dose of drug administered to be eliminated from the body (t1/2) was measured in the pharmacokinetic analysis set. The pharmacokinetic analysis set included all dosed patients with reportable plasma concentrations and no important adverse events or protocol deviations that may impact PK.

Here, 999.999 indicates that the value was not calculated due to an insufficient number of participants analyzed.

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

End point timeframe:

Cycle 1 (5 weeks in total) on Day 1 of Week 1, 2 and 3, and Cycle 2 (3 weeks in total) on Day 1 of Week 1

Notes:

[25] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: The endpoint title is specific to the arms which are presented only. Participants in Module 2: Periods 1 and 2 were not assessed for this outcome measure. Hence, only the arms which are referenced in the title are presented per outcome measure.

| End point values | Module 1 Part A: AZD4573 9 mg + 100g acalabrutinib BID | Module 1 Part B: AZD4573 12 mg + 100g acalabrutinib BID | | |
|---|--|---|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 6 | 6 | | |
| Units: Hours (h) | | | | |
| geometric mean (geometric coefficient of variation) | | | | |
| Cycle 1 Week 1 Day 1 (n=3, 5) | 1.332 (± 22.01) | 1.108 (± 12.06) | | |

| | | | | |
|-------------------------------|------------------------|--------------------|--|--|
| Cycle 1 Week 2 Day 1 (n=3, 6) | 1.383 (± 49.15) | 1.274 (± 25.09) | | |
| Cycle 1 Week 3 Day 1 (n=6, 6) | 1.238 (± 20.93) | 1.546 (± 38.08) | | |
| Cycle 2 Week 1 Day 1 (n=2, 4) | 999.999 (± 999.999) | 1.398 (± 32.20) | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From Screening (Day -30 to Day -1) until disease progression or survival until death (approximately 2.5 years)

| | |
|-----------------|----------------|
| Assessment type | Non-systematic |
|-----------------|----------------|

Dictionary used

| | |
|--------------------|--------|
| Dictionary name | MedDRA |
| Dictionary version | 26.0 |

Reporting groups

| | |
|-----------------------|--|
| Reporting group title | Module 1 Part A: AZD4573 9 mg + 100g acalabrutinib BID |
|-----------------------|--|

Reporting group description:

Participants received AZD4573 9 mg as Intravenous (IV) infusion once weekly with acalabrutinib 100 mg twice daily.

| | |
|-----------------------|---|
| Reporting group title | Module 1 Part B: AZD4573 12 mg + 100g acalabrutinib BID |
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Reporting group description:

Participants received AZD4573 dose expansion to RP2D 12 mg as IV infusion once weekly with acalabrutinib 100 mg twice daily.

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| Reporting group title | Module 2 Period 1 + 2: AZD4573 12 mg monotherapy + combination |
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Reporting group description:

Participants received AZD4573 12 mg monotherapy until progression and thereafter received a combination regimen of AZD4573 12 mg once weekly and acalabrutinib 100 mg twice daily.

| Serious adverse events | Module 1 Part A: AZD4573 9 mg + 100g acalabrutinib BID | Module 1 Part B: AZD4573 12 mg + 100g acalabrutinib BID | Module 2 Period 1 + 2: AZD4573 12 mg monotherapy + combination |
|---|---|--|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 4 / 9 (44.44%) | 16 / 28 (57.14%) | 2 / 3 (66.67%) |
| number of deaths (all causes) | 4 | 16 | 0 |
| number of deaths resulting from adverse events | 0 | 2 | 0 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Tumour pain | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 1 / 28 (3.57%) | 0 / 3 (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 |
| Metastatic neoplasm | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 1 / 28 (3.57%) | 0 / 3 (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 |
| Investigations | | | |

| | | | |
|---|----------------|----------------|---------------|
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 1 / 28 (3.57%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood bilirubin increased | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 1 / 28 (3.57%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 1 / 28 (3.57%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood creatinine increased | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 2 / 28 (7.14%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatic enzyme increased | | | |
| subjects affected / exposed | 1 / 9 (11.11%) | 0 / 28 (0.00%) | 0 / 3 (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 |
| Liver function test abnormal | | | |
| subjects affected / exposed | 1 / 9 (11.11%) | 0 / 28 (0.00%) | 0 / 3 (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 |
| Nervous system disorders | | | |
| Presyncope | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 1 / 28 (3.57%) | 0 / 3 (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 |
| Syncope | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 1 / 28 (3.57%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

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|--|----------------|----------------|---------------|
| Seizure | | | |
| subjects affected / exposed | 1 / 9 (11.11%) | 0 / 28 (0.00%) | 0 / 3 (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 |
| Blood and lymphatic system disorders | | | |
| Febrile neutropenia | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 2 / 28 (7.14%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Anaemia | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 1 / 28 (3.57%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General disorders and administration site conditions | | | |
| Pyrexia | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 1 / 28 (3.57%) | 0 / 3 (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 |
| Immune system disorders | | | |
| Hypogammaglobulinaemia | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 1 / 28 (3.57%) | 0 / 3 (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 |
| Gastrointestinal disorders | | | |
| Vomiting | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 1 / 28 (3.57%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Acute respiratory failure | | | |
| subjects affected / exposed | 1 / 9 (11.11%) | 0 / 28 (0.00%) | 0 / 3 (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 |
| Dyspnoea | | | |

| | | | |
|--|----------------|-----------------|----------------|
| subjects affected / exposed | 0 / 9 (0.00%) | 1 / 28 (3.57%) | 0 / 3 (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 |
| Infections and infestations | | | |
| Cellulitis | | | |
| subjects affected / exposed | 1 / 9 (11.11%) | 0 / 28 (0.00%) | 0 / 3 (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 |
| Device related infection | | | |
| subjects affected / exposed | 1 / 9 (11.11%) | 0 / 28 (0.00%) | 0 / 3 (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 |
| Infective exacerbation of chronic obstructive airways disease | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 1 / 28 (3.57%) | 0 / 3 (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 |
| Urosepsis | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 1 / 28 (3.57%) | 0 / 3 (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 |
| Hepatitis B reactivation | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 0 / 28 (0.00%) | 1 / 3 (33.33%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia adenoviral | | | |
| alternative dictionary used: MedDRA v26.0 | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 4 / 28 (14.29%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 4 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| COVID-19 virus test | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 2 / 28 (7.14%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| 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 | Module 1 Part A: AZD4573 9 mg + 100g acalabrutinib BID | Module 1 Part B: AZD4573 12 mg + 100g acalabrutinib BID | Module 2 Period 1 + 2: AZD4573 12 mg monotherapy + combination |
|---|---|--|--|
| Total subjects affected by non-serious adverse events subjects affected / exposed | 9 / 9 (100.00%) | 28 / 28 (100.00%) | 3 / 3 (100.00%) |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) Lip neoplasm benign subjects affected / exposed occurrences (all) | 1 / 9 (11.11%) 1 | 0 / 28 (0.00%) 0 | 0 / 3 (0.00%) 0 |
| Vascular disorders Orthostatic hypotension subjects affected / exposed occurrences (all) Hypotension subjects affected / exposed occurrences (all) Deep vein thrombosis subjects affected / exposed occurrences (all) | 1 / 9 (11.11%) 1 0 / 9 (0.00%) 0 0 / 9 (0.00%) 0 | 1 / 28 (3.57%) 1 4 / 28 (14.29%) 4 2 / 28 (7.14%) 2 | 0 / 3 (0.00%) 0 0 / 3 (0.00%) 0 0 / 3 (0.00%) 0 |
| General disorders and administration site conditions Chest discomfort subjects affected / exposed occurrences (all) Pyrexia subjects affected / exposed occurrences (all) Peripheral swelling subjects affected / exposed occurrences (all) Oedema peripheral | 0 / 9 (0.00%) 0 0 / 9 (0.00%) 0 0 / 9 (0.00%) 0 0 | 0 / 28 (0.00%) 0 6 / 28 (21.43%) 6 2 / 28 (7.14%) 2 | 1 / 3 (33.33%) 1 2 / 3 (66.67%) 2 0 / 3 (0.00%) 0 |

| | | | |
|--|---------------------|------------------------|---------------------|
| subjects affected / exposed occurrences (all) | 3 / 9 (33.33%) 3 | 2 / 28 (7.14%) 2 | 0 / 3 (0.00%) 0 |
| Injection site erythema subjects affected / exposed occurrences (all) | 1 / 9 (11.11%) 1 | 1 / 28 (3.57%) 1 | 0 / 3 (0.00%) 0 |
| Fatigue subjects affected / exposed occurrences (all) | 2 / 9 (22.22%) 3 | 11 / 28 (39.29%) 12 | 2 / 3 (66.67%) 2 |
| Device related thrombosis subjects affected / exposed occurrences (all) | 1 / 9 (11.11%) 1 | 0 / 28 (0.00%) 0 | 0 / 3 (0.00%) 0 |
| Catheter site related reaction subjects affected / exposed occurrences (all) | 1 / 9 (11.11%) 1 | 0 / 28 (0.00%) 0 | 0 / 3 (0.00%) 0 |
| Catheter site erythema subjects affected / exposed occurrences (all) | 1 / 9 (11.11%) 1 | 0 / 28 (0.00%) 0 | 0 / 3 (0.00%) 0 |
| Asthenia subjects affected / exposed occurrences (all) | 1 / 9 (11.11%) 1 | 2 / 28 (7.14%) 2 | 0 / 3 (0.00%) 0 |
| Application site erosion subjects affected / exposed occurrences (all) | 1 / 9 (11.11%) 1 | 0 / 28 (0.00%) 0 | 0 / 3 (0.00%) 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Hypoxia subjects affected / exposed occurrences (all) | 0 / 9 (0.00%) 0 | 0 / 28 (0.00%) 0 | 1 / 3 (33.33%) 1 |
| Rhinorrhea subjects affected / exposed occurrences (all) | 1 / 9 (11.11%) 1 | 0 / 28 (0.00%) 0 | 0 / 3 (0.00%) 0 |
| Oropharyngeal pain subjects affected / exposed occurrences (all) | 2 / 9 (22.22%) 2 | 0 / 28 (0.00%) 0 | 0 / 3 (0.00%) 0 |
| Nasal congestion | | | |

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|---|----------------------|------------------------|---------------------|
| subjects affected / exposed occurrences (all) | 0 / 9 (0.00%) 0 | 3 / 28 (10.71%) 3 | 0 / 3 (0.00%) 0 |
| Hiccups subjects affected / exposed occurrences (all) | 1 / 9 (11.11%) 1 | 1 / 28 (3.57%) 1 | 0 / 3 (0.00%) 0 |
| Epistaxis subjects affected / exposed occurrences (all) | 0 / 9 (0.00%) 0 | 2 / 28 (7.14%) 2 | 1 / 3 (33.33%) 1 |
| Dyspnoea subjects affected / exposed occurrences (all) | 0 / 9 (0.00%) 0 | 5 / 28 (17.86%) 5 | 2 / 3 (66.67%) 2 |
| Cough subjects affected / exposed occurrences (all) | 1 / 9 (11.11%) 2 | 4 / 28 (14.29%) 6 | 1 / 3 (33.33%) 1 |
| Psychiatric disorders Insomnia subjects affected / exposed occurrences (all) | 1 / 9 (11.11%) 1 | 3 / 28 (10.71%) 3 | 0 / 3 (0.00%) 0 |
| Investigations Aspartate aminotransferase increased subjects affected / exposed occurrences (all) | 3 / 9 (33.33%) 12 | 15 / 28 (53.57%) 55 | 0 / 3 (0.00%) 0 |
| Blood alkaline phosphatase increased subjects affected / exposed occurrences (all) | 1 / 9 (11.11%) 1 | 0 / 28 (0.00%) 0 | 0 / 3 (0.00%) 0 |
| Blood bilirubin increased subjects affected / exposed occurrences (all) | 1 / 9 (11.11%) 1 | 3 / 28 (10.71%) 5 | 0 / 3 (0.00%) 0 |
| Alanine aminotransferase increased subjects affected / exposed occurrences (all) | 3 / 9 (33.33%) 6 | 15 / 28 (53.57%) 46 | 0 / 3 (0.00%) 0 |
| Amylase increased subjects affected / exposed occurrences (all) | 0 / 9 (0.00%) 0 | 2 / 28 (7.14%) 2 | 0 / 3 (0.00%) 0 |
| Transaminases increased | | | |

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|--|----------------|-----------------|----------------|
| subjects affected / exposed | 1 / 9 (11.11%) | 1 / 28 (3.57%) | 0 / 3 (0.00%) |
| occurrences (all) | 2 | 1 | 0 |
| Weight increased | | | |
| subjects affected / exposed | 1 / 9 (11.11%) | 0 / 28 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Lipase increased | | | |
| subjects affected / exposed | 1 / 9 (11.11%) | 1 / 28 (3.57%) | 0 / 3 (0.00%) |
| occurrences (all) | 2 | 1 | 0 |
| Blood creatinine increased | | | |
| subjects affected / exposed | 1 / 9 (11.11%) | 4 / 28 (14.29%) | 1 / 3 (33.33%) |
| occurrences (all) | 1 | 5 | 2 |
| Fibrin D dimer increased | | | |
| subjects affected / exposed | 1 / 9 (11.11%) | 1 / 28 (3.57%) | 0 / 3 (0.00%) |
| occurrences (all) | 2 | 1 | 0 |
| Gamma-glutamyltransferase increased | | | |
| subjects affected / exposed | 2 / 9 (22.22%) | 3 / 28 (10.71%) | 0 / 3 (0.00%) |
| occurrences (all) | 3 | 6 | 0 |
| White blood cell count decreased | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 0 / 28 (0.00%) | 1 / 3 (33.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Hepatic enzyme increased | | | |
| subjects affected / exposed | 1 / 9 (11.11%) | 0 / 28 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Glutamate dehydrogenase increased | | | |
| subjects affected / exposed | 1 / 9 (11.11%) | 0 / 28 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Injury, poisoning and procedural complications | | | |
| Contusion | | | |
| subjects affected / exposed | 1 / 9 (11.11%) | 5 / 28 (17.86%) | 0 / 3 (0.00%) |
| occurrences (all) | 2 | 6 | 0 |
| Cardiac disorders | | | |
| Tachycardia | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 2 / 28 (7.14%) | 1 / 3 (33.33%) |
| occurrences (all) | 0 | 2 | 1 |
| Atrial fibrillation | | | |

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|--|-----------------------|-------------------------|----------------------|
| subjects affected / exposed occurrences (all) | 0 / 9 (0.00%) 0 | 2 / 28 (7.14%) 2 | 0 / 3 (0.00%) 0 |
| Nervous system disorders | | | |
| Dizziness | | | |
| subjects affected / exposed occurrences (all) | 1 / 9 (11.11%) 1 | 5 / 28 (17.86%) 7 | 0 / 3 (0.00%) 0 |
| Dizziness postural | | | |
| subjects affected / exposed occurrences (all) | 1 / 9 (11.11%) 1 | 1 / 28 (3.57%) 1 | 0 / 3 (0.00%) 0 |
| Headache | | | |
| subjects affected / exposed occurrences (all) | 1 / 9 (11.11%) 1 | 6 / 28 (21.43%) 8 | 1 / 3 (33.33%) 1 |
| Peripheral sensory neuropathy | | | |
| subjects affected / exposed occurrences (all) | 1 / 9 (11.11%) 2 | 0 / 28 (0.00%) 0 | 0 / 3 (0.00%) 0 |
| Presyncope | | | |
| subjects affected / exposed occurrences (all) | 0 / 9 (0.00%) 0 | 3 / 28 (10.71%) 4 | 0 / 3 (0.00%) 0 |
| Blood and lymphatic system disorders | | | |
| Thrombocytopenia | | | |
| subjects affected / exposed occurrences (all) | 6 / 9 (66.67%) 11 | 16 / 28 (57.14%) 46 | 1 / 3 (33.33%) 3 |
| Neutropenia | | | |
| subjects affected / exposed occurrences (all) | 9 / 9 (100.00%) 86 | 25 / 28 (89.29%) 126 | 3 / 3 (100.00%) 6 |
| Lymphopenia | | | |
| subjects affected / exposed occurrences (all) | 1 / 9 (11.11%) 1 | 0 / 28 (0.00%) 0 | 0 / 3 (0.00%) 0 |
| Leukopenia | | | |
| subjects affected / exposed occurrences (all) | 3 / 9 (33.33%) 3 | 2 / 28 (7.14%) 2 | 0 / 3 (0.00%) 0 |
| Anaemia | | | |
| subjects affected / exposed occurrences (all) | 3 / 9 (33.33%) 3 | 14 / 28 (50.00%) 23 | 1 / 3 (33.33%) 1 |
| Ear and labyrinth disorders | | | |

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|-----------------------------|----------------|------------------|----------------|
| Deafness | | | |
| subjects affected / exposed | 1 / 9 (11.11%) | 0 / 28 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Eye disorders | | | |
| Punctate keratitis | | | |
| subjects affected / exposed | 1 / 9 (11.11%) | 0 / 28 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Scintillating scotoma | | | |
| subjects affected / exposed | 1 / 9 (11.11%) | 0 / 28 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 2 / 9 (22.22%) | 2 / 28 (7.14%) | 2 / 3 (66.67%) |
| occurrences (all) | 2 | 2 | 2 |
| Abdominal distension | | | |
| subjects affected / exposed | 1 / 9 (11.11%) | 1 / 28 (3.57%) | 1 / 3 (33.33%) |
| occurrences (all) | 1 | 1 | 1 |
| Abdominal discomfort | | | |
| subjects affected / exposed | 1 / 9 (11.11%) | 1 / 28 (3.57%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Abdominal pain upper | | | |
| subjects affected / exposed | 1 / 9 (11.11%) | 1 / 28 (3.57%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Dry mouth | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 0 / 28 (0.00%) | 1 / 3 (33.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Abdominal pain lower | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 0 / 28 (0.00%) | 1 / 3 (33.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Vomiting | | | |
| subjects affected / exposed | 1 / 9 (11.11%) | 11 / 28 (39.29%) | 1 / 3 (33.33%) |
| occurrences (all) | 1 | 19 | 1 |
| Saliva altered | | | |
| subjects affected / exposed | 1 / 9 (11.11%) | 0 / 28 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Nausea | | | |

| | | | |
|--|----------------|------------------|-----------------|
| subjects affected / exposed | 4 / 9 (44.44%) | 19 / 28 (67.86%) | 2 / 3 (66.67%) |
| occurrences (all) | 7 | 33 | 2 |
| Gastroesophageal reflux disease | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 4 / 28 (14.29%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 4 | 0 |
| Epigastric discomfort | | | |
| subjects affected / exposed | 1 / 9 (11.11%) | 0 / 28 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Dysphagia | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 2 / 28 (7.14%) | 1 / 3 (33.33%) |
| occurrences (all) | 0 | 3 | 1 |
| Dyspepsia | | | |
| subjects affected / exposed | 1 / 9 (11.11%) | 1 / 28 (3.57%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Diarrhoea | | | |
| subjects affected / exposed | 3 / 9 (33.33%) | 14 / 28 (50.00%) | 3 / 3 (100.00%) |
| occurrences (all) | 7 | 32 | 5 |
| Constipation | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 4 / 28 (14.29%) | 2 / 3 (66.67%) |
| occurrences (all) | 0 | 4 | 2 |
| Hepatobiliary disorders | | | |
| Hyperbilirubinaemia | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 3 / 28 (10.71%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 9 | 0 |
| Skin and subcutaneous tissue disorders | | | |
| Rash macular | | | |
| subjects affected / exposed | 1 / 9 (11.11%) | 0 / 28 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Night sweats | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 3 / 28 (10.71%) | 1 / 3 (33.33%) |
| occurrences (all) | 0 | 4 | 1 |
| Keratosis pilaris | | | |
| subjects affected / exposed | 1 / 9 (11.11%) | 0 / 28 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Petechiae | | | |

| | | | |
|---|---------------------|----------------------|---------------------|
| subjects affected / exposed occurrences (all) | 0 / 9 (0.00%) 0 | 0 / 28 (0.00%) 0 | 1 / 3 (33.33%) 1 |
| Rash maculo-papular subjects affected / exposed occurrences (all) | 2 / 9 (22.22%) 3 | 2 / 28 (7.14%) 2 | 0 / 3 (0.00%) 0 |
| Renal and urinary disorders | | | |
| Glycosuria subjects affected / exposed occurrences (all) | 1 / 9 (11.11%) 1 | 2 / 28 (7.14%) 3 | 0 / 3 (0.00%) 0 |
| Proteinuria subjects affected / exposed occurrences (all) | 1 / 9 (11.11%) 1 | 0 / 28 (0.00%) 0 | 0 / 3 (0.00%) 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Bone pain subjects affected / exposed occurrences (all) | 0 / 9 (0.00%) 0 | 0 / 28 (0.00%) 0 | 1 / 3 (33.33%) 1 |
| Pain in extremity subjects affected / exposed occurrences (all) | 0 / 9 (0.00%) 0 | 0 / 28 (0.00%) 0 | 1 / 3 (33.33%) 1 |
| Myalgia subjects affected / exposed occurrences (all) | 2 / 9 (22.22%) 2 | 1 / 28 (3.57%) 1 | 0 / 3 (0.00%) 0 |
| Muscle spasms subjects affected / exposed occurrences (all) | 0 / 9 (0.00%) 0 | 3 / 28 (10.71%) 3 | 0 / 3 (0.00%) 0 |
| Back pain subjects affected / exposed occurrences (all) | 1 / 9 (11.11%) 1 | 5 / 28 (17.86%) 5 | 1 / 3 (33.33%) 1 |
| Arthralgia subjects affected / exposed occurrences (all) | 1 / 9 (11.11%) 2 | 2 / 28 (7.14%) 3 | 0 / 3 (0.00%) 0 |
| Infections and infestations | | | |
| COVID-19 subjects affected / exposed occurrences (all) | 3 / 9 (33.33%) 4 | 2 / 28 (7.14%) 2 | 0 / 3 (0.00%) 0 |
| Cellulitis | | | |

| | | | |
|---------------------------------------|----------------|----------------|----------------|
| subjects affected / exposed | 1 / 9 (11.11%) | 0 / 28 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Escherichia urinary tract infection | | | |
| subjects affected / exposed | 1 / 9 (11.11%) | 0 / 28 (0.00%) | 1 / 3 (33.33%) |
| occurrences (all) | 1 | 0 | 1 |
| Fungal skin infection | | | |
| subjects affected / exposed | 1 / 9 (11.11%) | 0 / 28 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Nasopharyngitis | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 2 / 28 (7.14%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Oral candidiasis | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 2 / 28 (7.14%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Oral herpes | | | |
| subjects affected / exposed | 1 / 9 (11.11%) | 0 / 28 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Pharyngitis | | | |
| subjects affected / exposed | 1 / 9 (11.11%) | 0 / 28 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Pneumonia | | | |
| subjects affected / exposed | 1 / 9 (11.11%) | 1 / 28 (3.57%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Respiratory syncytial virus infection | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 2 / 28 (7.14%) | 0 / 3 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Rhinovirus infection | | | |
| subjects affected / exposed | 1 / 9 (11.11%) | 0 / 28 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Diverticulitis | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 0 / 28 (0.00%) | 1 / 3 (33.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Catheter site infection | | | |
| subjects affected / exposed | 1 / 9 (11.11%) | 0 / 28 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Metabolism and nutrition disorders | | | |

| | | | |
|---|---------------------|-----------------------|---------------------|
| Decreased appetite subjects affected / exposed occurrences (all) | 1 / 9 (11.11%) 1 | 4 / 28 (14.29%) 4 | 1 / 3 (33.33%) 1 |
| Dehydration subjects affected / exposed occurrences (all) | 1 / 9 (11.11%) 1 | 1 / 28 (3.57%) 1 | 0 / 3 (0.00%) 0 |
| Hyperglycaemia subjects affected / exposed occurrences (all) | 0 / 9 (0.00%) 0 | 3 / 28 (10.71%) 4 | 0 / 3 (0.00%) 0 |
| Hyperkalaemia subjects affected / exposed occurrences (all) | 1 / 9 (11.11%) 1 | 2 / 28 (7.14%) 2 | 0 / 3 (0.00%) 0 |
| Hyperphosphataemia subjects affected / exposed occurrences (all) | 0 / 9 (0.00%) 0 | 8 / 28 (28.57%) 9 | 2 / 3 (66.67%) 3 |
| Hypertriglyceridaemia subjects affected / exposed occurrences (all) | 1 / 9 (11.11%) 4 | 1 / 28 (3.57%) 4 | 0 / 3 (0.00%) 0 |
| Hypoalbuminaemia subjects affected / exposed occurrences (all) | 0 / 9 (0.00%) 0 | 2 / 28 (7.14%) 2 | 0 / 3 (0.00%) 0 |
| Hypocalcaemia subjects affected / exposed occurrences (all) | 0 / 9 (0.00%) 0 | 4 / 28 (14.29%) 7 | 0 / 3 (0.00%) 0 |
| Hypokalaemia subjects affected / exposed occurrences (all) | 0 / 9 (0.00%) 0 | 8 / 28 (28.57%) 14 | 0 / 3 (0.00%) 0 |
| Hypomagnesaemia subjects affected / exposed occurrences (all) | 0 / 9 (0.00%) 0 | 2 / 28 (7.14%) 2 | 0 / 3 (0.00%) 0 |
| Hyponatraemia subjects affected / exposed occurrences (all) | 1 / 9 (11.11%) 1 | 1 / 28 (3.57%) 2 | 0 / 3 (0.00%) 0 |
| Hypophosphataemia subjects affected / exposed occurrences (all) | 0 / 9 (0.00%) 0 | 7 / 28 (25.00%) 14 | 0 / 3 (0.00%) 0 |

| | | | |
|---|--------------------|-----------------------|--------------------|
| Tumour lysis syndrome subjects affected / exposed occurrences (all) | 0 / 9 (0.00%) 0 | 6 / 28 (21.43%) 13 | 0 / 3 (0.00%) 0 |
|---|--------------------|-----------------------|--------------------|

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|----------------|--|
| 03 July 2020 | Amended core inclusion criteria to update calculated creatinine clearance from ≥ 50 mL/minute to ≥ 60 mL/minute, specify that participants should be able to swallow capsules and remove serum creatinine from criteria for adequate organ function; updated exclusion criteria regarding anticoagulant therapy; updated justification for dose; updated exclusion criteria regarding participants on anticoagulant therapy; updated DLT criteria for timing, febrile neutropenia and thrombocytopenia, and definition of isolated changes in GGT in DLT criteria exclusions; included warfarin or equivalent vitamin K antagonists to prohibited concomitant therapies; added requirement that acalabrutinib treatment must be discontinued if participants require vitamin K antagonist or combined administration of antiplatelet and therapeutic anticoagulation while on study; added additional safety monitoring and potential stopping criteria. |
| 21 July 2021 | Updated study design to include additional Module 2 AZD4573 monotherapy window followed by combination therapy with acalabrutinib; updated requirements for overnight hospitalization based on emerging data from ongoing FTIH study; updated exploratory objectives; amended Module 1 description to include MZL participants; changed data cut-off for primary analysis for each expansion subgroup from after all participants have had the opportunity to be followed for at least 12 months to at least 6 months; added clarification on TLS monitoring, updated study synopsis to reflect additional module and addition of participants with r/r MZL to Module 1. |
| 01 August 2022 | Updated core exclusion criteria: reduced CAR-T criteria to within 60 days prior to first dose of study drug; updated Module 1 part B: changed so that any safe dose level can be backfilled to approximately 21 patients instead of 12; removed Module 1 exclusion criteria for BTK inhibitors; updated schedule of activities to have less frequent assessments in earlier cycles; updated PHL process to reflect experience of AZD4573 liver safety profile. |
| 01 June 2023 | Updated overall study design to include rationale as to why study has permanently halted; added text throughout protocol to define that participants still receiving clinical benefit of treatment may continue to receive study treatment, initially planned interim analysis will not be performed, and Module 1 DLBCL cohorts will be pooled for the purpose of primary analysis; updated end of study definition in core section of the protocol. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Due to the overall AZD4573 development programme being discontinued as part of a strategic portfolio decision, available data analyzed for this study is limited.

Notes: