



## Clinical trial results:

### A Single-Arm, Open-Label, Phase 1/2 Study of ZN-d5 for the Treatment of Relapsed or Refractory Light Chain (AL) Amyloidosis

#### Summary

|                          |                  |
|--------------------------|------------------|
| EudraCT number           | 2021-003008-42   |
| Trial protocol           | GR IT CY         |
| Global end of trial date | 14 February 2024 |

#### Results information

|                                |                  |
|--------------------------------|------------------|
| Result version number          | v1 (current)     |
| This version publication date  | 22 February 2025 |
| First version publication date | 22 February 2025 |

#### Trial information

##### Trial identification

|                       |           |
|-----------------------|-----------|
| Sponsor protocol code | ZN-d5-003 |
|-----------------------|-----------|

##### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT05199337 |
| WHO universal trial number (UTN)   | -           |

Notes:

#### Sponsors

|                              |  |
|------------------------------|--|
| Sponsor organisation name    | Zentalis   |
| Sponsor organisation address | Science Center Drive, Suite 200, San Diego, United States, 10275               |
| Public contact               | Regulatory Affairs, K-Group Alpha, Inc, +1 732-666-5002, risrani@zentalis.com  |
| Scientific contact           | Regulatory Affairs, K-Group Alpha, Inc, +1 6096199909, afrederick@zentalis.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                       | 02 October 2024  |
| Is this the analysis of the primary completion data? | No               |
| Global end of trial reached?                         | Yes              |
| Global end of trial date                             | 14 February 2024 |
| Was the trial ended prematurely?                     | Yes              |

Notes:

## General information about the trial

Main objective of the trial:

Part A:

- To determine the safety, tolerability, and maximum tolerated dose of ZN d5
- To determine the recommended phase 2 dose of ZN d5

Part B:

- To assess the response to ZN d5 in subjects with RRAL with and without the t(11;14) translocation

Protection of trial subjects:

Subject confidentiality and privacy were held in trust by the participating Investigators, their staff, and the Sponsor(s) and its service providers. This confidentiality was extended to cover testing of biological samples in addition to the clinical information relating to subjects. Therefore, the study protocol, documentation, data, and all other information generated were held in confidence. Personal details of subjects were treated as confidential by the Investigator and staff at Sponsor's CRO, and handling of personal data was in compliance with applicable privacy laws. All research activities were conducted in a private setting.

The study monitor, other authorized representatives of the Sponsor (including but not limited to the CRO), representatives of the IRB/IEC, study research monitor, and regulatory agencies, and/or the pharmaceutical company supplying the study product inspected all documents and records required to be maintained by the Investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the subjects in this study, including records that identified the subject by name. The clinical study site permitted access to such records.

The study subject's contact information was securely stored at each clinical site for internal use during the study. At the end of the study, all records continued to be kept in a secure location for as long a period as dictated by applicable laws, the reviewing IRB/IEC, institutional policies, or Sponsor requirements. Study subject research data, which were for purposes of statistical analysis and scientific reporting, were transmitted to, and stored at, the Sponsor's service providers. This generally did not include the subject's contact or identifying information. Rather, individual subjects and their research data were identified by a unique study identification number.

Background therapy:

Standard AL amyloidosis supportive treatments to manage underlying organ system dysfunction were permitted, except for interventions considered treatments for AL amyloidosis (including systemic corticosteroids and tetracycline antibiotics) and contraindicated medications.

Evidence for comparator:

The study did not include a comparator.

|   |                  |
|---|------------------|
| Actual start date of recruitment                          | 01 November 2021 |
| Long term follow-up planned                               | No               |
| Independent data monitoring committee (IDMC) involvement? | No               |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |           |
|--------------------------------------|-----------|
| Country: Number of subjects enrolled | Spain: 2  |
| Country: Number of subjects enrolled | Greece: 6 |



|                                      |                  |
|--------------------------------------|------------------|
| Country: Number of subjects enrolled | Israel: 4        |
| Country: Number of subjects enrolled | Australia: 5     |
| Country: Number of subjects enrolled | United States: 1 |
| Worldwide total number of subjects   | 18               |
| EEA total number of subjects         | 8                |

Notes:

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### 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)                      | 10 |
| From 65 to 84 years                       | 8  |
| 85 years and over                         | 0  |



## Subject disposition

### Recruitment

Recruitment details:

Up to approximately 159 subjects with RRAL were planned to be enrolled, including up to approximately 27 subjects in dose escalation and up to 24 subjects in dose optimization during Part A.

A total of 18 subjects were enrolled in the study.

### Pre-assignment

Screening details:

Enrolled in this study were subjects with RRAL who had progression of disease after 1 to 3 prior lines of therapy.

Additional criteria for inclusion included age  $\geq 18$  years (or the minimum legal age, whichever was greater), a biopsy confirmed diagnosis of AL amyloidosis requiring treatment.

### Period 1

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

### Arms

|                              |                               |
|------------------------------|-------------------------------|
| Are arms mutually exclusive? | Yes                           |
| <b>Arm title</b>             | ZN-d5 400 mg QD Empty Stomach |

Arm description:

Bayesian Optimal Interval dose-escalation arm.

|  |              |
|--|--------------|
| Arm type                               | Experimental |
| Investigational medicinal product name | ZN-d5        |
| Investigational medicinal product code |              |
| Other name                             |              |
| Pharmaceutical forms                   | Tablet       |
| Routes of administration               | Oral use     |

Dosage and administration details:

ZN-d5 was provided as 25 mg and 100 mg tablets.

The initial dose cohort received 400 mg QD ZN-d5 administered orally on an empty stomach.

|                  |                           |
|------------------|---------------------------|
| <b>Arm title</b> | ZN-d5 200 mg QD With Food |
|------------------|---------------------------|

Arm description:

Bayesian Optimal Interval dose-escalation arm. Second dose cohort received 200 mg QD ZN-d5 administered orally with food.

|  |              |
|--|--------------|
| Arm type                               | Experimental |
| Investigational medicinal product name | ZN-d5        |
| Investigational medicinal product code |              |
| Other name                             |              |
| Pharmaceutical forms                   | Tablet       |
| Routes of administration               | Oral use     |

Dosage and administration details:

ZN-d5 was provided as 25 mg and 100 mg tablets.

The second dose cohort received 200 mg QD ZN-d5 administered orally with food.

|                  |                           |
|------------------|---------------------------|
| <b>Arm title</b> | ZN-d5 400 mg QD With Food |
|------------------|---------------------------|

Arm description:

Bayesian Optimal Interval dose-escalation arm. Dose escalations continued up to a daily dose of 1200 mg ZN-d5 administered with food.



|  |              |
|--|--------------|
| Arm type                               | Experimental |
| Investigational medicinal product name | ZN-d5        |
| Investigational medicinal product code |              |
| Other name                             |              |
| Pharmaceutical forms                   | Tablet       |
| Routes of administration               | Oral use     |

**Dosage and administration details:**

ZN-d5 was provided as 25 mg and 100 mg tablets.

The third dose cohort received 400 mg QD ZN-d5 administered orally with food.

|                  |                           |
|------------------|---------------------------|
| <b>Arm title</b> | ZN-d5 800 mg QD With Food |
|------------------|---------------------------|

**Arm description:**

Bayesian Optimal Interval dose-escalation arm. Dose escalations continued up to a daily dose of 1200 mg ZN-d5 administered with food.

|  |              |
|--|--------------|
| Arm type                               | Experimental |
| Investigational medicinal product name | ZN-d5        |
| Investigational medicinal product code |              |
| Other name                             |              |
| Pharmaceutical forms                   | Tablet       |
| Routes of administration               | Oral use     |

**Dosage and administration details:**

ZN-d5 was provided as 25 mg and 100 mg tablets.

The third dose cohort received 800 mg QD ZN-d5 administered orally with food.

|                  |                            |
|------------------|----------------------------|
| <b>Arm title</b> | ZN-d5 600 mg BID With Food |
|------------------|----------------------------|

**Arm description:**

Bayesian Optimal Interval dose-escalation arm. Dose escalations continued up to a daily dose of 1200 mg ZN-d5 administered with food.

|  |              |
|--|--------------|
| Arm type                               | Experimental |
| Investigational medicinal product name | ZN-d5        |
| Investigational medicinal product code |              |
| Other name                             |              |
| Pharmaceutical forms                   | Tablet       |
| Routes of administration               | Oral use     |

**Dosage and administration details:**

ZN-d5 was provided as 25 mg and 100 mg tablets. Dose escalations continued up to a daily dose of 1200 mg ZN-d5 administered with food. BID dosing was allowed for the

1200 mg cohort (administered as 600 mg BID), as well as at lower dose levels per Sponsor approval.

ZN-d5 was administered daily and continuously, in 28-day treatment cycles, with no interruption during or between cycles.

| <b>Number of subjects in period 1</b> | <b>ZN-d5 400 mg QD<br/>Empty Stomach</b> | <b>ZN-d5 200 mg QD<br/>With Food</b> | <b>ZN-d5 400 mg QD<br/>With Food</b> |
|---------------------------------------|--|--------------------------------------|--------------------------------------|
| Started                               | 3  | 5                                    | 3                                    |
| Completed                             | 0  | 0                                    | 0                                    |
| Not completed                         | 3  | 5                                    | 3                                    |
| Adverse event, serious fatal          | 1  | -                                    | -                                    |
| Consent withdrawn by subject          | -  | -                                    | 1                                    |
| Study Terminated By Sponsor           | -  | 1                                    | 1                                    |



|                          |   |   |   |
|--------------------------|---|---|---|
| Adverse event, non-fatal | - | - | - |
| Investigator Discretion  | 1 | 3 | 1 |
| Disease Progression      | 1 | 1 | - |

| <b>Number of subjects in period 1</b> | <b>ZN-d5 800 mg QD<br/>With Food</b> | <b>ZN-d5 600 mg BID<br/>With Food</b> |
|---------------------------------------|--------------------------------------|---------------------------------------|
| Started                               | 3                                    | 4                                     |
| Completed                             | 0                                    | 0                                     |
| Not completed                         | 3                                    | 4                                     |
| Adverse event, serious fatal          | -                                    | -                                     |
| Consent withdrawn by subject          | -                                    | -                                     |
| Study Terminated By Sponsor           | 1                                    | 1                                     |
| Adverse event, non-fatal              | 1                                    | -                                     |
| Investigator Discretion               | 1                                    | 2                                     |
| Disease Progression                   | -                                    | 1                                     |



## Baseline characteristics

### Reporting groups

|   |                               |
|---|-------------------------------|
| Reporting group title   | ZN-d5 400 mg QD Empty Stomach |
| Reporting group description:<br>Bayesian Optimal Interval dose-escalation arm.  |                               |
| Reporting group title   | ZN-d5 200 mg QD With Food     |
| Reporting group description:<br>Bayesian Optimal Interval dose-escalation arm. Second dose cohort received 200 mg QD ZN-d5 administered orally with food.             |                               |
| Reporting group title   | ZN-d5 400 mg QD With Food     |
| Reporting group description:<br>Bayesian Optimal Interval dose-escalation arm. Dose escalations continued up to a daily dose of 1200 mg ZN-d5 administered with food. |                               |
| Reporting group title   | ZN-d5 800 mg QD With Food     |
| Reporting group description:<br>Bayesian Optimal Interval dose-escalation arm. Dose escalations continued up to a daily dose of 1200 mg ZN-d5 administered with food. |                               |
| Reporting group title   | ZN-d5 600 mg BID With Food    |
| Reporting group description:<br>Bayesian Optimal Interval dose-escalation arm. Dose escalations continued up to a daily dose of 1200 mg ZN-d5 administered with food. |                               |

| Reporting group values                | ZN-d5 400 mg QD Empty Stomach | ZN-d5 200 mg QD With Food | ZN-d5 400 mg QD With Food |
|---------------------------------------|-------------------------------|---------------------------|---------------------------|
| Number of subjects                    | 3                             | 5                         | 3                         |
| Age categorical<br>Units: Subjects    |                               |                           |                           |
| Adults (18-64 years)                  | 2                             | 4                         | 1                         |
| From 65-84 years                      | 1                             | 1                         | 2                         |
| Age continuous<br>Units: years        |                               |                           |                           |
| arithmetic mean                       | 57.3                          | 61.6                      | 67.0                      |
| standard deviation                    | ± 9.61                        | ± 7.54                    | ± 9.17                    |
| Gender categorical<br>Units: Subjects |                               |                           |                           |
| Female                                | 1                             | 2                         | 1                         |
| Male                                  | 2                             | 3                         | 2                         |

| Reporting group values             | ZN-d5 800 mg QD With Food | ZN-d5 600 mg BID With Food | Total |
|------------------------------------|---------------------------|----------------------------|-------|
| Number of subjects                 | 3                         | 4                          | 18    |
| Age categorical<br>Units: Subjects |                           |                            |       |
| Adults (18-64 years)               | 2                         | 1                          | 10    |
| From 65-84 years                   | 1                         | 3                          | 8     |
| Age continuous<br>Units: years     |                           |                            |       |
| arithmetic mean                    | 62.3                      | 70.8                       | -     |
| standard deviation                 | ± 4.04                    | ± 9.91                     | -     |



|                    |   |   |    |
|--------------------|---|---|----|
| Gender categorical |   |   |    |
| Units: Subjects    |   |   |    |
| Female             | 0 | 2 | 6  |
| Male               | 3 | 2 | 12 |



## End points

### End points reporting groups

|   |                               |
|---|-------------------------------|
| Reporting group title   | ZN-d5 400 mg QD Empty Stomach |
| Reporting group description:<br>Bayesian Optimal Interval dose-escalation arm.  |                               |
| Reporting group title   | ZN-d5 200 mg QD With Food     |
| Reporting group description:<br>Bayesian Optimal Interval dose-escalation arm. Second dose cohort received 200 mg QD ZN-d5 administered orally with food.             |                               |
| Reporting group title   | ZN-d5 400 mg QD With Food     |
| Reporting group description:<br>Bayesian Optimal Interval dose-escalation arm. Dose escalations continued up to a daily dose of 1200 mg ZN-d5 administered with food. |                               |
| Reporting group title   | ZN-d5 800 mg QD With Food     |
| Reporting group description:<br>Bayesian Optimal Interval dose-escalation arm. Dose escalations continued up to a daily dose of 1200 mg ZN-d5 administered with food. |                               |
| Reporting group title   | ZN-d5 600 mg BID With Food    |
| Reporting group description:<br>Bayesian Optimal Interval dose-escalation arm. Dose escalations continued up to a daily dose of 1200 mg ZN-d5 administered with food. |                               |

### Primary: Dose-limiting toxicities

|   |   |
|---|---|
| End point title   | Dose-limiting toxicities <sup>[1]</sup> |
| End point description:  |   |
| End point type  | Primary                                 |
| End point timeframe:<br>Through Cycle 1, Day 28   |   |
| Notes:<br>[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.<br>Justification: All subjects were DLT-evaluable and no DLTs were identified, hence no data to report as there were no DLTs. |   |

| End point values            | ZN-d5 400 mg QD Empty Stomach | ZN-d5 200 mg QD With Food | ZN-d5 400 mg QD With Food | ZN-d5 800 mg QD With Food |
|-----------------------------|-------------------------------|---------------------------|---------------------------|---------------------------|
| Subject group type          | Reporting group               | Reporting group           | Reporting group           | Reporting group           |
| Number of subjects analysed | 3                             | 5                         | 3                         | 3                         |
| Units: Subjects             |                               |                           |                           |                           |
| Dose-limiting toxicities    | 0                             | 0                         | 0                         | 0                         |

| End point values            | ZN-d5 600 mg BID With Food |  |  |  |
|-----------------------------|----------------------------|--|--|--|
| Subject group type          | Reporting group            |  |  |  |
| Number of subjects analysed | 4                          |  |  |  |



|                          |   |  |  |  |
|--------------------------|---|--|--|--|
| Units: Subjects          |   |  |  |  |
| Dose-limiting toxicities | 0 |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Primary: Incidence and severity of AEs

|                 |                               |
|-----------------|-------------------------------|
| End point title | Incidence and severity of AEs |
|-----------------|-------------------------------|

End point description:

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

End point timeframe:

From the first dose through EOT or initiation of subsequent therapy

| End point values                                    | ZN-d5 400 mg<br>QD Empty<br>Stomach | ZN-d5 200 mg<br>QD With Food | ZN-d5 400 mg<br>QD With Food | ZN-d5 800 mg<br>QD With Food |
|---|-------------------------------------|------------------------------|------------------------------|------------------------------|
| Subject group type                                  | Reporting group                     | Reporting group              | Reporting group              | Reporting group              |
| Number of subjects analysed                         | 3                                   | 5                            | 3                            | 3                            |
| Units: Subjects                                     |                                     |                              |                              |                              |
| TEAE  | 2                                   | 5                            | 3                            | 3                            |
| Study drug-related TEAE                             | 2                                   | 3                            | 3                            | 3                            |
| Grade $\geq 3$ TEAE                                 | 2                                   | 3                            | 1                            | 1                            |
| TEAE study drug interruption and/or<br>modification | 0                                   | 2                            | 3                            | 1                            |
| TEAE leading to study drug<br>discontinuation       | 1                                   | 0                            | 0                            | 1                            |
| Serious TEAE  | 1                                   | 1                            | 0                            | 1                            |
| Fatal AE  | 0                                   | 0                            | 0                            | 0                            |

| End point values                                    | ZN-d5 600 mg<br>BID With Food |  |  |  |
|---|-------------------------------|--|--|--|
| Subject group type                                  | Reporting group               |  |  |  |
| Number of subjects analysed                         | 4                             |  |  |  |
| Units: Subjects                                     |                               |  |  |  |
| TEAE  | 3                             |  |  |  |
| Study drug-related TEAE                             | 2                             |  |  |  |
| Grade $\geq 3$ TEAE                                 | 1                             |  |  |  |
| TEAE study drug interruption and/or<br>modification | 1                             |  |  |  |
| TEAE leading to study drug<br>discontinuation       | 0                             |  |  |  |
| Serious TEAE  | 0                             |  |  |  |
| Fatal AE  | 0                             |  |  |  |



## Statistical analyses

|  |  |
|--|--|
| <b>Statistical analysis title</b>  | All Enrolled Subjects  |
| Statistical analysis description:<br>All subjects who signed an Informed Consent Form for the study, met all inclusion criteria, and were enrolled |  |
| Comparison groups  | ZN-d5 400 mg QD Empty Stomach v ZN-d5 200 mg QD With Food v ZN-d5 400 mg QD With Food v ZN-d5 800 mg QD With Food v ZN-d5 600 mg BID With Food |
| Number of subjects included in analysis  | 18   |
| Analysis specification   | Pre-specified  |
| Analysis type  | equivalence  |
| P-value  | = 18   |
| Method   | Mixed models analysis  |



## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

The AE and SAE Reporting Periods began at the time a study subject signed an ICF and ended 30 days after the last dose of study drug or at the start of subsequent disease therapy.

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

### Dictionary used

|                    |        |
|--------------------|--------|
| Dictionary name    | MedDRA |
| Dictionary version | 26.1   |

### Reporting groups

|                                |                             |
|--------------------------------|-----------------------------|
| Reporting group title          | Empty Stomach: 400 mg/day   |
| Reporting group description: - |                             |
| Reporting group title          | With Food: 200 mg/day       |
| Reporting group description: - |                             |
| Reporting group title          | With Food: 400 mg/day       |
| Reporting group description: - |                             |
| Reporting group title          | With Food: 800 mg/day       |
| Reporting group description: - |                             |
| Reporting group title          | With Food: 600 mg/day (BID) |
| Reporting group description: - |                             |

| Serious adverse events                            | Empty Stomach:<br>400 mg/day | With Food: 200<br>mg/day | With Food: 400<br>mg/day |
|---|------------------------------|--------------------------|--------------------------|
| Total subjects affected by serious adverse events |                              |                          |                          |
| subjects affected / exposed                       | 1 / 3 (33.33%)               | 1 / 5 (20.00%)           | 0 / 3 (0.00%)            |
| number of deaths (all causes)                     | 2                            | 1                        | 0                        |
| number of deaths resulting from adverse events    | 0                            |                          | 0                        |
| Cardiac disorders                                 |                              |                          |                          |
| Myocarditis                                       |                              |                          |                          |
| subjects affected / exposed                       | 0 / 3 (0.00%)                | 0 / 5 (0.00%)            | 0 / 3 (0.00%)            |
| occurrences causally related to treatment / all   | 0 / 0                        | 0 / 0                    | 0 / 0                    |
| deaths causally related to treatment / all        | 0 / 0                        | 0 / 0                    | 0 / 0                    |
| Infections and infestations                       |                              |                          |                          |
| Lower respiratory tract infection                 |                              |                          |                          |
| subjects affected / exposed                       | 1 / 3 (33.33%)               | 1 / 5 (20.00%)           | 0 / 3 (0.00%)            |
| occurrences causally related to treatment / all   | 1 / 1                        | 1 / 1                    | 0 / 0                    |
| deaths causally related to treatment / all        | 0 / 0                        | 0 / 0                    | 0 / 0                    |

| Serious adverse events                            | With Food: 800<br>mg/day | With Food: 600<br>mg/day (BID) |  |
|---|--------------------------|--------------------------------|--|
| Total subjects affected by serious adverse events |                          |                                |  |



|   |                |               |  |
|---|----------------|---------------|--|
| subjects affected / exposed                     | 1 / 3 (33.33%) | 0 / 4 (0.00%) |  |
| number of deaths (all causes)                   | 0              | 0             |  |
| number of deaths resulting from adverse events  |                |               |  |
| Cardiac disorders                               |                |               |  |
| Myocarditis                                     |                |               |  |
| subjects affected / exposed                     | 1 / 3 (33.33%) | 0 / 4 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1          | 0 / 0         |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         |  |
| Infections and infestations                     |                |               |  |
| Lower respiratory tract infection               |                |               |  |
| subjects affected / exposed                     | 0 / 3 (0.00%)  | 0 / 4 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0         |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         |  |

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

| <b>Non-serious adverse events</b>                                   | Empty Stomach:<br>400 mg/day | With Food: 200<br>mg/day | With Food: 400<br>mg/day |
|---|------------------------------|--------------------------|--------------------------|
| Total subjects affected by non-serious adverse events               |                              |                          |                          |
| subjects affected / exposed   | 2 / 3 (66.67%)               | 5 / 5 (100.00%)          | 3 / 3 (100.00%)          |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                              |                          |                          |
| Basal cell carcinoma  |                              |                          |                          |
| subjects affected / exposed   | 0 / 3 (0.00%)                | 1 / 5 (20.00%)           | 0 / 3 (0.00%)            |
| occurrences (all)   | 0                            | 2                        | 0                        |
| Bowen's disease   |                              |                          |                          |
| subjects affected / exposed   | 0 / 3 (0.00%)                | 1 / 5 (20.00%)           | 0 / 3 (0.00%)            |
| occurrences (all)   | 0                            | 1                        | 0                        |
| Squamous cell carcinoma of skin                                     |                              |                          |                          |
| subjects affected / exposed   | 0 / 3 (0.00%)                | 1 / 5 (20.00%)           | 0 / 3 (0.00%)            |
| occurrences (all)   | 0                            | 1                        | 0                        |
| Vascular disorders  |                              |                          |                          |
| Orthostatic hypotension   |                              |                          |                          |
| subjects affected / exposed   | 1 / 3 (33.33%)               | 1 / 5 (20.00%)           | 0 / 3 (0.00%)            |
| occurrences (all)   | 3                            | 1                        | 0                        |
| Hypotension   |                              |                          |                          |
| subjects affected / exposed   | 0 / 3 (0.00%)                | 2 / 5 (40.00%)           | 0 / 3 (0.00%)            |
| occurrences (all)   | 0                            | 2                        | 0                        |



|  |                     |                     |                     |
|--|---------------------|---------------------|---------------------|
| Embolism<br>subjects affected / exposed<br>occurrences (all)               | 0 / 3 (0.00%)<br>0  | 1 / 5 (20.00%)<br>1 | 0 / 3 (0.00%)<br>0  |
| General disorders and administration<br>site conditions                    |                     |                     |                     |
| Fatigue<br>subjects affected / exposed<br>occurrences (all)                | 1 / 3 (33.33%)<br>4 | 2 / 5 (40.00%)<br>2 | 1 / 3 (33.33%)<br>2 |
| Oedema peripheral<br>subjects affected / exposed<br>occurrences (all)      | 1 / 3 (33.33%)<br>1 | 1 / 5 (20.00%)<br>1 | 0 / 3 (0.00%)<br>0  |
| Chills<br>subjects affected / exposed<br>occurrences (all)                 | 0 / 3 (0.00%)<br>0  | 1 / 5 (20.00%)<br>1 | 0 / 3 (0.00%)<br>0  |
| Mucosal ulceration<br>subjects affected / exposed<br>occurrences (all)     | 0 / 3 (0.00%)<br>0  | 1 / 5 (20.00%)<br>1 | 0 / 3 (0.00%)<br>0  |
| Non-cardiac chest pain<br>subjects affected / exposed<br>occurrences (all) | 0 / 3 (0.00%)<br>0  | 1 / 5 (20.00%)<br>1 | 0 / 3 (0.00%)<br>0  |
| Localised oedema<br>subjects affected / exposed<br>occurrences (all)       | 0 / 3 (0.00%)<br>0  | 1 / 5 (20.00%)<br>1 | 0 / 3 (0.00%)<br>0  |
| Asthenia<br>subjects affected / exposed<br>occurrences (all)               | 0 / 3 (0.00%)<br>0  | 0 / 5 (0.00%)<br>0  | 0 / 3 (0.00%)<br>0  |
| Reproductive system and breast<br>disorders                                |                     |                     |                     |
| Prostatomegaly<br>subjects affected / exposed<br>occurrences (all)         | 0 / 3 (0.00%)<br>0  | 1 / 5 (20.00%)<br>1 | 0 / 3 (0.00%)<br>0  |
| Bartholin's cyst<br>subjects affected / exposed<br>occurrences (all)       | 0 / 3 (0.00%)<br>0  | 1 / 5 (20.00%)<br>1 | 0 / 3 (0.00%)<br>0  |
| Breast enlargement<br>subjects affected / exposed<br>occurrences (all)     | 0 / 3 (0.00%)<br>0  | 0 / 5 (0.00%)<br>0  | 1 / 3 (33.33%)<br>1 |
| Respiratory, thoracic and mediastinal                                      |                     |                     |                     |



|                                      |               |                |                |
|--------------------------------------|---------------|----------------|----------------|
| disorders                            |               |                |                |
| Dyspnoea                             |               |                |                |
| subjects affected / exposed          | 0 / 3 (0.00%) | 1 / 5 (20.00%) | 0 / 3 (0.00%)  |
| occurrences (all)                    | 0             | 1              | 0              |
| Oropharyngeal pain                   |               |                |                |
| subjects affected / exposed          | 0 / 3 (0.00%) | 1 / 5 (20.00%) | 1 / 3 (33.33%) |
| occurrences (all)                    | 0             | 1              | 1              |
| Upper respiratory tract irritation   |               |                |                |
| subjects affected / exposed          | 0 / 3 (0.00%) | 1 / 5 (20.00%) | 0 / 3 (0.00%)  |
| occurrences (all)                    | 0             | 1              | 0              |
| Sleep apnoea syndrome                |               |                |                |
| subjects affected / exposed          | 0 / 3 (0.00%) | 1 / 5 (20.00%) | 0 / 3 (0.00%)  |
| occurrences (all)                    | 0             | 1              | 0              |
| Cough                                |               |                |                |
| subjects affected / exposed          | 0 / 3 (0.00%) | 0 / 5 (0.00%)  | 1 / 3 (33.33%) |
| occurrences (all)                    | 0             | 0              | 1              |
| Psychiatric disorders                |               |                |                |
| Confusional state                    |               |                |                |
| subjects affected / exposed          | 0 / 3 (0.00%) | 0 / 5 (0.00%)  | 1 / 3 (33.33%) |
| occurrences (all)                    | 0             | 0              | 1              |
| Investigations                       |               |                |                |
| Holotranscobalamin decreased         |               |                |                |
| subjects affected / exposed          | 0 / 3 (0.00%) | 1 / 5 (20.00%) | 0 / 3 (0.00%)  |
| occurrences (all)                    | 0             | 1              | 0              |
| Glomerular filtration rate decreased |               |                |                |
| subjects affected / exposed          | 0 / 3 (0.00%) | 1 / 5 (20.00%) | 0 / 3 (0.00%)  |
| occurrences (all)                    | 0             | 1              | 0              |
| Neutrophil count decreased           |               |                |                |
| subjects affected / exposed          | 0 / 3 (0.00%) | 0 / 5 (0.00%)  | 1 / 3 (33.33%) |
| occurrences (all)                    | 0             | 0              | 1              |
| Lymphocyte count decreased           |               |                |                |
| subjects affected / exposed          | 0 / 3 (0.00%) | 0 / 5 (0.00%)  | 1 / 3 (33.33%) |
| occurrences (all)                    | 0             | 0              | 1              |
| Troponin T increased                 |               |                |                |
| subjects affected / exposed          | 0 / 3 (0.00%) | 0 / 5 (0.00%)  | 0 / 3 (0.00%)  |
| occurrences (all)                    | 0             | 0              | 0              |
| Human metapneumovirus test           |               |                |                |



|  |  |  |   |
|--|--|--|---|
| positive<br>subjects affected / exposed<br>occurrences (all)   | 0 / 3 (0.00%)<br>0   | 0 / 5 (0.00%)<br>0   | 0 / 3 (0.00%)<br>0  |
| Injury, poisoning and procedural complications<br>Contusion<br>subjects affected / exposed<br>occurrences (all)  | 0 / 3 (0.00%)<br>0   | 1 / 5 (20.00%)<br>1  | 0 / 3 (0.00%)<br>0  |
| Cardiac disorders<br>Myocardial infarction<br>subjects affected / exposed<br>occurrences (all)   | 0 / 3 (0.00%)<br>0   | 1 / 5 (20.00%)<br>1  | 0 / 3 (0.00%)<br>0  |
| Nervous system disorders<br>Headache<br>subjects affected / exposed<br>occurrences (all)<br><br>Neuropathy peripheral<br>subjects affected / exposed<br>occurrences (all)<br><br>Tremor<br>subjects affected / exposed<br>occurrences (all)<br><br>Presyncope<br>subjects affected / exposed<br>occurrences (all)<br><br>Dizziness<br>subjects affected / exposed<br>occurrences (all)<br><br>Depressed level of consciousness<br>subjects affected / exposed<br>occurrences (all) | 0 / 3 (0.00%)<br>0<br><br>0 / 3 (0.00%)<br>0<br><br>0 / 3 (0.00%)<br>0<br><br>0 / 3 (0.00%)<br>0<br><br>0 / 3 (0.00%)<br>0<br><br>0 / 3 (0.00%)<br>0 | 1 / 5 (20.00%)<br>1<br><br>1 / 5 (20.00%)<br>1<br><br>0 / 5 (0.00%)<br>0<br><br>0 / 5 (0.00%)<br>0<br><br>0 / 5 (0.00%)<br>0 | 1 / 3 (33.33%)<br>1<br><br>0 / 3 (0.00%)<br>0<br><br>0 / 3 (0.00%)<br>0<br><br>0 / 3 (0.00%)<br>0 |
| Blood and lymphatic system disorders<br>Anaemia macrocytic<br>subjects affected / exposed<br>occurrences (all)   | 0 / 3 (0.00%)<br>0   | 1 / 5 (20.00%)<br>1  | 0 / 3 (0.00%)<br>0  |
| Ear and labyrinth disorders  |  |  |   |



|  |                     |                     |                     |
|--|---------------------|---------------------|---------------------|
| Tinnitus<br>subjects affected / exposed<br>occurrences (all)                         | 0 / 3 (0.00%)<br>0  | 0 / 5 (0.00%)<br>0  | 1 / 3 (33.33%)<br>1 |
| Gastrointestinal disorders   |                     |                     |                     |
| Nausea<br>subjects affected / exposed<br>occurrences (all)                           | 1 / 3 (33.33%)<br>2 | 1 / 5 (20.00%)<br>1 | 0 / 3 (0.00%)<br>0  |
| Diarrhoea<br>subjects affected / exposed<br>occurrences (all)                        | 2 / 3 (66.67%)<br>4 | 1 / 5 (20.00%)<br>1 | 2 / 3 (66.67%)<br>3 |
| Abdominal pain<br>subjects affected / exposed<br>occurrences (all)                   | 1 / 3 (33.33%)<br>3 | 1 / 5 (20.00%)<br>2 | 1 / 3 (33.33%)<br>3 |
| Lip ulceration<br>subjects affected / exposed<br>occurrences (all)                   | 0 / 3 (0.00%)<br>0  | 1 / 5 (20.00%)<br>1 | 0 / 3 (0.00%)<br>0  |
| Gastrooesophageal reflux disease<br>subjects affected / exposed<br>occurrences (all) | 0 / 3 (0.00%)<br>0  | 1 / 5 (20.00%)<br>1 | 0 / 3 (0.00%)<br>0  |
| Change of bowel habit<br>subjects affected / exposed<br>occurrences (all)            | 0 / 3 (0.00%)<br>0  | 1 / 5 (20.00%)<br>1 | 0 / 3 (0.00%)<br>0  |
| Vomiting<br>subjects affected / exposed<br>occurrences (all)                         | 0 / 3 (0.00%)<br>0  | 0 / 5 (0.00%)<br>0  | 1 / 3 (33.33%)<br>1 |
| Abdominal distension<br>subjects affected / exposed<br>occurrences (all)             | 0 / 3 (0.00%)<br>0  | 0 / 5 (0.00%)<br>0  | 1 / 3 (33.33%)<br>1 |
| Constipation<br>subjects affected / exposed<br>occurrences (all)                     | 0 / 3 (0.00%)<br>0  | 0 / 5 (0.00%)<br>0  | 0 / 3 (0.00%)<br>0  |
| Dysphagia<br>subjects affected / exposed<br>occurrences (all)                        | 0 / 3 (0.00%)<br>0  | 0 / 5 (0.00%)<br>0  | 0 / 3 (0.00%)<br>0  |
| Skin and subcutaneous tissue disorders   |                     |                     |                     |



|  |                     |                     |                     |
|--|---------------------|---------------------|---------------------|
| Eczema<br>subjects affected / exposed<br>occurrences (all)   | 0 / 3 (0.00%)<br>0  | 1 / 5 (20.00%)<br>1 | 0 / 3 (0.00%)<br>0  |
| Ecchymosis<br>subjects affected / exposed<br>occurrences (all)   | 0 / 3 (0.00%)<br>0  | 0 / 5 (0.00%)<br>0  | 1 / 3 (33.33%)<br>1 |
| Renal and urinary disorders<br>Renal impairment<br>subjects affected / exposed<br>occurrences (all)            | 0 / 3 (0.00%)<br>0  | 1 / 5 (20.00%)<br>3 | 0 / 3 (0.00%)<br>0  |
| Renal cyst<br>subjects affected / exposed<br>occurrences (all)   | 0 / 3 (0.00%)<br>0  | 1 / 5 (20.00%)<br>1 | 0 / 3 (0.00%)<br>0  |
| Musculoskeletal and connective tissue disorders<br>Myalgia<br>subjects affected / exposed<br>occurrences (all) | 1 / 3 (33.33%)<br>2 | 0 / 5 (0.00%)<br>0  | 0 / 3 (0.00%)<br>0  |
| Arthralgia<br>subjects affected / exposed<br>occurrences (all)   | 0 / 3 (0.00%)<br>0  | 2 / 5 (40.00%)<br>2 | 0 / 3 (0.00%)<br>0  |
| Pain in extremity<br>subjects affected / exposed<br>occurrences (all)  | 0 / 3 (0.00%)<br>0  | 1 / 5 (20.00%)<br>1 | 0 / 3 (0.00%)<br>0  |
| Neck pain<br>subjects affected / exposed<br>occurrences (all)  | 0 / 3 (0.00%)<br>0  | 1 / 5 (20.00%)<br>1 | 0 / 3 (0.00%)<br>0  |
| Muscular weakness<br>subjects affected / exposed<br>occurrences (all)  | 0 / 3 (0.00%)<br>0  | 0 / 5 (0.00%)<br>0  | 1 / 3 (33.33%)<br>1 |
| Muscle spasms<br>subjects affected / exposed<br>occurrences (all)  | 0 / 3 (0.00%)<br>0  | 0 / 5 (0.00%)<br>0  | 1 / 3 (33.33%)<br>1 |
| Infections and infestations<br>Urinary tract infection<br>subjects affected / exposed<br>occurrences (all)     | 0 / 3 (0.00%)<br>0  | 1 / 5 (20.00%)<br>2 | 0 / 3 (0.00%)<br>0  |



|  |                     |                     |                     |
|--|---------------------|---------------------|---------------------|
| Skin infection<br>subjects affected / exposed<br>occurrences (all)     | 0 / 3 (0.00%)<br>0  | 1 / 5 (20.00%)<br>1 | 0 / 3 (0.00%)<br>0  |
| COVID-19<br>subjects affected / exposed<br>occurrences (all)           | 0 / 3 (0.00%)<br>0  | 0 / 5 (0.00%)<br>0  | 0 / 3 (0.00%)<br>0  |
| Metabolism and nutrition disorders                                     |                     |                     |                     |
| Decreased appetite<br>subjects affected / exposed<br>occurrences (all) | 1 / 3 (33.33%)<br>1 | 1 / 5 (20.00%)<br>1 | 0 / 3 (0.00%)<br>0  |
| Hypocalcaemia<br>subjects affected / exposed<br>occurrences (all)      | 1 / 3 (33.33%)<br>2 | 0 / 5 (0.00%)<br>0  | 0 / 3 (0.00%)<br>0  |
| Folate deficiency<br>subjects affected / exposed<br>occurrences (all)  | 0 / 3 (0.00%)<br>0  | 1 / 5 (20.00%)<br>1 | 0 / 3 (0.00%)<br>0  |
| Hypoalbuminaemia<br>subjects affected / exposed<br>occurrences (all)   | 0 / 3 (0.00%)<br>0  | 0 / 5 (0.00%)<br>0  | 1 / 3 (33.33%)<br>3 |
| Dehydration<br>subjects affected / exposed<br>occurrences (all)        | 0 / 3 (0.00%)<br>0  | 0 / 5 (0.00%)<br>0  | 0 / 3 (0.00%)<br>0  |

| <b>Non-serious adverse events</b>   | With Food: 800<br>mg/day | With Food: 600<br>mg/day (BID) |  |
|---|--------------------------|--------------------------------|--|
| Total subjects affected by non-serious<br>adverse events<br>subjects affected / exposed | 3 / 3 (100.00%)          | 3 / 4 (75.00%)                 |  |
| Neoplasms benign, malignant and<br>unspecified (incl cysts and polyps)                  |                          |                                |  |
| Basal cell carcinoma<br>subjects affected / exposed<br>occurrences (all)                | 0 / 3 (0.00%)<br>0       | 0 / 4 (0.00%)<br>0             |  |
| Bowen's disease<br>subjects affected / exposed<br>occurrences (all)                     | 0 / 3 (0.00%)<br>0       | 0 / 4 (0.00%)<br>0             |  |
| Squamous cell carcinoma of skin<br>subjects affected / exposed<br>occurrences (all)     | 0 / 3 (0.00%)<br>0       | 0 / 4 (0.00%)<br>0             |  |



|  |                     |                     |  |
|--|---------------------|---------------------|--|
| Vascular disorders<br>Orthostatic hypotension<br>subjects affected / exposed<br>occurrences (all)<br><br>Hypotension<br>subjects affected / exposed<br>occurrences (all)<br><br>Embolism<br>subjects affected / exposed<br>occurrences (all)   | 0 / 3 (0.00%)<br>0  | 0 / 4 (0.00%)<br>0  |  |
|  | 1 / 3 (33.33%)<br>1 | 0 / 4 (0.00%)<br>0  |  |
|  | 0 / 3 (0.00%)<br>0  | 0 / 4 (0.00%)<br>0  |  |
|  |                     |                     |  |
|  |                     |                     |  |
|  |                     |                     |  |
| General disorders and administration site conditions<br>Fatigue<br>subjects affected / exposed<br>occurrences (all)<br><br>Oedema peripheral<br>subjects affected / exposed<br>occurrences (all)<br><br>Chills<br>subjects affected / exposed<br>occurrences (all)<br><br>Mucosal ulceration<br>subjects affected / exposed<br>occurrences (all)<br><br>Non-cardiac chest pain<br>subjects affected / exposed<br>occurrences (all)<br><br>Localised oedema<br>subjects affected / exposed<br>occurrences (all)<br><br>Asthenia<br>subjects affected / exposed<br>occurrences (all) | 0 / 3 (0.00%)<br>0  | 0 / 4 (0.00%)<br>0  |  |
|  | 0 / 3 (0.00%)<br>0  | 0 / 4 (0.00%)<br>0  |  |
|  | 0 / 3 (0.00%)<br>0  | 0 / 4 (0.00%)<br>0  |  |
|  | 0 / 3 (0.00%)<br>0  | 0 / 4 (0.00%)<br>0  |  |
|  | 0 / 3 (0.00%)<br>0  | 0 / 4 (0.00%)<br>0  |  |
|  | 0 / 3 (0.00%)<br>0  | 1 / 4 (25.00%)<br>1 |  |
|  | 0 / 3 (0.00%)<br>0  | 0 / 4 (0.00%)<br>0  |  |
|  | 1 / 3 (33.33%)<br>2 | 0 / 4 (0.00%)<br>0  |  |
|  |                     |                     |  |
|  |                     |                     |  |
| Reproductive system and breast disorders<br>Prostatomegaly<br>subjects affected / exposed<br>occurrences (all)   | 0 / 3 (0.00%)<br>0  | 0 / 4 (0.00%)<br>0  |  |
|  |                     |                     |  |



|  |                    |                     |  |
|--|--------------------|---------------------|--|
| Bartholin's cyst<br>subjects affected / exposed<br>occurrences (all)                     | 0 / 3 (0.00%)<br>0 | 0 / 4 (0.00%)<br>0  |  |
| Breast enlargement<br>subjects affected / exposed<br>occurrences (all)                   | 0 / 3 (0.00%)<br>0 | 0 / 4 (0.00%)<br>0  |  |
| Respiratory, thoracic and mediastinal disorders  |                    |                     |  |
| Dyspnoea<br>subjects affected / exposed<br>occurrences (all)                             | 0 / 3 (0.00%)<br>0 | 0 / 4 (0.00%)<br>0  |  |
| Oropharyngeal pain<br>subjects affected / exposed<br>occurrences (all)                   | 0 / 3 (0.00%)<br>0 | 0 / 4 (0.00%)<br>0  |  |
| Upper respiratory tract irritation<br>subjects affected / exposed<br>occurrences (all)   | 0 / 3 (0.00%)<br>0 | 0 / 4 (0.00%)<br>0  |  |
| Sleep apnoea syndrome<br>subjects affected / exposed<br>occurrences (all)                | 0 / 3 (0.00%)<br>0 | 0 / 4 (0.00%)<br>0  |  |
| Cough<br>subjects affected / exposed<br>occurrences (all)                                | 0 / 3 (0.00%)<br>0 | 0 / 4 (0.00%)<br>0  |  |
| Psychiatric disorders  |                    |                     |  |
| Confusional state<br>subjects affected / exposed<br>occurrences (all)                    | 0 / 3 (0.00%)<br>0 | 0 / 4 (0.00%)<br>0  |  |
| Investigations   |                    |                     |  |
| Holotranscobalamin decreased<br>subjects affected / exposed<br>occurrences (all)         | 0 / 3 (0.00%)<br>0 | 0 / 4 (0.00%)<br>0  |  |
| Glomerular filtration rate decreased<br>subjects affected / exposed<br>occurrences (all) | 0 / 3 (0.00%)<br>0 | 1 / 4 (25.00%)<br>1 |  |
| Neutrophil count decreased<br>subjects affected / exposed<br>occurrences (all)           | 0 / 3 (0.00%)<br>0 | 0 / 4 (0.00%)<br>0  |  |



|  |                     |                     |  |
|--|---------------------|---------------------|--|
| Lymphocyte count decreased<br>subjects affected / exposed<br>occurrences (all)                                     | 0 / 3 (0.00%)<br>0  | 0 / 4 (0.00%)<br>0  |  |
| Troponin T increased<br>subjects affected / exposed<br>occurrences (all)   | 1 / 3 (33.33%)<br>1 | 0 / 4 (0.00%)<br>0  |  |
| Human metapneumovirus test<br>positive<br>subjects affected / exposed<br>occurrences (all)                         | 0 / 3 (0.00%)<br>0  | 1 / 4 (25.00%)<br>1 |  |
| Injury, poisoning and procedural<br>complications<br>Contusion<br>subjects affected / exposed<br>occurrences (all) | 0 / 3 (0.00%)<br>0  | 0 / 4 (0.00%)<br>0  |  |
| Cardiac disorders<br>Myocardial infarction<br>subjects affected / exposed<br>occurrences (all)                     | 0 / 3 (0.00%)<br>0  | 0 / 4 (0.00%)<br>0  |  |
| Nervous system disorders<br>Headache<br>subjects affected / exposed<br>occurrences (all)                           | 0 / 3 (0.00%)<br>0  | 0 / 4 (0.00%)<br>0  |  |
| Neuropathy peripheral<br>subjects affected / exposed<br>occurrences (all)  | 0 / 3 (0.00%)<br>0  | 0 / 4 (0.00%)<br>0  |  |
| Tremor<br>subjects affected / exposed<br>occurrences (all)   | 1 / 3 (33.33%)<br>1 | 0 / 4 (0.00%)<br>0  |  |
| Presyncope<br>subjects affected / exposed<br>occurrences (all)   | 1 / 3 (33.33%)<br>1 | 0 / 4 (0.00%)<br>0  |  |
| Dizziness<br>subjects affected / exposed<br>occurrences (all)  | 0 / 3 (0.00%)<br>0  | 1 / 4 (25.00%)<br>1 |  |
| Depressed level of consciousness<br>subjects affected / exposed<br>occurrences (all)                               | 0 / 3 (0.00%)<br>0  | 1 / 4 (25.00%)<br>1 |  |



|                                      |                 |                |  |
|--------------------------------------|-----------------|----------------|--|
| Blood and lymphatic system disorders |                 |                |  |
| Anaemia macrocytic                   |                 |                |  |
| subjects affected / exposed          | 0 / 3 (0.00%)   | 0 / 4 (0.00%)  |  |
| occurrences (all)                    | 0               | 0              |  |
| Ear and labyrinth disorders          |                 |                |  |
| Tinnitus                             |                 |                |  |
| subjects affected / exposed          | 0 / 3 (0.00%)   | 0 / 4 (0.00%)  |  |
| occurrences (all)                    | 0               | 0              |  |
| Gastrointestinal disorders           |                 |                |  |
| Nausea                               |                 |                |  |
| subjects affected / exposed          | 0 / 3 (0.00%)   | 1 / 4 (25.00%) |  |
| occurrences (all)                    | 0               | 1              |  |
| Diarrhoea                            |                 |                |  |
| subjects affected / exposed          | 3 / 3 (100.00%) | 3 / 4 (75.00%) |  |
| occurrences (all)                    | 7               | 5              |  |
| Abdominal pain                       |                 |                |  |
| subjects affected / exposed          | 0 / 3 (0.00%)   | 0 / 4 (0.00%)  |  |
| occurrences (all)                    | 0               | 0              |  |
| Lip ulceration                       |                 |                |  |
| subjects affected / exposed          | 0 / 3 (0.00%)   | 0 / 4 (0.00%)  |  |
| occurrences (all)                    | 0               | 0              |  |
| Gastrooesophageal reflux disease     |                 |                |  |
| subjects affected / exposed          | 0 / 3 (0.00%)   | 0 / 4 (0.00%)  |  |
| occurrences (all)                    | 0               | 0              |  |
| Change of bowel habit                |                 |                |  |
| subjects affected / exposed          | 0 / 3 (0.00%)   | 0 / 4 (0.00%)  |  |
| occurrences (all)                    | 0               | 0              |  |
| Vomiting                             |                 |                |  |
| subjects affected / exposed          | 1 / 3 (33.33%)  | 0 / 4 (0.00%)  |  |
| occurrences (all)                    | 5               | 0              |  |
| Abdominal distension                 |                 |                |  |
| subjects affected / exposed          | 0 / 3 (0.00%)   | 0 / 4 (0.00%)  |  |
| occurrences (all)                    | 0               | 0              |  |
| Constipation                         |                 |                |  |
| subjects affected / exposed          | 1 / 3 (33.33%)  | 0 / 4 (0.00%)  |  |
| occurrences (all)                    | 1               | 0              |  |
| Dysphagia                            |                 |                |  |



|  |                    |                     |  |
|--|--------------------|---------------------|--|
| subjects affected / exposed<br>occurrences (all) | 0 / 3 (0.00%)<br>0 | 1 / 4 (25.00%)<br>1 |  |
| Skin and subcutaneous tissue disorders           |                    |                     |  |
| Eczema   |                    |                     |  |
| subjects affected / exposed                      | 0 / 3 (0.00%)      | 0 / 4 (0.00%)       |  |
| occurrences (all)                                | 0                  | 0                   |  |
| Ecchymosis                                       |                    |                     |  |
| subjects affected / exposed                      | 0 / 3 (0.00%)      | 0 / 4 (0.00%)       |  |
| occurrences (all)                                | 0                  | 0                   |  |
| Renal and urinary disorders                      |                    |                     |  |
| Renal impairment                                 |                    |                     |  |
| subjects affected / exposed                      | 0 / 3 (0.00%)      | 0 / 4 (0.00%)       |  |
| occurrences (all)                                | 0                  | 0                   |  |
| Renal cyst                                       |                    |                     |  |
| subjects affected / exposed                      | 0 / 3 (0.00%)      | 0 / 4 (0.00%)       |  |
| occurrences (all)                                | 0                  | 0                   |  |
| Musculoskeletal and connective tissue disorders  |                    |                     |  |
| Myalgia  |                    |                     |  |
| subjects affected / exposed                      | 0 / 3 (0.00%)      | 0 / 4 (0.00%)       |  |
| occurrences (all)                                | 0                  | 0                   |  |
| Arthralgia                                       |                    |                     |  |
| subjects affected / exposed                      | 0 / 3 (0.00%)      | 0 / 4 (0.00%)       |  |
| occurrences (all)                                | 0                  | 0                   |  |
| Pain in extremity                                |                    |                     |  |
| subjects affected / exposed                      | 0 / 3 (0.00%)      | 0 / 4 (0.00%)       |  |
| occurrences (all)                                | 0                  | 0                   |  |
| Neck pain  |                    |                     |  |
| subjects affected / exposed                      | 0 / 3 (0.00%)      | 0 / 4 (0.00%)       |  |
| occurrences (all)                                | 0                  | 0                   |  |
| Muscular weakness                                |                    |                     |  |
| subjects affected / exposed                      | 0 / 3 (0.00%)      | 0 / 4 (0.00%)       |  |
| occurrences (all)                                | 0                  | 0                   |  |
| Muscle spasms                                    |                    |                     |  |
| subjects affected / exposed                      | 0 / 3 (0.00%)      | 0 / 4 (0.00%)       |  |
| occurrences (all)                                | 0                  | 0                   |  |
| Infections and infestations                      |                    |                     |  |



|   |                     |                     |  |
|---|---------------------|---------------------|--|
| Urinary tract infection<br>subjects affected / exposed<br>occurrences (all) | 0 / 3 (0.00%)<br>0  | 0 / 4 (0.00%)<br>0  |  |
| Skin infection<br>subjects affected / exposed<br>occurrences (all)          | 0 / 3 (0.00%)<br>0  | 0 / 4 (0.00%)<br>0  |  |
| COVID-19<br>subjects affected / exposed<br>occurrences (all)                | 1 / 3 (33.33%)<br>1 | 0 / 4 (0.00%)<br>0  |  |
| Metabolism and nutrition disorders  |                     |                     |  |
| Decreased appetite<br>subjects affected / exposed<br>occurrences (all)      | 1 / 3 (33.33%)<br>1 | 1 / 4 (25.00%)<br>1 |  |
| Hypocalcaemia<br>subjects affected / exposed<br>occurrences (all)           | 0 / 3 (0.00%)<br>0  | 0 / 4 (0.00%)<br>0  |  |
| Folate deficiency<br>subjects affected / exposed<br>occurrences (all)       | 0 / 3 (0.00%)<br>0  | 0 / 4 (0.00%)<br>0  |  |
| Hypoalbuminaemia<br>subjects affected / exposed<br>occurrences (all)        | 0 / 3 (0.00%)<br>0  | 0 / 4 (0.00%)<br>0  |  |
| Dehydration<br>subjects affected / exposed<br>occurrences (all)             | 1 / 3 (33.33%)<br>1 | 0 / 4 (0.00%)<br>0  |  |



## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date             | Amendment   |
|------------------|---|
| 01 February 2022 | <ul style="list-style-type: none"><li>- Clarified the starting dose cohort and escalation cohorts for Part A.</li><li>- Added text in section 6.1.2. to allow administration of ZN-d5 with a meal based on findings from the food effect study (ZN-d5-002).</li><li>- Added a secondary efficacy endpoint in Part B to better assess hematological response and progression.</li><li>- Removed the bone marrow plasma cell requirement at baseline because we have clarified that any subject with a diagnosis of multiple myeloma according to International Myeloma Working Group (IMWG) is excluded from the study, and the bone marrow plasma cell count above or below 30% does not affect the diagnosis.</li><li>- Deleted timing of bone marrow function assessment to include eligible patients and align with body of protocol. Edited platelet count criteria to include eligible antibody light chain (AL) amyloidosis patients who would otherwise be excluded.</li><li>- Clarified that subjects with any type of multiple myeloma will be excluded.</li><li>- Plasma cell counts were removed as an eligibility criterion.</li><li>- A specific exclusion of subjects with HIV is not needed, although most HIV subjects will be unable to participate because of prohibited concomitant medications.</li><li>- p-GP inhibitors are allowed to be used with caution during ZN-d5 treatment.</li><li>- More detailed dosing interruption criteria and suggested dose reduction levels could provide more accurate instructions to clinical site.</li><li>- Specific B cell count assessments at some time points were removed, as the counts at the other designated time points are sufficient to evaluate potential biomarkers. Removed biomarker assessment considering this assessment does not provide useful biomarker information.</li><li>- There will be no ZN-d5 concentration in blood before dosing; thus it is unnecessary to collect a pharmacokinetic (PK) sample at Screening.</li><li>- ORR is replaced with HRR across the document as HRR is a term of convention to assess response.</li></ul> |
| 30 June 2023     | <ul style="list-style-type: none"><li>- Part A was initially designed to evaluate the safety and identify the RP2D of ZN-d5 for patients with relapsed/refractory light chain (AL) amyloidosis. Part A is updated to allow for the evaluation of intermediate doses based on emerging clinical and PK data and to include a more robust assessment of PK, safety, and efficacy data at additional dose levels (rather than only the initially presumed RP2D) to support dose optimization. The study duration and patient enrollment is updated to accommodate for time required to enroll subjects into these cohorts.</li><li>- Study is modified to allow the opportunity for a one-time intrasubject dose escalation to a dose that has been deemed safe by the SRC. Subjects must be on their current dose of ZN-d5 for at least 4 months without treatment related adverse events leading to a dose interruption, reduction, or discontinuation, and must obtain Sponsor approval. This option provides patients, particularly those enrolled in early dose levels, with the potential of a greater benefit:risk ratio.</li><li>- A 60-day washout for prior therapeutic antibodies (eg, daratumumab) was considered too long of a treatment interruption for patients with active, relapsed/refractory disease.</li><li>- The previous toxicity monitoring section was designed to evaluate events using a Bayesian design in predefined increments of 10 patients. To facilitate improved and timely assessment of potential AEs associated with the use of ZN-d5/BCL2 inhibitors, we used the Toxicity Monitoring Criteria section to establish AESIs that require immediate reporting and therefore evaluation by the Sponsor.</li><li>- DLT criteria were updated to be more conservative per FDA request.</li></ul>   |

Notes:



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## **Interruptions (globally)**

Were there any global interruptions to the trial? No

## **Limitations and caveats**

None reported