



Clinical trial results:

A PHASE 1/2 OPEN LABEL, MULTICENTER STUDY TO ASSESS THE SAFETY, TOLERABILITY, PHARMACOKINETICS, AND ANTI-TUMOR ACTIVITY OF ZN-C5 ALONE AND IN COMBINATION WITH PALBOCICLIB IN SUBJECTS WITH ESTROGEN-RECEPTOR POSITIVE, HUMAN EPIDERMAL GROWTH FACTOR RECEPTOR-2 NEGATIVE ADVANCED BREAST CANCER

Summary

EudraCT number	2018-001364-27
Trial protocol	CZ LT BG HU
Global end of trial date	22 December 2022

Results information

Result version number	v1
This version publication date	02 May 2024
First version publication date	02 May 2024

Trial information

Trial identification

Sponsor protocol code	ZN-c5-001
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03560531
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Zeno Alpha Inc.
Sponsor organisation address	10275 Science Center Drive, Suite 200, San Diego, California, United States,
Public contact	Regulatory Head, Zeno Alpha, Inc., , +1 (858) 263-4333, RegLeads@zentalis.com
Scientific contact	Head of Regulatory, Zeno Alpha, Inc., , +1 (858) 263-4333, RegLeads@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	22 December 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	26 April 2022
Global end of trial reached?	Yes
Global end of trial date	22 December 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Phase 1

- Monotherapy Dose Escalation: Determine a maximum tolerated dose (MTD) or recommended Phase 2 dose (RP2D) for ZN-c5 as a monotherapy
- Monotherapy Expansion: Investigate the safety and tolerability of ZN-c5 as a monotherapy in subjects with Estrogen Receptor (ER) positive, Human Epidermal Growth Factor Receptor-2 (HER2) negative advanced breast cancer
- Combination Dose Escalation: Determine an MTD or RP2D for ZN-c5 when administered in combination with palbociclib

Phase 2

- Monotherapy Phase 2: Determine preliminary anti-tumor efficacy [Clinical Benefit Rate (CBR)] for ZN-c5 as a monotherapy
- Combination Phase 2: Determine preliminary anti-tumor efficacy (CBR) for ZN-c5 when administered in combination with palbociclib

Protection of trial subjects:

This study was conducted in accordance with the ethical principles of Good Clinical Practice, according to the International Conference on Harmonization Guidelines.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	30 November 2018
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	United States: 109
Country: Number of subjects enrolled	European Union: 72
Worldwide total number of subjects	181
EEA total number of subjects	0

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)	105
From 65 to 84 years	74
85 years and over	2

Subject disposition

Recruitment

Recruitment details:

Study was initiated on 30 November 2018 and completed on 22 December 2022 (last participant last visit). 29 centers in Belarus, Bosnia and Herzegovina, the Czech Republic, Hungary, Lithuania, Russia, Serbia, Ukraine, and the United States enrolled the participants.

Pre-assignment

Screening details:

Subjects received study drug once daily for 28-days cycle. At the same time some subjects could also receive the study drug twice daily. The study also has End-of-Treatment visit; 30 day safety follow up and disease assessment and long term follow up for every 12 weeks.

Period 1

Period 1 title	Full Analysis Set (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
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Arm title	ZN-c5 monotherapy (Phase 1)
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Arm description:

Participants who received ZN-c5 in Phase 1 (Dose escalation) were included in this arm.

Arm type	Experimental
Investigational medicinal product name	ZN-c5
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Dose escalation cohorts are planned to determine MTD or RP2D of ZN-c5 as well as expansion cohorts and a Phase 2 cohort.

Arm title	ZN-c5 Monotherapy (Phase 2)
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Arm description:

Participants who received ZN-c5 in Phase 2 (Dose expansion) were included in this arm.

Arm type	Experimental
Investigational medicinal product name	ZN-c5
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Dose escalation cohorts are planned to determine MTD or RP2D of ZN-c5 as well as expansion cohorts and a Phase 2 cohort.

Arm title	ZN-c5 + Palbociclib Combination Therapy (Phase 1)
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Arm description:

Participants who received ZN-c5 along with Palbociclib (IBRANCE®) in Phase 1 were included in this arm.

Arm type	Experimental
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Investigational medicinal product name	ZN-c5
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Dose escalation cohorts are planned to determine MTD or RP2D of ZN-c5 as well as expansion cohorts and a Phase 2 cohort.

Investigational medicinal product name	Palbociclib
Investigational medicinal product code	
Other name	IBRANCE®
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Palbociclib was dosed orally at 125 mg QD for 21 consecutive days, followed by 7 days off treatment to comprise a complete cycle of 28 days.

Number of subjects in period 1	ZN-c5 monotherapy (Phase 1)	ZN-c5 Monotherapy (Phase 2)	ZN-c5 + Palbociclib Combination Therapy (Phase 1)
	Started	56	75
Completed	0	0	0
Not completed	56	75	50
Study end per-protocol	5	-	-
Consent withdrawn by subject	1	3	4
Death	19	8	11
Early study termination by sponsor	28	64	35
Lost to follow-up	3	-	-

Baseline characteristics

Reporting groups

Reporting group title	ZN-c5 monotherapy (Phase 1)
Reporting group description:	
Participants who received ZN-c5 in Phase 1 (Dose escalation) were included in this arm.	
Reporting group title	ZN-c5 Monotherapy (Phase 2)
Reporting group description:	
Participants who received ZN-c5 in Phase 2 (Dose expansion) were included in this arm.	
Reporting group title	ZN-c5 + Palbociclib Combination Therapy (Phase 1)
Reporting group description:	
Participants who received ZN-c5 along with Palbociclib (IBRANCE®) in Phase 1 were included in this arm.	

Reporting group values	ZN-c5 monotherapy (Phase 1)	ZN-c5 Monotherapy (Phase 2)	ZN-c5 + Palbociclib Combination Therapy (Phase 1)
Number of subjects	56	75	50
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	37	39	29
From 65-84 years	18	35	21
85 years and over	1	1	0
Age continuous			
Units: years			
arithmetic mean	61.0	62.1	60.1
standard deviation	± 9.70	± 11.75	± 11.30
Gender categorical			
Units: Subjects			
Female	56	75	49
Male	0	0	1
Race			
Units: Subjects			
American Indian or Alaska Native	0	0	1
Asian	3	0	0
Native Hawaiian or Other Pacific Islander	0	0	1
Black or African American	2	0	3
White	47	74	44
More than one race	0	0	0
Unknown or Not Reported	4	1	1
Region of Enrollment			
Units: Subjects			

United States	46	13	50
Europe	10	62	0

Reporting group values	Total		
Number of subjects	181		
Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	0		
Infants and toddlers (28 days-23 months)	0		
Children (2-11 years)	0		
Adolescents (12-17 years)	0		
Adults (18-64 years)	105		
From 65-84 years	74		
85 years and over	2		
Age continuous Units: years arithmetic mean standard deviation	-		
Gender categorical Units: Subjects			
Female	180		
Male	1		
Race Units: Subjects			
American Indian or Alaska Native	1		
Asian	3		
Native Hawaiian or Other Pacific Islander	1		
Black or African American	5		
White	165		
More than one race	0		
Unknown or Not Reported	6		
Region of Enrollment Units: Subjects			
United States	109		
Europe	72		

End points

End points reporting groups

Reporting group title	ZN-c5 monotherapy (Phase 1)
Reporting group description:	
Participants who received ZN-c5 in Phase 1 (Dose escalation) were included in this arm.	
Reporting group title	ZN-c5 Monotherapy (Phase 2)
Reporting group description:	
Participants who received ZN-c5 in Phase 2 (Dose expansion) were included in this arm.	
Reporting group title	ZN-c5 + Palbociclib Combination Therapy (Phase 1)
Reporting group description:	
Participants who received ZN-c5 along with Palbociclib (IBRANCE®) in Phase 1 were included in this arm.	

Primary: Clinical Benefit Rate for ZN-c5 as a Monotherapy

End point title	Clinical Benefit Rate for ZN-c5 as a Monotherapy ^{[1][2]}
End point description:	
CBR is defined as the percentage of participants who have at least one confirmed response of complete response (CR) or partial response (PR) (only if participant has measurable disease), or stable disease (SD) ≥ 24 weeks (or non- CR/non-progressive disease (PD) ≥24 weeks for participants with non-measurable disease) prior to any evidence of progression.	
End point type	Primary
End point timeframe:	
24 weeks	

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: Only descriptive statistical analysis was performed for the primary end point.

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

Justification: Only reporting groups in which participants received monotherapy were evaluated for this end point.

End point values	ZN-c5 monotherapy (Phase 1)	ZN-c5 Monotherapy (Phase 2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	75		
Units: Participants	7	38		

Statistical analyses

No statistical analyses for this end point

Primary: Best Overall Response (BOR) for ZN-c5 as a Monotherapy

End point title	Best Overall Response (BOR) for ZN-c5 as a Monotherapy ^{[3][4]}
End point description:	
Best overall response was summarized categorically based on the four RECIST categories: CR, PR, SD and PD.	

End point type	Primary
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End point timeframe:

24 Weeks

Notes:

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

Justification: Only descriptive statistical analysis was performed for the primary end point.

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

Justification: Only reporting groups in which participants received monotherapy were evaluated for this end point.

End point values	ZN-c5 monotherapy (Phase 1)	ZN-c5 Monotherapy (Phase 2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	75		
Units: Participants				
CR	0	0		
PR	0	3		
SD	13	50		
SD ≥24 weeks	6	35		
8 weeks < SD <24 weeks	7	15		
PD	3	19		
Non-Responders (NR)	0	3		
Not Evaluable (NE)	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-Free Survival (PFS) at 2 Months

End point title	Progression-Free Survival (PFS) at 2 Months ^[5]
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End point description:

PFS is defined as the time (in months) from the date of first dosing until the date of objective PD (as defined by RECIST version 1.1) or death (by any cause in the absence of progression), whichever occurs earlier. Kaplan-Meier estimates at 2 months and their confidence intervals are calculated with the log-log transformation methodology of Kalbfleisch and Prentice. The Tumor Response-Evaluable Set includes all participants in the full analysis set with at least 1 evaluable postbaseline response assessment using RECIST 1.1.

End point type	Secondary
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End point timeframe:

2 months

Notes:

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

Justification: Only reporting groups in which participants received monotherapy were evaluated for this end point.

End point values	ZN-c5 monotherapy (Phase 1)	ZN-c5 Monotherapy (Phase 2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	72		
Units: estimate probability				
number (confidence interval 95%)	87.1 (57.3 to 96.6)	77.8 (66.3 to 85.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-Free Survival at 4 Months

End point title	Progression-Free Survival at 4 Months ^[6]
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End point description:

PFS is defined as the time (in months) from the date of first dosing until the date of objective PD (as defined by RECIST version 1.1) or death (by any cause in the absence of progression), whichever occurs earlier. Kaplan-Meier estimates at 4 months and their confidence intervals are calculated with the log-log transformation methodology of Kalbfleisch and Prentice. The Tumor Response-Evaluable Set includes all participants in the full analysis set with at least 1 evaluable postbaseline response assessment using RECIST 1.1.

End point type	Secondary
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End point timeframe:

4 months

Notes:

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

Justification: Only reporting groups in which participants received monotherapy were evaluated for this end point.

End point values	ZN-c5 monotherapy (Phase 1)	ZN-c5 Monotherapy (Phase 2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	72		
Units: estimate probability				
number (confidence interval 95%)	73.7 (44.1 to 89.2)	60.8 (48.5 to 71.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-Free Survival at 6 Months

End point title	Progression-Free Survival at 6 Months ^[7]
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End point description:

PFS is defined as the time (in months) from the date of first dosing until the date of objective PD (as defined by RECIST version 1.1) or death (by any cause in the absence of progression), whichever occurs earlier. Kaplan-Meier estimates at 6 months and their confidence intervals are calculated with the log-log transformation methodology of Kalbfleisch and Prentice. The Tumor Response-Evaluable Set includes all participants in the full analysis set with at least 1 evaluable postbaseline response assessment using

RECIST 1.1.

End point type	Secondary
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End point timeframe:

6 months

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Only reporting groups in which participants received monotherapy were evaluated for this end point.

End point values	ZN-c5 monotherapy (Phase 1)	ZN-c5 Monotherapy (Phase 2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	72		
Units: estimate probability				
number (confidence interval 95%)	64.5 (33.6 to 83.8)	50.3 (38.1 to 61.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-Free Survival at 8 Months

End point title	Progression-Free Survival at 8 Months ^[8]
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End point description:

PFS is defined as the time (in months) from the date of first dosing until the date of objective PD (as defined by RECIST version 1.1) or death (by any cause in the absence of progression), whichever occurs earlier. Kaplan-Meier estimates at 8 months and their confidence intervals are calculated with the log-log transformation methodology of Kalbfleisch and Prentice. The Tumor Response-Evaluable Set includes all participants in the full analysis set with at least 1 evaluable postbaseline response assessment using RECIST 1.1.

End point type	Secondary
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End point timeframe:

8 months

Notes:

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Only reporting groups in which participants received monotherapy were evaluated for this end point.

End point values	ZN-c5 monotherapy (Phase 1)	ZN-c5 Monotherapy (Phase 2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	72		
Units: estimate probability				
number (confidence interval 95%)	64.5 (33.6 to 83.8)	44.2 (32.3 to 55.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-Free Survival at 10 Months

End point title | Progression-Free Survival at 10 Months^[9]

End point description:

PFS is defined as the time (in months) from the date of first dosing until the date of objective PD (as defined by RECIST version 1.1) or death (by any cause in the absence of progression), whichever occurs earlier. Kaplan-Meier estimates at 10 months and their confidence intervals are calculated with the log-log transformation methodology of Kalbfleisch and Prentice. The Tumor Response-Evaluable Set includes all participants in the full analysis set with at least 1 evaluable postbaseline response assessment using RECIST 1.1.

End point type | Secondary

End point timeframe:

10 months

Notes:

[9] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Only reporting groups in which participants received monotherapy were evaluated for this end point.

End point values	ZN-c5 monotherapy (Phase 1)	ZN-c5 Monotherapy (Phase 2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	72		
Units: estimate probability				
number (confidence interval 95%)	55.2 (25.2 to 77.5)	35.9 (24.6 to 47.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-Free Survival at 12 Months

End point title | Progression-Free Survival at 12 Months^[10]

End point description:

PFS is defined as the time (in months) from the date of first dosing until the date of objective PD (as defined by RECIST version 1.1) or death (by any cause in the absence of progression), whichever occurs earlier. Kaplan-Meier estimates at 12 months and their confidence intervals are calculated with the log-log transformation methodology of Kalbfleisch and Prentice. The Tumor Response-Evaluable Set includes all participants in the full analysis set with at least 1 evaluable postbaseline response assessment using RECIST 1.1.

End point type | Secondary

End point timeframe:

12 months

Notes:

[10] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Only reporting groups in which participants received monotherapy were evaluated for this end point.

End point values	ZN-c5 monotherapy (Phase 1)	ZN-c5 Monotherapy (Phase 2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	72		
Units: estimate probability				
number (confidence interval 95%)	27.6 (6.9 to 53.9)	26.2 (15.8 to 37.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS) at 2 Months

End point title	Overall Survival (OS) at 2 Months ^[11]
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End point description:

OS is defined as the time from the date of enrollment to the date of death from any cause. Kaplan-Meier estimates at 2 months and their confidence intervals are calculated with the log-log transformation methodology of Kalbfleisch and Prentice. Full Analysis Set consisted of all participants who received ≥ 1 dose of study drug and was used in the analyses of participant characteristics and efficacy endpoints.

End point type	Secondary
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End point timeframe:

2 months

Notes:

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

Justification: Only reporting groups in which participants received monotherapy were evaluated for this end point.

End point values	ZN-c5 monotherapy (Phase 1)	ZN-c5 Monotherapy (Phase 2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	75		
Units: estimate probability				
number (confidence interval 95%)	100 (100 to 100)	98.7 (90.9 to 99.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival at 4 Months

End point title	Overall Survival at 4 Months ^[12]
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End point description:

OS is defined as the time from the date of enrollment to the date of death from any cause. Kaplan-Meier estimates at 4 months and their confidence intervals are calculated with the log-log transformation methodology of Kalbfleisch and Prentice. Full Analysis Set consisted of all participants who received ≥ 1 dose of study drug and was used in the analyses of participant characteristics and efficacy endpoints.

End point type	Secondary
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End point timeframe:

4 months

Notes:

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

Justification: Only reporting groups in which participants received monotherapy were evaluated for this end point.

End point values	ZN-c5 monotherapy (Phase 1)	ZN-c5 Monotherapy (Phase 2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	75		
Units: estimate probability				
number (confidence interval 95%)	100 (100 to 100)	97.3 (89.6 to 99.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival at 6 Months

End point title Overall Survival at 6 Months^[13]

End point description:

OS is defined as the time from the date of enrollment to the date of death from any cause. Kaplan-Meier estimates at 6 months and their confidence intervals are calculated with the log-log transformation methodology of Kalbfleisch and Prentice. Full Analysis Set consisted of all participants who received ≥ 1 dose of study drug and was used in the analyses of participant characteristics and efficacy endpoints

End point type Secondary

End point timeframe:

6 months

Notes:

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

Justification: Only reporting groups in which participants received monotherapy were evaluated for this end point.

End point values	ZN-c5 monotherapy (Phase 1)	ZN-c5 Monotherapy (Phase 2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	75		
Units: estimate probability				
number (confidence interval 95%)	100 (100 to 100)	97.3 (89.6 to 99.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival at 8 Months

End point title	Overall Survival at 8 Months ^[14]
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End point description:

OS is defined as the time from the date of enrollment to the date of death from any cause. Kaplan-Meier estimates at 8 months and their confidence intervals are calculated with the log-log transformation methodology of Kalbfleisch and Prentice. Full Analysis Set consisted of all participants who received ≥ 1 dose of study drug and was used in the analyses of participant characteristics and efficacy endpoints

End point type	Secondary
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End point timeframe:

8 months

Notes:

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

Justification: Only reporting groups in which participants received monotherapy were evaluated for this end point.

End point values	ZN-c5 monotherapy (Phase 1)	ZN-c5 Monotherapy (Phase 2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	75		
Units: estimate probability				
number (confidence interval 95%)	100 (100 to 100)	94.0 (84.8 to 97.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival at 10 Months

End point title	Overall Survival at 10 Months ^[15]
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End point description:

OS is defined as the time from the date of enrollment to the date of death from any cause. Kaplan-Meier estimates at 10 months and their confidence intervals are calculated with the log-log transformation methodology of Kalbfleisch and Prentice. Full Analysis Set consisted of all participants who received ≥ 1 dose of study drug and was used in the analyses of participant characteristics and efficacy endpoints.

End point type	Secondary
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End point timeframe:

10 months

Notes:

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

Justification: Only reporting groups in which participants received monotherapy were evaluated for this end point.

End point values	ZN-c5 monotherapy (Phase 1)	ZN-c5 Monotherapy (Phase 2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	75		
Units: estimate probability				
number (confidence interval 95%)	100 (100 to 100)	90.0 (78.8 to 90.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival at 12 Months

End point title	Overall Survival at 12 Months ^[16]
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End point description:

OS is defined as the time from the date of enrollment to the date of death from any cause. Kaplan-Meier estimates at 12 months and their confidence intervals are calculated with the log-log transformation methodology of Kalbfleisch and Prentice. Full Analysis Set consisted of all participants who received ≥ 1 dose of study drug and was used in the analyses of participant characteristics and efficacy endpoints.

End point type	Secondary
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End point timeframe:

12 months

Notes:

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

Justification: Only reporting groups in which participants received monotherapy were evaluated for this end point.

End point values	ZN-c5 monotherapy (Phase 1)	ZN-c5 Monotherapy (Phase 2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	75		
Units: estimate probability				
number (confidence interval 95%)	100 (100 to 100)	84.2 (69.8 to 92.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Objective Response Rate (ORR) for ZN-c5 as a Monotherapy

End point title	Objective Response Rate (ORR) for ZN-c5 as a Monotherapy ^[17]
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End point description:

ORR is defined as the percentage of participants with measurable disease who have at least 1 confirmed response of CR or PR prior to any evidence of progression (as defined by RECIST v1.1). Full Analysis Set consisted of all participants who received ≥ 1 dose of study drug and was used in the analyses of participant characteristics and efficacy endpoints.

End point type	Secondary
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End point timeframe:

24 weeks

Notes:

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

Justification: Only reporting groups in which participants received monotherapy were evaluated for this end point.

End point values	ZN-c5 monotherapy (Phase 1)	ZN-c5 Monotherapy (Phase 2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	75		
Units: participants	0	3		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

12 months

Adverse event reporting additional description:

For the safety analysis, Phase 1 Monotherapy group was combined with Phase 2 Monotherapy group.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	25.1
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Reporting groups

Reporting group title	ZN-c5 Monotherapy (Phase 1)
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Reporting group description:

Participants who received ZN-c5 in Phase 1 (Dose escalation) were included in this arm.

Reporting group title	ZN-c5 Monotherapy (Phase 2)
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Reporting group description:

Participants who received ZN-c5 in Phase 2 (Dose expansion) were included in this arm.

Reporting group title	ZN-c5 + Palbociclib Combination Therapy (Phase 1)
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Reporting group description:

Participants who received ZN-c5 along with Palbociclib (IBRANCE®) in Phase 1 were included in this arm.

Serious adverse events	ZN-c5 Monotherapy (Phase 1)	ZN-c5 Monotherapy (Phase 2)	ZN-c5 + Palbociclib Combination Therapy (Phase 1)
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 56 (10.71%)	9 / 75 (12.00%)	10 / 50 (20.00%)
number of deaths (all causes)	19	8	12
number of deaths resulting from adverse events	0	1	0
Injury, poisoning and procedural complications			
Femur fracture			
subjects affected / exposed	0 / 56 (0.00%)	1 / 75 (1.33%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Foot fracture			
subjects affected / exposed	0 / 56 (0.00%)	1 / 75 (1.33%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal fracture			

subjects affected / exposed	0 / 56 (0.00%)	1 / 75 (1.33%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Embolism			
subjects affected / exposed	0 / 56 (0.00%)	0 / 75 (0.00%)	2 / 50 (4.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	3 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Cardiac disorder			
subjects affected / exposed	0 / 56 (0.00%)	1 / 75 (1.33%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Aphasia			
subjects affected / exposed	0 / 56 (0.00%)	1 / 75 (1.33%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Headache			
subjects affected / exposed	0 / 56 (0.00%)	0 / 75 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ischaemic stroke			
subjects affected / exposed	0 / 56 (0.00%)	0 / 75 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient ischaemic attack			
subjects affected / exposed	1 / 56 (1.79%)	0 / 75 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Pyrexia			

subjects affected / exposed	0 / 56 (0.00%)	0 / 75 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	1 / 56 (1.79%)	0 / 75 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 56 (1.79%)	0 / 75 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ascites			
subjects affected / exposed	0 / 56 (0.00%)	1 / 75 (1.33%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	0 / 56 (0.00%)	0 / 75 (0.00%)	2 / 50 (4.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural effusion			
subjects affected / exposed	0 / 56 (0.00%)	2 / 75 (2.67%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumothorax			
subjects affected / exposed	0 / 56 (0.00%)	0 / 75 (0.00%)	2 / 50 (4.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	0 / 56 (0.00%)	1 / 75 (1.33%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0

Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 56 (0.00%)	0 / 75 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Calculus urinary			
subjects affected / exposed	0 / 56 (0.00%)	0 / 75 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 56 (1.79%)	0 / 75 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Back pain			
subjects affected / exposed	0 / 56 (0.00%)	0 / 75 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
COVID-19			
subjects affected / exposed	1 / 56 (1.79%)	2 / 75 (2.67%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	1 / 56 (1.79%)	0 / 75 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device related infection			
subjects affected / exposed	1 / 56 (1.79%)	0 / 75 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			

subjects affected / exposed	0 / 56 (0.00%)	1 / 75 (1.33%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	ZN-c5 Monotherapy (Phase 1)	ZN-c5 Monotherapy (Phase 2)	ZN-c5 + Palbociclib Combination Therapy (Phase 1)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	54 / 56 (96.43%)	52 / 75 (69.33%)	50 / 50 (100.00%)
Vascular disorders			
Hot flush			
subjects affected / exposed	8 / 56 (14.29%)	2 / 75 (2.67%)	8 / 50 (16.00%)
occurrences (all)	9	2	10
Hypertension			
subjects affected / exposed	6 / 56 (10.71%)	3 / 75 (4.00%)	2 / 50 (4.00%)
occurrences (all)	12	10	8
Hypotension			
subjects affected / exposed	4 / 56 (7.14%)	1 / 75 (1.33%)	5 / 50 (10.00%)
occurrences (all)	6	1	6
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	14 / 56 (25.00%)	6 / 75 (8.00%)	22 / 50 (44.00%)
occurrences (all)	15	9	29
Asthenia			
subjects affected / exposed	0 / 56 (0.00%)	7 / 75 (9.33%)	0 / 50 (0.00%)
occurrences (all)	0	7	0
Oedema peripheral			
subjects affected / exposed	2 / 56 (3.57%)	2 / 75 (2.67%)	4 / 50 (8.00%)
occurrences (all)	3	2	4
Pyrexia			
subjects affected / exposed	4 / 56 (7.14%)	0 / 75 (0.00%)	2 / 50 (4.00%)
occurrences (all)	6	0	2
Reproductive system and breast disorders			

Breast pain subjects affected / exposed occurrences (all)	4 / 56 (7.14%) 4	2 / 75 (2.67%) 5	2 / 50 (4.00%) 2
Vaginal discharge subjects affected / exposed occurrences (all)	3 / 56 (5.36%) 3	2 / 75 (2.67%) 2	1 / 50 (2.00%) 1
Respiratory, thoracic and mediastinal disorders			
Cough subjects affected / exposed occurrences (all)	5 / 56 (8.93%) 5	0 / 75 (0.00%) 0	6 / 50 (12.00%) 6
Dyspnoea subjects affected / exposed occurrences (all)	3 / 56 (5.36%) 4	7 / 75 (9.33%) 8	7 / 50 (14.00%) 7
Oropharyngeal pain subjects affected / exposed occurrences (all)	3 / 56 (5.36%) 4	0 / 75 (0.00%) 0	4 / 50 (8.00%) 4
Rhinitis allergic subjects affected / exposed occurrences (all)	3 / 56 (5.36%) 3	0 / 75 (0.00%) 0	2 / 50 (4.00%) 2
Psychiatric disorders			
Insomnia subjects affected / exposed occurrences (all)	4 / 56 (7.14%) 4	0 / 75 (0.00%) 0	10 / 50 (20.00%) 12
Anxiety subjects affected / exposed occurrences (all)	3 / 56 (5.36%) 3	0 / 75 (0.00%) 0	3 / 50 (6.00%) 3
Investigations			
ALT increased subjects affected / exposed occurrences (all)	7 / 56 (12.50%) 9	6 / 75 (8.00%) 7	6 / 50 (12.00%) 10
AST increased subjects affected / exposed occurrences (all)	4 / 56 (7.14%) 4	7 / 75 (9.33%) 9	10 / 50 (20.00%) 23
Blood cholesterol increased subjects affected / exposed occurrences (all)	4 / 56 (7.14%) 4	1 / 75 (1.33%) 1	9 / 50 (18.00%) 10

Blood creatinine increased subjects affected / exposed occurrences (all)	3 / 56 (5.36%) 3	6 / 75 (8.00%) 10	10 / 50 (20.00%) 13
GGT increased subjects affected / exposed occurrences (all)	11 / 56 (19.64%) 23	11 / 75 (14.67%) 16	6 / 50 (12.00%) 15
Lymphocyte count decreased subjects affected / exposed occurrences (all)	5 / 56 (8.93%) 10	3 / 75 (4.00%) 5	18 / 50 (36.00%) 58
Neutrophil count decreased subjects affected / exposed occurrences (all)	3 / 56 (5.36%) 3	0 / 75 (0.00%) 0	36 / 50 (72.00%) 138
Platelet count decreased subjects affected / exposed occurrences (all)	3 / 56 (5.36%) 3	0 / 75 (0.00%) 0	13 / 50 (26.00%) 26
White blood cell count decreased subjects affected / exposed occurrences (all)	6 / 56 (10.71%) 8	2 / 75 (2.67%) 4	38 / 50 (76.00%) 137
Blood alkaline phosphatase increased subjects affected / exposed occurrences (all)	4 / 56 (7.14%) 5	7 / 75 (9.33%) 8	3 / 50 (6.00%) 3
Electrocardiogram QT prolonged subjects affected / exposed occurrences (all)	0 / 56 (0.00%) 0	6 / 75 (8.00%) 8	1 / 50 (2.00%) 1
Weight decreased subjects affected / exposed occurrences (all)	2 / 56 (3.57%) 2	4 / 75 (5.33%) 4	3 / 50 (6.00%) 4
Injury, poisoning and procedural complications Contusion subjects affected / exposed occurrences (all)	0 / 56 (0.00%) 0	1 / 75 (1.33%) 1	4 / 50 (8.00%) 4
Cardiac disorders Sinus tachycardia subjects affected / exposed occurrences (all)	3 / 56 (5.36%) 3	3 / 75 (4.00%) 5	0 / 50 (0.00%) 0
Nervous system disorders			

Dizziness subjects affected / exposed occurrences (all)	3 / 56 (5.36%) 3	1 / 75 (1.33%) 1	5 / 50 (10.00%) 5
Headache subjects affected / exposed occurrences (all)	10 / 56 (17.86%) 35	3 / 75 (4.00%) 3	6 / 50 (12.00%) 10
Blood and lymphatic system disorders			
Anaemia subjects affected / exposed occurrences (all)	7 / 56 (12.50%) 16	5 / 75 (6.67%) 8	27 / 50 (54.00%) 47
Neutropenia subjects affected / exposed occurrences (all)	0 / 56 (0.00%) 0	6 / 75 (8.00%) 9	0 / 50 (0.00%) 0
Gastrointestinal disorders			
Constipation subjects affected / exposed occurrences (all)	4 / 56 (7.14%) 4	2 / 75 (2.67%) 2	8 / 50 (16.00%) 9
Diarrhoea subjects affected / exposed occurrences (all)	7 / 56 (12.50%) 11	7 / 75 (9.33%) 12	9 / 50 (18.00%) 13
Dyspepsia subjects affected / exposed occurrences (all)	5 / 56 (8.93%) 7	0 / 75 (0.00%) 0	10 / 50 (20.00%) 11
Nausea subjects affected / exposed occurrences (all)	17 / 56 (30.36%) 24	6 / 75 (8.00%) 7	18 / 50 (36.00%) 21
Stomatitis subjects affected / exposed occurrences (all)	1 / 56 (1.79%) 3	0 / 75 (0.00%) 0	6 / 50 (12.00%) 6
Vomiting subjects affected / exposed occurrences (all)	9 / 56 (16.07%) 15	0 / 75 (0.00%) 0	5 / 50 (10.00%) 6
Abdominal pain subjects affected / exposed occurrences (all)	3 / 56 (5.36%) 3	4 / 75 (5.33%) 6	2 / 50 (4.00%) 2
Skin and subcutaneous tissue disorders			

Rash maculo-papular subjects affected / exposed occurrences (all)	1 / 56 (1.79%) 1	1 / 75 (1.33%) 1	8 / 50 (16.00%) 10
Alopecia subjects affected / exposed occurrences (all)	1 / 56 (1.79%) 1	0 / 75 (0.00%) 0	3 / 50 (6.00%) 3
Pruritus subjects affected / exposed occurrences (all)	2 / 56 (3.57%) 2	1 / 75 (1.33%) 1	4 / 50 (8.00%) 5
Renal and urinary disorders Proteinuria subjects affected / exposed occurrences (all)	0 / 56 (0.00%) 0	0 / 75 (0.00%) 0	3 / 50 (6.00%) 3
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all)	11 / 56 (19.64%) 16	4 / 75 (5.33%) 4	16 / 50 (32.00%) 22
Back pain subjects affected / exposed occurrences (all)	6 / 56 (10.71%) 10	5 / 75 (6.67%) 8	4 / 50 (8.00%) 6
Myalgia subjects affected / exposed occurrences (all)	3 / 56 (5.36%) 3	0 / 75 (0.00%) 0	5 / 50 (10.00%) 6
Pain in extremity subjects affected / exposed occurrences (all)	6 / 56 (10.71%) 8	0 / 75 (0.00%) 0	4 / 50 (8.00%) 7
Bone pain subjects affected / exposed occurrences (all)	3 / 56 (5.36%) 5	4 / 75 (5.33%) 7	2 / 50 (4.00%) 2
Flank pain subjects affected / exposed occurrences (all)	2 / 56 (3.57%) 3	0 / 75 (0.00%) 0	3 / 50 (6.00%) 3
Muscle spasms subjects affected / exposed occurrences (all)	2 / 56 (3.57%) 2	0 / 75 (0.00%) 0	3 / 50 (6.00%) 4
Musculoskeletal chest pain			

subjects affected / exposed occurrences (all)	3 / 56 (5.36%) 5	1 / 75 (1.33%) 1	0 / 50 (0.00%) 0
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	1 / 56 (1.79%)	3 / 75 (4.00%)	5 / 50 (10.00%)
occurrences (all)	1	3	8
COVID-19			
subjects affected / exposed	1 / 56 (1.79%)	7 / 75 (9.33%)	3 / 50 (6.00%)
occurrences (all)	1	8	3
Upper respiratory tract infection			
subjects affected / exposed	2 / 56 (3.57%)	0 / 75 (0.00%)	4 / 50 (8.00%)
occurrences (all)	2	0	4
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	8 / 56 (14.29%)	0 / 75 (0.00%)	13 / 50 (26.00%)
occurrences (all)	16	0	26
Hypertriglyceridaemia			
subjects affected / exposed	5 / 56 (8.93%)	0 / 75 (0.00%)	11 / 50 (22.00%)
occurrences (all)	6	0	11
Hypoalbuminaemia			
subjects affected / exposed	3 / 56 (5.36%)	1 / 75 (1.33%)	5 / 50 (10.00%)
occurrences (all)	4	1	5
Hypocalcaemia			
subjects affected / exposed	4 / 56 (7.14%)	0 / 75 (0.00%)	6 / 50 (12.00%)
occurrences (all)	7	0	10
Hypokalaemia			
subjects affected / exposed	2 / 56 (3.57%)	0 / 75 (0.00%)	9 / 50 (18.00%)
occurrences (all)	5	0	27
Hyponatraemia			
subjects affected / exposed	6 / 56 (10.71%)	1 / 75 (1.33%)	7 / 50 (14.00%)
occurrences (all)	16	1	8
Hypophosphataemia			
subjects affected / exposed	6 / 56 (10.71%)	0 / 75 (0.00%)	9 / 50 (18.00%)
occurrences (all)	9	0	15
Decreased appetite			

subjects affected / exposed occurrences (all)	3 / 56 (5.36%) 3	4 / 75 (5.33%) 4	2 / 50 (4.00%) 2
Hypercalcaemia subjects affected / exposed occurrences (all)	1 / 56 (1.79%) 2	3 / 75 (4.00%) 5	4 / 50 (8.00%) 4
Hypoglycaemia subjects affected / exposed occurrences (all)	3 / 56 (5.36%) 5	0 / 75 (0.00%) 0	1 / 50 (2.00%) 3
Hypomagnesaemia subjects affected / exposed occurrences (all)	3 / 56 (5.36%) 3	1 / 75 (1.33%) 1	2 / 50 (4.00%) 4

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
09 April 2018	EudraCT number added and investigator prompt removed from title page.
12 July 2018	The language throughout the protocol clarified, updated and streamlined to improve flow and readability.
25 June 2019	The study design updated.
14 February 2020	The study design updated.
14 September 2020	The study design updated.
20 April 2021	The clarification for Phase 2 assessment, food intake and abbreviated PK sampling updated.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

In the Phase 2 Monotherapy efficacy analysis, efficacy was to be determined by the CBR, combining results with similar treatment groups. Yet, Phase 1 Monotherapy group was combined with Phase 2 Monotherapy group.

Notes: