Clinical trial results:
Phase II study of disulfiram and cisplatin in refractory testicular germ cell cancer.

Summary

EudraCT number	2019-000558-68
Trial protocol	SK
Global end of trial date	13 December 2021

Results information

Result version number	v1 (current)
This version publication date	04 September 2022
First version publication date	04 September 2022

Trial information

Trial identification

Sponsor protocol code	GCTSK006

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03950830
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Národný onkologický ústav
Sponsor organisation address	Klenova 1, Bratislava, Slovakia, 833 10
Public contact	Oddelenie klinického skúšania, Národný onkologický ústav, 00421 259378592, daniela.svetlovska@nou.sk
Scientific contact	Oddelenie klinického skúšania, Národný onkologický ústav, 00421 259378592, daniela.svetlovska@nou.sk

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	03 November 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	03 November 2021
Global end of trial reached?	Yes
Global end of trial date	13 December 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine the efficacy (as measured by overall response rate) (ORR) by RECIST of disulfiram and cisplatin in patients with multiple relapsed/refractory germ cell tumors (GCTs).

Protection of trial subjects:

All the procedures performed in study involving human participants were conducted in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual paricipants included in the study.

Background therapy:

Cisplatin will be administered intravenously 50mg/m2 day 1 and 2, every 3 weeks, Disulfiram 400mg daily p.o. continuously. Cycles will be repeated every 21 days until progression or unacceptable toxicity or up to 4 cycles of treatment. Treatment could be continued at the discretion of investigator in case that patient benefit from the treatment.

Evidence for comparator:

NA

Actual start date of recruitment	17 May 2019
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	Slovakia: 12
Worldwide total number of subjects	12
EEA total number of subjects	12

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)	12
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Enrollment period started on 14.5.2019 and ended on 3.11.2021. Fisrt patient was enrolled on 17.5.2019, last one on 17.9.2021. Total of 13 patients were screened into the study. One patient did not meet study eligibility criteria, was rescreened and finally 12 subjects were enrolled and receive study treatment.

Pre-assignment

Screening details:

Adult men with relapsed/refractory GCTs e.g., at least 2 lines of previous chemotherapy and/or patients relapsing after high-dose chemotherapy or for patients non fit enough for high-dose chemotherapy. Primary mediastinal GCTs in first relapse were eligible too. Patient’s disease could not be amenable to cure with either surgery or chemotherapy.

Pre-assignment period milestones

Number of subjects started	12
Number of subjects completed	12

Period 1

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

Arms

Arm title	Cisplatin + Disulfiram

Arm description:

Cisplatin will be administered intravenously 50mg/m2 day 1 and 2, every 3 weeks, Disulfiram 400mg daily p.o. continuously. Cycles will be repeated every 21 days until progression or unacceptable toxicity or up to 4 cycles of treatment. Treatment could be continued at the discretion of investigator in case that patient benefit from the treatment.

Arm type	Experimental
Investigational medicinal product name	Cisplatin
Investigational medicinal product code	SUB07483MIG
Other name	Cisplatin Accord, Cisplatin EBEWE
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Cisplatin will be administered intravenously 50mg/m2 day 1 and 2, every 3 weeks, Disulfiram 400mg daily p.o. continuously. Cycles will be repeated every 21 days until progression or unacceptable toxicity or up to 4 cycles of treatment. Treatment could be continued at the discretion of investigator in case that patient benefit from the treatment.
Standard emesis prophylaxis will be used (e.g. dexamethason, setron, aprepitant), before cisplatin.

Investigational medicinal product name	Disulfiram
Investigational medicinal product code	SUB06326MIG
Other name	Antabus
Pharmaceutical forms	Effervescent tablet
Routes of administration	Oral use

Dosage and administration details:

Disulfiram effervescent p.o. tablets 400mg daily, continuously. Disulfiram tablet must be dissolved in glass of water and mix immediately before use. It should be taken after evening meal, once daily, every day. No premedication or patient monitoring after administration of Disulfiram is required. Patients will

take disulfiram after their evening meal. Treatment will take until progression or unacceptable toxicit or could be continued at the discretion of investigator in case that patient benefit from the treatment. In case of intolerance doses will be reduced for hematological and other toxicity. Dose adjustments are to be made according to the system showing the greatest degree of toxicity. In case of intolerance, lower dose up to 200 mg per day is allowed. Patients will avoid alcohol and other disulfiram-drug interactions will be considered.

Number of subjects in period 1	Cisplatin + Disulfiram
Started	12
Completed	12

Baseline characteristics

Reporting groups

Reporting group title	Cisplatin + Disulfiram

Reporting group description:

Cisplatin will be administered intravenously 50mg/m2 day 1 and 2, every 3 weeks, Disulfiram 400mg daily p.o. continuously. Cycles will be repeated every 21 days until progression or unacceptable toxicity or up to 4 cycles of treatment. Treatment could be continued at the discretion of investigator in case that patient benefit from the treatment.

Reporting group values	Cisplatin + Disulfiram	Total	
Number of subjects	12	12	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	12	12	
From 65-84 years	0	0	
85 years and over	0	0	
Gender categorical Units: Subjects			
Female	0	0	
Male	12	12	

Subject analysis sets

Subject analysis set title	Overall study (overall period)
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Cisplatin will be administered intravenously 50mg/m2 day 1 and 2, every 3 weeks, Disulfiram 400mg daily p.o. continuously. Cycles will be repeated every 21 days until progression or unacceptable toxicity or up to 4 cycles of treatment. Treatment could be continued at the discretion of investigator in case that patient benefit from the treatment.

Reporting group values	Overall study (overall period)		
Number of subjects	12		
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)	12		
From 65-84 years	0		
85 years and over	0		
Gender categorical Units: Subjects			
Female	0		
Male	12		

End points

End points reporting groups

Reporting group title	Cisplatin + Disulfiram

Reporting group description:

Cisplatin will be administered intravenously 50mg/m2 day 1 and 2, every 3 weeks, Disulfiram 400mg daily p.o. continuously. Cycles will be repeated every 21 days until progression or unacceptable toxicity or up to 4 cycles of treatment. Treatment could be continued at the discretion of investigator in case that patient benefit from the treatment.

Subject analysis set title	Overall study (overall period)
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Cisplatin will be administered intravenously 50mg/m2 day 1 and 2, every 3 weeks, Disulfiram 400mg daily p.o. continuously. Cycles will be repeated every 21 days until progression or unacceptable toxicity or up to 4 cycles of treatment. Treatment could be continued at the discretion of investigator in case that patient benefit from the treatment.

Primary: Overall response rate

End point title	Overall response rate

End point description:

Objective response rate is defined as sum of complete and partial responses.

End point type	Primary

End point timeframe:

Objective response rate was calculated from the start of the treatment until progression or death.

End point values	Cisplatin + Disulfiram	Overall study (overall period)		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	12[1]	12[2]		
Units: number of patients	0	0		

Notes:

[1] - None of patients achieved objective response to treatment so the study was terminated in first stage

[2] - None of patients achieved objective response to treatment so the study was terminated in first stage

Statistical analyses

Statistical analysis title	Intention-to treat analysis
Comparison groups	Cisplatin + Disulfiram v Overall study (overall period)
Number of subjects included in analysis	24
Analysis specification	Pre-specified
Analysis type	other
P-value	< 5
Method	Chi-squared

Secondary: Progression-free survival

End point title	Progression-free survival

End point description:

End point type	Secondary

End point timeframe:

The progression-free survival was calculated from the beginning of the treatment until progression or death from disease-specific cause on intention-to-treat basis.

End point values	Cisplatin + Disulfiram	Overall study (overall period)		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	12[3]	12[4]		
Units: months				
median (confidence interval 95%)	1.4 (0.7 to 1.5)	1.4 (0.7 to 1.5)		

Notes:

[3] - Median progression-free survival was 1.4 months, 95% CI (0.7 – 1.5 months)

[4] - Median progression-free survival was 1.4 months, 95% CI (0.7 – 1.5 months)

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival

End point title	Overall survival

End point description:

End point type	Secondary

End point timeframe:

Overall survival (OS) was be calculated from the beginning of the treatment until death from any cause on intention-to-treat basis.

End point values	Cisplatin + Disulfiram	Overall study (overall period)		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	12[5]	12[6]		
Units: months				
median (confidence interval 95%)	2.9 (1.5 to 4.7)	2.9 (1.5 to 4.7)		

Notes:

[5] - median overall survival was 2.9 months 95% CI (1.5 – 4.7 months)

[6] - median overall survival was 2.9 months 95% CI (1.5 – 4.7 months)

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events and serious adverse events were evaluated in all patients from the time of first administration of any study drug until 28 days after after disulfiram or cisplatin discotinuation, which one was later.

Adverse event reporting additional description:

Adverse eventse were be monitored on an ongoing basis. Adverse events were categorized using the NCI Common Terminology Criteria for Adverse Events, Version 5.0.

Assessment type	Systematic

Dictionary used

Dictionary name	CTCAE
Dictionary version	5.0

Reporting groups

Reporting group title	all subjects

Reporting group description:

Adverse events and serious adverse events will be evaluated in all patients from the time of first administration of the Disulfiram with cisplatin until 28 days after after disulfiram or cisplatin discotinuation, which one was later.Adverse events will be monitored on an ongoing basis. Adverse events will be categorized using the NCI Common Terminology Criteria for Adverse Events, Version 5.0.

Serious adverse events	all subjects		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 12 (8.33%)		
number of deaths (all causes)	12		
number of deaths resulting from adverse events	0		
General disorders and administration site conditions			
Fatique	Additional description: 1 Subject was hospitaised for SAE Fatigue.		
subjects affected / exposed	1 / 12 (8.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Ileus adhesive	Additional description: 1 subject was hospitalised for SAE Adhesive ileus.		
subjects affected / exposed	1 / 12 (8.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Confusion	Additional description: 1 Subject was hospitalised for SAE Confusion.		

subjects affected / exposed	1 / 12 (8.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	all subjects		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	10 / 12 (83.33%)		
Investigations			
Neutropenia	Additional description: 2 subjects experienced Neutropenia, Gr.3		
subjects affected / exposed	2 / 12 (16.67%)		
occurrences (all)	2		
Thrombocytopenia	Additional description: 3 subjects experienced Thrombocytopenia Gr.3 and one subject experienced Thrombocytopenia Gr.4.		
subjects affected / exposed	4 / 12 (33.33%)		
occurrences (all)	4		
Hyponatremia	Additional description: 1 subject experienced Hypnatremia, Gr.3.		
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumor related pain	Additional description: 1 subject experienced Tumor related pain, Gr.3.		
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Nervous system disorders			
Syncope	Additional description: 1 subject experienced Syncopen Gr.3.		
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Polyneuropathy sensory	Additional description: 1 subject expeirnced Polyneuropathy sensory, Gr.3.		
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Peripheral sensory neuropathy	Additional description: 1 subject experienced Peripheral sensory neuropathy.		
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Blood and lymphatic system disorders			

Anaemia	Additional description: 3 subjects experienced Anaemia, Gr.3		
subjects affected / exposed	3 / 12 (25.00%)		
occurrences (all)	3		
General disorders and administration site conditions			
Fatique	Additional description: 4 subjects experienced non-serious AE Fatique, Gr.3.		
subjects affected / exposed	4 / 12 (33.33%)		
occurrences (all)	4		
Eye disorders			
Bilateral amaurosis	Additional description: 1 subject experienced BIlateral amaurosis, Gr.3.		
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Gastrointestinal disorders			
Nausea	Additional description: 2 subjects experienced Nausea, Gr.3.		
subjects affected / exposed	2 / 12 (16.67%)		
occurrences (all)	2		
Constipation	Additional description: 1 subject experienced Constipation, Gr.3.		
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Reproductive system and breast disorders			
Pain after surgery	Additional description: 1 subject experienced Pain after surgery, Gr.3.		
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Dyspnoe	Additional description: 1 subject experienced Dyspnoe, Gr.3		
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Infections and infestations			
Pneumonia	Additional description: 1 subject experienced Pneumonia, Gr.3.		
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Infection not otherwise specified	Additional description: 1 subject experienced Infection not otherwise specified, Gr.3.		
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Metabolism and nutrition disorders			
Hyperkaliemia	Additional description: 1 subject experienced Hyperkaliemia, Gr.3.		

subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
24 April 2019	Protocol ver.2.0 of 24 April 2019, summary of changes to Protocol ver.1.0 of 23 Jan 2019: - section Contact addresses was amended - section 1.4 /Pharmaceutical Data of Study Drugs was amended with Composition, storage and route of adminístraton for Disulfiram ad Cisplatin - section 5.2 Concomitant medicaton was updated with Box 1: Other indications - section 16. Administrative responsibiities was added
18 October 2019	Protocol ver.3.0 dated 18 Oct 2019, summary of changes to Protocol 2.0 dated 24 April 2019: - Change of screening period from 21 to 28 days - added chapter 8.0 Biological sampling - Change of Monitor

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported