Clinical trial results:
The histone deacetylase inhibitor (HDAC) valproic acid as second line treatment for hormone refractory metastatic prostate cancer. A phase II. study.

Summary

EudraCT number	2006-003554-15
Trial protocol	SK
Global end of trial date	28 February 2009

Results information

Result version number	v1 (current)
This version publication date	14 August 2022
First version publication date	14 August 2022

Trial information

Trial identification

Sponsor protocol code	18031977

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Národný onkologický ústav
Sponsor organisation address	Klenova 1, Bratislava, Slovakia, 833 10
Public contact	Prof Michal Mego MD, DSc, Národný onkologický ústav, 00421 259378108, michal.mego@nou.sk
Scientific contact	Prof Michal Mego MD, DSc, Národný onkologický ústav, 00421 259378108, michal.mego@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	28 November 2008
Is this the analysis of the primary completion data?	Yes
Primary completion date	28 November 2008
Global end of trial reached?	Yes
Global end of trial date	28 February 2009
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine the efficacy (as measured by tumor response) of valproic acid given orally to patients with hormone refractory metastatic prostate cancer after first line chemotherapy.

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:

NA

Evidence for comparator:

NA

Actual start date of recruitment	15 November 2006
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: 9
Worldwide total number of subjects	9
EEA total number of subjects	9

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)	7
From 65 to 84 years	2

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Between December 2006 and November 2007 nine patients with hormone refractory metastatic prostate cancer who have progressed on standard first line chemotherapy.were enrolled.

Pre-assignment

Screening details:

9 patients with metstatic HRPC were screened, all subjects met Inclusion/ Exclusion criteria. Median age was 64 years (54-79 years), Karnofski PS 90% (range: 80-100 %). All patients were pretreated with doxataxel based chemtherapy. Additionally 8 patients were also pretreated with vinorelbin and 3 patients with mitoxantron-based therapy.

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	valproic acid

Arm description:

Valproic acid will be administered at a dose of 20mg/kg/day orally once a day. One cycle of therapy consists of 28 days.A minimum of 2 cycles of the treatment will be administered to each patient in the absence of unacceptable toxicity or disease progression. Treatment cycles will be repeated until progression or unacceptable toxicity.

Arm type	Experimental
Investigational medicinal product name	Valproic acid
Investigational medicinal product code	21/034/83-S/C
Other name	Everiden , Orfiril, Desitin, Convulex
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Valproic acid will be administered at a dose of 20mg/kg/day orally once a day. One cycle of therapy consists of 28 days. In the first cycle the starting dose is 10mg/kg/day (dose level –2), which is escalated on day 4 (15mgkg/day; dose level –1) and on day 7 (dose 20mg/kg/day; dose level 0) in the absence of grade 3-4 neurological toxixicity. In other cycles the starting dose is 20mg/kg/day, or the dose according to dose adjustments from the previous treatment cycle.
Doses will be reduced for hematological and other adverse events. A minimum of 2 cycles of the treamtment will be administered to each patient in the absence of unacceptable toxicity or disease progression. Treatment cycles will be repeated untill progression or unacceptable toxicity.

Number of subjects in period 1	valproic acid
Started	9
Completed	9

Baseline characteristics

Reporting groups

Reporting group title	Overall Study (overall period)

Reporting group description:

Non-randomized, open-label, single centre trial with treatment regimen consisted of valproic acid given orally at a dose of 20mg/kg/day orally once a day. A minimum of 2 cycles of the treamtment will be administered to each patient and repeated until progression or unacceptable toxicity.

Reporting group values	Overall Study (overall period)	Total	
Number of subjects	9	9	
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)	7	7	
From 65-84 years	2	2	
85 years and over	0	0	
Adults from 18 years	0	0	
Gender categorical Units: Subjects			
Female	0	0	
Male	9	9	

Subject analysis sets

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

Subject analysis set description:

Non-randomized, open-label, single centre trial with treatment regimen consisted of valproic acid given orally at a dose of 20mg/kg/day orally once a day. A minimum of 2 cycles of the treamtment will be administered to each patient and repeated until progression or unacceptable toxicity.

Reporting group values	Overall study (overall period)		
Number of subjects	9		
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)	7		
From 65-84 years	2		
85 years and over	0		
Adults from 18 years	0		
Gender categorical Units: Subjects			
Female			
Male	9		

End points

End points reporting groups

Reporting group title	valproic acid

Reporting group description:

Valproic acid will be administered at a dose of 20mg/kg/day orally once a day. One cycle of therapy consists of 28 days.A minimum of 2 cycles of the treatment will be administered to each patient in the absence of unacceptable toxicity or disease progression. Treatment cycles will be repeated until progression or unacceptable toxicity.

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

Subject analysis set description:

Non-randomized, open-label, single centre trial with treatment regimen consisted of valproic acid given orally at a dose of 20mg/kg/day orally once a day. A minimum of 2 cycles of the treamtment will be administered to each patient and repeated until progression or unacceptable toxicity.

Primary: Response rate (PSA response)

End point title	Response rate (PSA response)

End point description:

PSA decline of at least 50%, which must be confirmed by a second PSA value 4 or more weeks later.The reference PSA for these declines should be a PSA measured within 2 weeks before starting therapy. Patients may not demonstrate clinical or radiographic evidence of disease progression during this time period.

End point type	Primary

End point timeframe:

PSA will be measured at baseline and every 4 weeks following first dose.

End point values	valproic acid	Overall study (overall period)		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	9	9		
Units: number of patients	0	0		

Statistical analyses

Statistical analysis title	descriptive statistics
Comparison groups	valproic acid v Overall study (overall period)
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	other
P-value	< 5
Method	Chi-squared

Secondary: Time to progression

End point title	Time to progression

End point description:

In the absence of evidence of clinical progression, the time to PSA progression is an appropriate outcome to report (especially for noncytotoxic agents). PSA progression may occur before clinical progression. The start of the time to PSA progression is the day treatment is initiated. If at least a 50% decline in PSA has been achieved, the end date is the time the PSA has increased 25% above the nadir at a minimum of 5 ng/mL (this is the same as the parameter for PSA response). For patients without a PSA decrease of this magnitude (or no decrease in PSA), the end point for progression will be calculated at the time a 25% increase in PSA has been achieved. All end dates require a confirmatory PSA.

End point type	Secondary

End point timeframe:

Time to progression was calculated from the start of the treatment until progression or death.

End point values	valproic acid	Overall study (overall period)		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	9	9		
Units: weeks				
median (full range (min-max))	8 (4 to 18)	8 (4 to 18)		

Statistical analyses

No statistical analyses for this end point

Secondary: Toxicity

End point title	Toxicity

End point description:

Toxicity grade 3-4

End point type	Secondary

End point timeframe:

From start of the treatment to last follow up.

End point values	valproic acid	Overall study (overall period)		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	9[1]	9		
Units: number of patients	2	2		

Notes:

[1] - 2 subjects experienced toxicity grade 3-4

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Adverse events were recorded from start of study treatment until last follow up.	
Adverse event reporting additional description:	
Grade 3 and 4 non serious or any grade serious adverse events are reported.	
Assessment type	Systematic

Dictionary used	
Dictionary name	CTCAE
Dictionary version	3.0

Reporting groups	
Reporting group title	all subjects
Reporting group description:	
Grade 3 and 4 non serious or any grade serious adverse events are reported.	

Serious adverse events	all subjects		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 9 (11.11%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Infections and infestations			
Fever	Additional description: 1 patient was hospitalised for fever.		
subjects affected / exposed	1 / 9 (11.11%)		
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	2 / 9 (22.22%)		
General disorders and administration site conditions			
Fatigue	Additional description: Only grade 3/4 adverse events.		
subjects affected / exposed	2 / 9 (22.22%)		
occurrences (all)	2		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
03 November 2006	Everiden is replaced with Convulex or Orfiril,. Composition is deleted.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported