



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
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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:

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 ≥ 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
Arm title	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.

Arm title	ZN-d5 200 mg QD With Food
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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.

Arm title	ZN-d5 400 mg QD With Food
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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.

Arm title	ZN-d5 800 mg QD With Food
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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.

Arm title	ZN-d5 600 mg BID With Food
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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.

Number of subjects in period 1	ZN-d5 400 mg QD Empty Stomach	ZN-d5 200 mg QD With Food	ZN-d5 400 mg QD With Food
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	-

Number of subjects in period 1	ZN-d5 800 mg QD With Food	ZN-d5 600 mg BID With Food
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: Bayesian Optimal Interval dose-escalation arm.	
Reporting group title	ZN-d5 200 mg QD With Food
Reporting group description: 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: 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: 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: 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 Units: Subjects			
Adults (18-64 years)	2	4	1
From 65-84 years	1	1	2
Age continuous Units: years			
arithmetic mean	57.3	61.6	67.0
standard deviation	± 9.61	± 7.54	± 9.17
Gender categorical 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 Units: Subjects			
Adults (18-64 years)	2	1	10
From 65-84 years	1	3	8
Age continuous 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: Bayesian Optimal Interval dose-escalation arm.	
Reporting group title	ZN-d5 200 mg QD With Food
Reporting group description: 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: 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: 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: 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 ^[1]
End point description:	
End point type	Primary
End point timeframe: Through Cycle 1, Day 28	
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: 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
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End point description:

End point type	Primary
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End point timeframe:

From the first dose through EOT or initiation of subsequent therapy

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				
TEAE	2	5	3	3
Study drug-related TEAE	2	3	3	3
Grade ≥ 3 TEAE	2	3	1	1
TEAE study drug interruption and/or modification	0	2	3	1
TEAE leading to study drug discontinuation	1	0	0	1
Serious TEAE	1	1	0	1
Fatal AE	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				
TEAE	3			
Study drug-related TEAE	2			
Grade ≥ 3 TEAE	1			
TEAE study drug interruption and/or modification	1			
TEAE leading to study drug discontinuation	0			
Serious TEAE	0			
Fatal AE	0			

Statistical analyses

Statistical analysis title	All Enrolled Subjects
Statistical analysis description: 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
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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: 400 mg/day	With Food: 200 mg/day	With Food: 400 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 mg/day	With Food: 600 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 %

Non-serious adverse events	Empty Stomach: 400 mg/day	With Food: 200 mg/day	With Food: 400 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			
subjects affected / exposed	0 / 3 (0.00%)	1 / 5 (20.00%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	1 / 3 (33.33%)	2 / 5 (40.00%)	1 / 3 (33.33%)
occurrences (all)	4	2	2
Oedema peripheral			
subjects affected / exposed	1 / 3 (33.33%)	1 / 5 (20.00%)	0 / 3 (0.00%)
occurrences (all)	1	1	0
Chills			
subjects affected / exposed	0 / 3 (0.00%)	1 / 5 (20.00%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Mucosal ulceration			
subjects affected / exposed	0 / 3 (0.00%)	1 / 5 (20.00%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Non-cardiac chest pain			
subjects affected / exposed	0 / 3 (0.00%)	1 / 5 (20.00%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Localised oedema			
subjects affected / exposed	0 / 3 (0.00%)	1 / 5 (20.00%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Asthenia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Reproductive system and breast disorders			
Prostatomegaly			
subjects affected / exposed	0 / 3 (0.00%)	1 / 5 (20.00%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Bartholin's cyst			
subjects affected / exposed	0 / 3 (0.00%)	1 / 5 (20.00%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Breast enlargement			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	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 subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 5 (0.00%) 0	0 / 3 (0.00%) 0
Injury, poisoning and procedural complications Contusion subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	1 / 5 (20.00%) 1	0 / 3 (0.00%) 0
Cardiac disorders Myocardial infarction subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	1 / 5 (20.00%) 1	0 / 3 (0.00%) 0
Nervous system disorders Headache subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	1 / 5 (20.00%) 1	1 / 3 (33.33%) 1
Neuropathy peripheral subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	1 / 5 (20.00%) 1	0 / 3 (0.00%) 0
Tremor subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 5 (0.00%) 0	0 / 3 (0.00%) 0
Presyncope subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 5 (0.00%) 0	0 / 3 (0.00%) 0
Dizziness subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 5 (0.00%) 0	0 / 3 (0.00%) 0
Depressed level of consciousness subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 5 (0.00%) 0	0 / 3 (0.00%) 0
Blood and lymphatic system disorders Anaemia macrocytic subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	1 / 5 (20.00%) 1	0 / 3 (0.00%) 0
Ear and labyrinth disorders			

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

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

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

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

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

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

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

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

subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	1 / 4 (25.00%) 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 subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 4 (0.00%) 0	
Skin infection subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 4 (0.00%) 0	
COVID-19 subjects affected / exposed occurrences (all)	1 / 3 (33.33%) 1	0 / 4 (0.00%) 0	
Metabolism and nutrition disorders			
Decreased appetite subjects affected / exposed occurrences (all)	1 / 3 (33.33%) 1	1 / 4 (25.00%) 1	
Hypocalcaemia subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 4 (0.00%) 0	
Folate deficiency subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 4 (0.00%) 0	
Hypoalbuminaemia subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 4 (0.00%) 0	
Dehydration subjects affected / exposed occurrences (all)	1 / 3 (33.33%) 1	0 / 4 (0.00%) 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">- Clarified the starting dose cohort and escalation cohorts for Part A.- 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).- Added a secondary efficacy endpoint in Part B to better assess hematological response and progression.- 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.- 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.- Clarified that subjects with any type of multiple myeloma will be excluded.- Plasma cell counts were removed as an eligibility criterion.- A specific exclusion of subjects with HIV is not needed, although most HIV subjects will be unable to participate because of prohibited concomitant medications.- p-GP inhibitors are allowed to be used with caution during ZN-d5 treatment.- More detailed dosing interruption criteria and suggested dose reduction levels could provide more accurate instructions to clinical site.- 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.- There will be no ZN-d5 concentration in blood before dosing; thus it is unnecessary to collect a pharmacokinetic (PK) sample at Screening.- ORR is replaced with HRR across the document as HRR is a term of convention to assess response.
30 June 2023	<ul style="list-style-type: none">- 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.- 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.- 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.- 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.- DLT criteria were updated to be more conservative per FDA request.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported