Clinical trial results:
A Phase 1/2 Dose Escalation and Dose Expansion Study of ZN-c3 in Combination with Gemcitabine in Adult and Pediatric Subjects with Relapsed or Refractory Osteosarcoma

Summary

EudraCT number	2021-000021-27
Trial protocol	DE ES NL
Global end of trial date	07 March 2024

Results information

Result version number	v1 (current)
This version publication date	09 October 2024
First version publication date	09 October 2024

Trial information

Trial identification

Sponsor protocol code	ZN-c3-003

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04833582
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	K-Group Beta
Sponsor organisation address	10275 Science Center Dr, Suite 200 , San Diego, United States, CA 92121
Public contact	VP Regulatory Affairs, K-Group Beta, +1 732-666-5002, risrani@zentalis.com
Scientific contact	VP Regulatory Affairs, K-Group Beta, +1 732-666-5002, risrani@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 August 2024
Is this the analysis of the primary completion data?	Yes
Primary completion date	07 March 2024
Global end of trial reached?	Yes
Global end of trial date	07 March 2024
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

Phase 1:
- To investigate the safety and tolerability, including identification of the maximum tolerated dose (MTD) and recommended Phase 2 dose (RP2D) of ZN-c3 in combination with gemcitabine
Phase 2:
- To evaluate the clinical activity of WEE1 inhibition by ZN-c3 in combination with gemcitabine in subjects with relapsed/refractory osteosarcoma as assessed by the event-free survival (EFS) at 18 weeks, per response evaluation criteria in solid tumors RECIST Guideline version 1.1

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:

Not applicable

Evidence for comparator:

Not applicable

Actual start date of recruitment	20 August 2021
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	1 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	France: 6
Country: Number of subjects enrolled	United States: 25
Worldwide total number of subjects	31
EEA total number of subjects	6

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)	5
Adults (18-64 years)	25
From 65 to 84 years	1
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Phase I Subject screening occurred in France and the USA from August 2021 up to including June 2023. First patient signed consent on 20 August 2021 and last patient consented in USA on 26 June 2023. 10 sites were recruiting subjects. The study did not start in Spain and the Netherlands. It was decided not to conduct the phase 2 part of the study.

Pre-assignment

Screening details:

A total of 40 subject were screened after consent. One subject screen failed. 8 subjects were not enrolled in the study due to various reasons. (e.g. full cohort or at the decision of the investigator)

Period 1

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

Blinding implementation details:

not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	ZN-c3 150mg QD + Gemcitabine 800mg/m2

Arm description:

treatment cycles of 21 days with ZN-c3 150mg daily dose in combination with gemcitabine 800mg/m2, until
progression of disease or any of the withdrawal criteria included in the protocol are met

Arm type	Experimental
Investigational medicinal product name	ZN-c3
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

The dose of ZN-c3 was 150 mg daily continuous dosing Subjects took ZN-c3 in 21-day cycles (± 3 days) with food.

Investigational medicinal product name	Gemcitabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

The gemcitabine dose was 800 mg/m2 administered intravenously over
30 minutes (or per institutional standard) on Days 1 and 8 of a 21-day cycle

Arm title	ZN-c3 200mg QD + Gemcitabine 1000mg/m2

Arm description:

treatment cycles of 21 days with ZN-c3 200mg daily dose in combination with gemcitabine 1000mg/m2, until
progression of disease or any of the withdrawal criteria included in the protocol are met

Arm type	Experimental

Investigational medicinal product name	ZN-c3
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

The dose of ZN-c3 was 200 mg daily continuous dosing. Subjects took ZN-c3 in 21-day cycles (± 3 days) with food.

Investigational medicinal product name	Gemcitabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

The gemcitabine dose was 1000 mg/m2 administered intravenously over 30 minutes (or per institutional standard) on Days 1 and 8 of a 21-day cycle

Arm title	ZN-c3 150mg QD 5:2 + Gemcitabine 800mg/m2

Arm description:

treatment cycles of 21 days with ZN-c3 150mg given intermittent 5 days on and 2 days off in combination with gemcitabine 800mg/m2, until progression of disease or any of the withdrawal criteria included in the protocol are met

Arm type	Experimental
Investigational medicinal product name	ZN-c3
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

treatment cycles of 21 days with ZN-c3 150mg given intermittent 5 days on and 2 days off.

Investigational medicinal product name	Gemcitabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

The gemcitabine dose was 800 mg/m2 administered intravenously over 30 minutes (or per institutional standard) on Days 1 and 8 of a 21-day cycle

Arm title	ZN-c3 200mg QD 5:2 + Gemcitabine 675mg/m2

Arm description:

treatment cycles of 21 days with ZN-c3 200mg given intermittent 5 days on and 2 days off in combination with gemcitabine 675mg/m2, until progression of disease or any of the withdrawal criteria included in the protocol are met

Arm type	Experimental
Investigational medicinal product name	ZN-c3
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

treatment cycles of 21 days with ZN-c3 200mg given intermittent 5 days on and 2 days off.

Investigational medicinal product name	Gemcitabine
Investigational medicinal product code	
Other name	

Pharmaceutical forms	Powder for solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

The gemcitabine dose was 675 mg/m2 administered intravenously over 30 minutes (or per institutional standard) on Days 1 and 8 of a 21-day cycle

Arm title	ZN-c3 200mg QD 5:2 + Gemcitabine 800mg/m2

Arm description:

treatment cycles of 21 days with ZN-c3 200mg given intermittent 5 days on and 2 days off in combination with gemcitabine 800mg/m2, until progression of disease or any of the withdrawal criteria included in the protocol are met

Arm type	Experimental
Investigational medicinal product name	Gemcitabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

The gemcitabine dose was 800 mg/m2 administered intravenously over 30 minutes (or per institutional standard) on Days 1 and 8 of a 21-day cycle

Investigational medicinal product name	ZN-c3
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

treatment cycles of 21 days with ZN-c3 200mg given intermittent 5 days on and 2 days off.

Arm title	ZN-c3 200mg QD 4:3 + Gemcitabine 800mg/m2

Arm description:

treatment cycles of 21 days with ZN-c3 200mg given intermittent 4 days on and 3 days off in combination with gemcitabine 800mg/m2, until progression of disease or any of the withdrawal criteria included in the protocol are met

Arm type	Experimental
Investigational medicinal product name	ZN-c3
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

treatment cycles of 21 days with ZN-c3 200mg given intermittent 4 days on and 3 days off.

Investigational medicinal product name	Gemcitabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

The gemcitabine dose was 800 mg/m2 administered intravenously over 30 minutes (or per institutional standard) on Days 1 and 8 of a 21-day cycle

Number of subjects in period 1	ZN-c3 150mg QD + Gemcitabine 800mg/m2	ZN-c3 200mg QD + Gemcitabine 1000mg/m2	ZN-c3 150mg QD 5:2 + Gemcitabine 800mg/m2
Started	5	9	6
Completed	0	0	0
Not completed	5	9	6
Consent withdrawn by subject	1	1	1
death	1	5	4
study terminated by sponsor	2	1	1
subject decision	-	2	-
Lost to follow-up	1	-	-

Number of subjects in period 1	ZN-c3 200mg QD 5:2 + Gemcitabine 675mg/m2	ZN-c3 200mg QD 5:2 + Gemcitabine 800mg/m2	ZN-c3 200mg QD 4:3 + Gemcitabine 800mg/m2
Started	6	3	2
Completed	0	0	0
Not completed	6	3	2
Consent withdrawn by subject	1	-	-
death	2	1	2
study terminated by sponsor	3	2	-
subject decision	-	-	-
Lost to follow-up	-	-	-

Baseline characteristics

Reporting groups	
Reporting group title	ZN-c3 150mg QD + Gemcitabine 800mg/m2
Reporting group description:	
treatment cycles of 21 days with ZN-c3 150mg daily dose in combination with gemcitabine 800mg/m2, until progression of disease or any of the withdrawal criteria included in the protocol are met	
Reporting group title	ZN-c3 200mg QD + Gemcitabine 1000mg/m2
Reporting group description:	
treatment cycles of 21 days with ZN-c3 200mg daily dose in combination with gemcitabine 1000mg/m2, until progression of disease or any of the withdrawal criteria included in the protocol are met	
Reporting group title	ZN-c3 150mg QD 5:2 + Gemcitabine 800mg/m2
Reporting group description:	
treatment cycles of 21 days with ZN-c3 150mg given intermittent 5 days on and 2 days off in combination with gemcitabine 800mg/m2, until progression of disease or any of the withdrawal criteria included in the protocol are met	
Reporting group title	ZN-c3 200mg QD 5:2 + Gemcitabine 675mg/m2
Reporting group description:	
treatment cycles of 21 days with ZN-c3 200mg given intermittent 5 days on and 2 days off in combination with gemcitabine 675mg/m2, until progression of disease or any of the withdrawal criteria included in the protocol are met	
Reporting group title	ZN-c3 200mg QD 5:2 + Gemcitabine 800mg/m2
Reporting group description:	
treatment cycles of 21 days with ZN-c3 200mg given intermittent 5 days on and 2 days off in combination with gemcitabine 800mg/m2, until progression of disease or any of the withdrawal criteria included in the protocol are met	
Reporting group title	ZN-c3 200mg QD 4:3 + Gemcitabine 800mg/m2
Reporting group description:	
treatment cycles of 21 days with ZN-c3 200mg given intermittent 4 days on and 3 days off in combination with gemcitabine 800mg/m2, until progression of disease or any of the withdrawal criteria included in the protocol are met	

Reporting group values	ZN-c3 150mg QD + Gemcitabine 800mg/m2	ZN-c3 200mg QD + Gemcitabine 1000mg/m2	ZN-c3 150mg QD 5:2 + Gemcitabine 800mg/m2
Number of subjects	5	9	6
Age categorical			
Age of subjects per category			
Units: Subjects			
Adolescents (12-17 years)	1	3	0
Adults (18-64 years)	4	5	6
From 65-84 years	0	1	0
Gender categorical Units: Subjects			
Female	2	4	1
Male	3	5	5
race Units: Subjects			
white	3	5	3
asian	1	1	0
black or African American	0	2	1

other	0	0	0
not reported	1	1	2
Region of Enrollment Units: Subjects			
USA	5	9	4
France	0	0	2

Reporting group values	ZN-c3 200mg QD 5:2 + Gemcitabine 675mg/m2	ZN-c3 200mg QD 5:2 + Gemcitabine 800mg/m2	ZN-c3 200mg QD 4:3 + Gemcitabine 800mg/m2
Number of subjects	6	3	2
Age categorical			
Age of subjects per category			
Units: Subjects			
Adolescents (12-17 years)	1	0	0
Adults (18-64 years)	5	3	2
From 65-84 years	0	0	0
Gender categorical Units: Subjects			
Female	4	3	1
Male	2	0	1
race Units: Subjects			
white	3	2	0
asian	1	0	0
black or African American	0	0	0
other	1	0	0
not reported	1	1	2
Region of Enrollment Units: Subjects			
USA	5	2	
France	1	1	2

Reporting group values	Total		
Number of subjects	31		
Age categorical			
Age of subjects per category			
Units: Subjects			
Adolescents (12-17 years)	5		
Adults (18-64 years)	25		
From 65-84 years	1		
Gender categorical Units: Subjects			
Female	15		
Male	16		
race Units: Subjects			
white	16		
asian	3		
black or African American	3		
other	1		
not reported	8		

Region of Enrollment Units: Subjects			
USA	25		
France	6		

Subject analysis sets

Subject analysis set title	Full Analysis Set
Subject analysis set type	Full analysis

Subject analysis set description:

The Full Analysis Set includes all subjects who received at least 1 dose of study drug (either ZN-c3 or gemcitabine). This analysis set was used for subject disposition, demographics and baseline characteristics, study drug exposure and dose modifications, and safety and clinical activity analyses (unless otherwise noted). The Full Analysis Set includes all 31 enrolled subjects.

Subject analysis set title	DLT-Evaluable Set
Subject analysis set type	Sub-group analysis

Subject analysis set description:

DLT-Evaluable Set: The DLT-Evaluable Set includes all subjects in the Full Analysis Set, excluding those for whom the cumulative dose of ZN-c3 was <75% in Cycle 1 for reasons other than AEs. This analysis set is applicable to Phase 1 only and was used to summarize DLTs. The DLT-Evaluable Set includes 29 subjects

Subject analysis set title	Response-Evaluable Set
Subject analysis set type	Sub-group analysis

Subject analysis set description:

The Response-Evaluable Set includes all subjects in the Full Analysis Set who had measurable disease at baseline and at least 1 postbaseline disease assessment

Reporting group values	Full Analysis Set	DLT-Evaluable Set	Response-Evaluable Set
Number of subjects	31	29	28
Age categorical			
Age of subjects per category			
Units: Subjects			
Adolescents (12-17 years)	5	5	5
Adults (18-64 years)	25	24	23
From 65-84 years	1	0	0
Gender categorical Units: Subjects			
Female	15	14	15
Male	16	15	13
race Units: Subjects			
white	16	16	16
asian	3	3	2
black or African American	3	2	2
other	1	1	1
not reported	8	7	7
Region of Enrollment Units: Subjects			
USA	25		
France	6		

End points

End points reporting groups

Reporting group title	ZN-c3 150mg QD + Gemcitabine 800mg/m2
Reporting group description:	
treatment cycles of 21 days with ZN-c3 150mg daily dose in combination with gemcitabine 800mg/m2, until progression of disease or any of the withdrawal criteria included in the protocol are met	
Reporting group title	ZN-c3 200mg QD + Gemcitabine 1000mg/m2
Reporting group description:	
treatment cycles of 21 days with ZN-c3 200mg daily dose in combination with gemcitabine 1000mg/m2, until progression of disease or any of the withdrawal criteria included in the protocol are met	
Reporting group title	ZN-c3 150mg QD 5:2 + Gemcitabine 800mg/m2
Reporting group description:	
treatment cycles of 21 days with ZN-c3 150mg given intermittent 5 days on and 2 days off in combination with gemcitabine 800mg/m2, until progression of disease or any of the withdrawal criteria included in the protocol are met	
Reporting group title	ZN-c3 200mg QD 5:2 + Gemcitabine 675mg/m2
Reporting group description:	
treatment cycles of 21 days with ZN-c3 200mg given intermittent 5 days on and 2 days off in combination with gemcitabine 675mg/m2, until progression of disease or any of the withdrawal criteria included in the protocol are met	
Reporting group title	ZN-c3 200mg QD 5:2 + Gemcitabine 800mg/m2
Reporting group description:	
treatment cycles of 21 days with ZN-c3 200mg given intermittent 5 days on and 2 days off in combination with gemcitabine 800mg/m2, until progression of disease or any of the withdrawal criteria included in the protocol are met	
Reporting group title	ZN-c3 200mg QD 4:3 + Gemcitabine 800mg/m2
Reporting group description:	
treatment cycles of 21 days with ZN-c3 200mg given intermittent 4 days on and 3 days off in combination with gemcitabine 800mg/m2, until progression of disease or any of the withdrawal criteria included in the protocol are met	
Subject analysis set title	Full Analysis Set
Subject analysis set type	Full analysis
Subject analysis set description:	
The Full Analysis Set includes all subjects who received at least 1 dose of study drug (either ZN-c3 or gemcitabine). This analysis set was used for subject disposition, demographics and baseline characteristics, study drug exposure and dose modifications, and safety and clinical activity analyses (unless otherwise noted). The Full Analysis Set includes all 31 enrolled subjects.	
Subject analysis set title	DLT-Evaluable Set
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
DLT-Evaluable Set: The DLT-Evaluable Set includes all subjects in the Full Analysis Set, excluding those for whom the cumulative dose of ZN-c3 was <75% in Cycle 1 for reasons other than AEs. This analysis set is applicable to Phase 1 only and was used to summarize DLTs. The DLT-Evaluable Set includes 29 subjects	
Subject analysis set title	Response-Evaluable Set
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
The Response-Evaluable Set includes all subjects in the Full Analysis Set who had measurable disease at baseline and at least 1 postbaseline disease assessment	

Primary: Incidence and severity of DLTs in DLT-evaluable subjects during Cycle 1 of Phase 1

End point title	Incidence and severity of DLTs in DLT-evaluable subjects during Cycle 1 of Phase 1[1]

End point description:

Objective Phase 1: To investigate the safety and tolerability, MTD, and RP2D of ZN-c3 in combination with gemcitabine.

End point type	Primary

End point timeframe:

analysis after 1 cycle (21 days)

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analysis performed for this endpoint. this is a safety endpoint and it is a listing of occurring DLT events

End point values	ZN-c3 150mg QD + Gemcitabine 800mg/m2	ZN-c3 200mg QD + Gemcitabine 1000mg/m2	ZN-c3 150mg QD 5:2 + Gemcitabine 800mg/m2	ZN-c3 200mg QD 5:2 + Gemcitabine 675mg/m2
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	5	7	6	6
Units: events	2	3	0	2

End point values	ZN-c3 200mg QD 5:2 + Gemcitabine 800mg/m2	ZN-c3 200mg QD 4:3 + Gemcitabine 800mg/m2	DLT-Evaluable Set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	3	2	29	
Units: events	2	1	10	

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical activity: o According to RECIST v1.1 and clinical criteria: EFS

End point title	Clinical activity: o According to RECIST v1.1 and clinical criteria: EFS

End point description:

Efficacy analyses are based on the Response-Evaluable Set, which had 28 subjects (5 pediatric subjects and 23 adult subjects).
EFS Event-Free Survival for all subjects (adult and pediatric). presented in weeks

End point type	Secondary

End point timeframe:

up to 12 months after ZN-c3 treatment

End point values	ZN-c3 150mg QD + Gemcitabine 800mg/m2	ZN-c3 200mg QD + Gemcitabine 1000mg/m2	ZN-c3 150mg QD 5:2 + Gemcitabine 800mg/m2	ZN-c3 200mg QD 5:2 + Gemcitabine 675mg/m2
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	5	7	5	6
Units: weeks				
median (full range (min-max))	12.9 (7.0 to 26.1)	37.1 (6.0 to 37.1)	8.1 (6.3 to 26.3)	21.4 (6.6 to 43.3)

End point values	ZN-c3 200mg QD 5:2 + Gemcitabine 800mg/m2	ZN-c3 200mg QD 4:3 + Gemcitabine 800mg/m2	Response-Evaluable Set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	3	2	28	
Units: weeks				
median (full range (min-max))	9.1 (6.3 to 68.9)	12.5 (3.7 to 21.3)	12.9 (3.7 to 68.9)	

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical activity: o According to RECIST v1.1 and clinical criteria: OS (median and at 12 months)

End point title	Clinical activity: o According to RECIST v1.1 and clinical criteria: OS (median and at 12 months)

End point description:

Efficacy analyses are based on the Response-Evaluable Set, which had 28 subjects (5 pediatric subjects and 23 adult subjects).
OS overall Survival for all subjects (adult and pediatric). Only presented for the total for 28 Subjects, as some timepoints in the various dosing groups were not evaluable.

End point type	Secondary

End point timeframe:

up to 12 months after last dose of ZN-c3

End point values	Response-Evaluable Set			
Subject group type	Subject analysis set			
Number of subjects analysed	28			
Units: months				
median (full range (min-max))	11.5 (0.8 to 22.6)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

30 days after the last dose

Adverse event reporting additional description:

SAE presented when occurrence >1 subject (Except for cardiac arrest). Relatedness to Zn-c3 and or gemcitabine.
TEAEs are defined as AEs that occur or worsen from the first dose of study drug to 30 days after the last dose of study drug. The Non SAE presented are all defined as related to ZN-c3 and occurrence >10% of total subjects

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	26.1

Reporting groups

Reporting group title	ZN-c3 150mg QD + Gemcitabine 800mg/m2

Reporting group description:

treatment cycles of 21 days with ZN-c3 150mg daily dose in combination with gemcitabine 800mg/m2, until
progression of disease or any of the withdrawal criteria included in the protocol are
met

Reporting group title	ZN-c3 200mg QD + Gemcitabine 1000mg/m2

Reporting group description:

treatment cycles of 21 days with ZN-c3 200mg daily dose in combination with gemcitabine 1000mg/m2, until
progression of disease or any of the withdrawal criteria included in the protocol are
met

Reporting group title	ZN-c3 150mg QD 5:2 + Gemcitabine 800mg/m2

Reporting group description:

treatment cycles of 21 days with ZN-c3 150mg given intermittent 5 days on and 2 days off in combination with gemcitabine 800mg/m2, until progression of disease or any of the withdrawal criteria included in the protocol are
met

Reporting group title	ZN-c3 200mg QD 5:2 + Gemcitabine 675mg/m2

Reporting group description:

treatment cycles of 21 days with ZN-c3 200mg given intermittent 5 days on and 2 days off in combination with gemcitabine 675mg/m2, until progression of disease or any of the withdrawal criteria included in the protocol are
met

Reporting group title	ZN-c3 200mg QD 5:2 + Gemcitabine 800mg/m2

Reporting group description:

treatment cycles of 21 days with ZN-c3 200mg given intermittent 5 days on and 2 days off in combination with gemcitabine 800mg/m2, until progression of disease or any of the withdrawal criteria included in the protocol are
met

Reporting group title	ZN-c3 200mg QD 4:3 + Gemcitabine 800mg/m2

Reporting group description:

treatment cycles of 21 days with ZN-c3 200mg given intermittent 4 days on and 3 days off in combination with gemcitabine 800mg/m2, until progression of disease or any of the withdrawal criteria included in the protocol are
met

Serious adverse events	ZN-c3 150mg QD + Gemcitabine 800mg/m2	ZN-c3 200mg QD + Gemcitabine 1000mg/m2	ZN-c3 150mg QD 5:2 + Gemcitabine 800mg/m2
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 5 (40.00%)	5 / 9 (55.56%)	3 / 6 (50.00%)
number of deaths (all causes)	1	5	4
number of deaths resulting from adverse events	0	0	0
Cardiac disorders			
Cardiac arrest			
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Blood and lymphatic system disorders			
Thrombocytopenia	Additional description: Thrombocytopenia includes the preferred terms Platelet count decreased and Thrombocytopenia		
subjects affected / exposed	0 / 5 (0.00%)	1 / 9 (11.11%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenia	Additional description: Neutropenia includes the preferred terms Neutropenia, Neutrophil count decreased, and Neutrophil percentage decreased.		
subjects affected / exposed	0 / 5 (0.00%)	0 / 9 (0.00%)	0 / 6 (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
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 5 (0.00%)	1 / 9 (11.11%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	0 / 5 (0.00%)	1 / 9 (11.11%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Pneumonia			
subjects affected / exposed	1 / 5 (20.00%)	0 / 9 (0.00%)	0 / 6 (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

Serious adverse events	ZN-c3 200mg QD 5:2 + Gemcitabine 675mg/m2	ZN-c3 200mg QD 5:2 + Gemcitabine 800mg/m2	ZN-c3 200mg QD 4:3 + Gemcitabine 800mg/m2
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 6 (50.00%)	1 / 3 (33.33%)	2 / 2 (100.00%)
number of deaths (all causes)	2	1	2
number of deaths resulting from adverse events	0	0	0
Cardiac disorders			
Cardiac arrest			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 2 (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
Blood and lymphatic system disorders			
Thrombocytopenia	Additional description: Thrombocytopenia includes the preferred terms Platelet count decreased and Thrombocytopenia		
subjects affected / exposed	2 / 6 (33.33%)	0 / 3 (0.00%)	1 / 2 (50.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenia	Additional description: Neutropenia includes the preferred terms Neutropenia, Neutrophil count decreased, and Neutrophil percentage decreased.		
subjects affected / exposed	1 / 6 (16.67%)	1 / 3 (33.33%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	1 / 1	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	1 / 2 (50.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	2 / 6 (33.33%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Pneumonia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	1 / 2 (50.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	ZN-c3 150mg QD + Gemcitabine 800mg/m2	ZN-c3 200mg QD + Gemcitabine 1000mg/m2	ZN-c3 150mg QD 5:2 + Gemcitabine 800mg/m2
Total subjects affected by non-serious adverse events			
subjects affected / exposed	5 / 5 (100.00%)	9 / 9 (100.00%)	6 / 6 (100.00%)
Blood and lymphatic system disorders			
Thrombocytopenia	Additional description: Thrombocytopenia includes the preferred terms Platelet count decreased and Thrombocytopenia.		
subjects affected / exposed	2 / 5 (40.00%)	6 / 9 (66.67%)	2 / 6 (33.33%)
occurrences (all)	4	24	3
Neutropenia	Additional description: Neutropenia includes the preferred terms Neutropenia, Neutrophil count decreased, and Neutrophil percentage decreased.		
subjects affected / exposed	1 / 5 (20.00%)	4 / 9 (44.44%)	0 / 6 (0.00%)
occurrences (all)	8	14	0
Anaemia	Additional description: Anaemia includes the preferred terms Anaemia, Haematocrit decreased, Haemoglobin decreased, and RBC count decreased		
subjects affected / exposed	2 / 5 (40.00%)	3 / 9 (33.33%)	1 / 6 (16.67%)
occurrences (all)	8	14	3
Leukopenia	Additional description: Leukopenia includes the preferred terms Leukopenia and WBC count decreased.		
subjects affected / exposed	2 / 5 (40.00%)	4 / 9 (44.44%)	1 / 6 (16.67%)
occurrences (all)	12	29	2
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	1 / 5 (20.00%)	5 / 9 (55.56%)	2 / 6 (33.33%)
occurrences (all)	2	8	3
Metabolism and nutrition disorders			
Nausea			
subjects affected / exposed	1 / 5 (20.00%)	5 / 9 (55.56%)	1 / 6 (16.67%)
occurrences (all)	2	9	1

Non-serious adverse events	ZN-c3 200mg QD 5:2 + Gemcitabine 675mg/m2	ZN-c3 200mg QD 5:2 + Gemcitabine 800mg/m2	ZN-c3 200mg QD 4:3 + Gemcitabine 800mg/m2
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 6 (100.00%)	3 / 3 (100.00%)	2 / 2 (100.00%)
Blood and lymphatic system disorders			
Thrombocytopenia	Additional description: Thrombocytopenia includes the preferred terms Platelet count decreased and Thrombocytopenia.		
subjects affected / exposed	3 / 6 (50.00%)	3 / 3 (100.00%)	1 / 2 (50.00%)
occurrences (all)	8	10	1

Neutropenia	Additional description: Neutropenia includes the preferred terms Neutropenia, Neutrophil count decreased, and Neutrophil percentage decreased.		
subjects affected / exposed	4 / 6 (66.67%)	3 / 3 (100.00%)	0 / 2 (0.00%)
occurrences (all)	15	13	0
Anaemia	Additional description: Anaemia includes the preferred terms Anaemia, Haematocrit decreased, Haemoglobin decreased, and RBC count decreased		
subjects affected / exposed	2 / 6 (33.33%)	2 / 3 (66.67%)	1 / 2 (50.00%)
occurrences (all)	4	7	1
Leukopenia	Additional description: Leukopenia includes the preferred terms Leukopenia and WBC count decreased.		
subjects affected / exposed	1 / 6 (16.67%)	2 / 3 (66.67%)	0 / 2 (0.00%)
occurrences (all)	15	18	0
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	2 / 6 (33.33%)	2 / 3 (66.67%)	0 / 2 (0.00%)
occurrences (all)	12	2	0
Metabolism and nutrition disorders			
Nausea			
subjects affected / exposed	3 / 6 (50.00%)	1 / 3 (33.33%)	0 / 2 (0.00%)
occurrences (all)	4	1	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
03 August 2022	in France the protocol was amendment from protocol 4.3 to protocol version 6.0 The main changes in Protocol version 6.0 against Protocol version 4.3 were: Update to inclusion and exclusion criteria Update to contraceptive requirements Update to the schedule of activities Number of study participants Prolongation of study duration period Revised guidance on IMP administration based on food effect evaluation Modification of ZN-c3 and Gemcitabine dosing Implementation of prophylactic treatment with antiemetics (previously introduced by Protocol Clarification Letter) Limitation of blood volume collection Other changes including clarifications and guidance Minor editorial, organizational, and administrative changes

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.

Decision was made to terminate the phase I study while some patients were in safety follow up (12 months)
The Phase 2 part of this study was never conducted.

Notes: