Clinical trial results:
Estudio en fase II de everolimus, un inhibidor mTOR (de formulación oral), junto con OcteotrideLAR®, en pacientes adultos con tumores neuroendocrinos gastrointestinales avanzados no funcionales y bien diferenciados (TNE GI).

Summary

EudraCT number	2010-023422-20
Trial protocol	ES
Global end of trial date	07 June 2017

Results information

Result version number	v1 (current)
This version publication date	22 May 2022
First version publication date	22 May 2022
Summary attachment (see zip file)	Phase II Study of Everolimus and Octreotide LAR in Patients with Nonfunctioning Gastrointestinal Neuroendocrine Tumors: The GETNE1003_EVERLAR Study (Capdevila_et_al-2019-The_Oncologist.pdf)

Trial information

Trial identification

Sponsor protocol code	GETNE1003

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01567488
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Grupo Español de Tumores Neuroendocrinos
Sponsor organisation address	C/ Velázquez nº 7, piso 3, Madrid, Spain, 28001
Public contact	GETNE secretariat desk, GETNE, getne@getne.org
Scientific contact	Secretaría Técnica de GETNE , Grupo Españolde Tumores Neuroendocrinos (GETNE), getne@getne.org

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	08 March 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	07 June 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

El objetivo principal del estudio es evaluar la eficacia de 10 mg/día de everolimus en combinación con 30 mg de octeotride LAR® i.m. cada 28 días, en el tratamiento de TNE GI avanzado

Protection of trial subjects:

None out of clinical practice.

Background therapy: -

Evidence for comparator:

No comparator is used. This is a one arm study.

Actual start date of recruitment	08 June 2011
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 44
Worldwide total number of subjects	44
EEA total number of subjects	44

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)	24
From 65 to 84 years	18
85 years and over	2

Subject disposition

Recruitment

Recruitment details:

Los pacientes se incluyeron entre el 08/06/2011 y el 17/04/2013 en España.

Pre-assignment

Screening details:

Enfermedad medible según los criterios RECIST 1.0, mediante una valoración radiológica de TAC trifásico o RM de fase múltiple. Progresión de la enfermedad en los 12 meses anteriores a su inclusión en el estudio, documentada de forma radiológica. Estado funcional 0-2 (OMS), función adecuada de la médula ósea, hepática y renal, colesterol.

Period 1

Period 1 title	Treatment (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Treatment subject disposition

Arm description:

Tratamiento combinado de dos principios activos: Everolimus y Octreorida LAR

Arm type	One arm study
Investigational medicinal product name	Everolimus
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

10 mg daily in combination with Octreotida LAR

Investigational medicinal product name	Octreotida LAR
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solvent for solution for injection/infusion
Routes of administration	Intramuscular use

Dosage and administration details:

30mg i.m. each 28 days

Number of subjects in period 1	Treatment subject disposition
Started	44
Completed	44

Baseline characteristics

Reporting groups

Reporting group title	Treatment

Reporting group description: -

Reporting group values	Treatment	Total	
Number of subjects	44	44	
Age categorical			
Pacientes mayores o de 18 años.			
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)	24	24	
From 65-84 years	18	18	
85 years and over	2	2	
Age continuous			
Se han reclutado pacientes mayores o de 18 años.			
Units: years			
arithmetic mean	61		
standard deviation	± 12	-	
Gender categorical			
Units: Subjects			
Female	20	20	
Male	24	24	

Subject analysis sets

Subject analysis set title	Treatment baseline characteristics
Subject analysis set type	Full analysis

Subject analysis set description:

This is a one arm study. 43 patients of 44 included were analyzed.

Reporting group values	Treatment baseline characteristics		
Number of subjects	43		
Age categorical			
Pacientes mayores o de 18 años.			
Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			

Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)	12		
From 65-84 years	9		
85 years and over	1		
Age continuous			
Se han reclutado pacientes mayores o de 18 años.			
Units: years			
arithmetic mean			
standard deviation	±		
Gender categorical			
Units: Subjects			
Female			
Male			

End points

End points reporting groups

Reporting group title	Treatment subject disposition
Reporting group description:	
Tratamiento combinado de dos principios activos: Everolimus y Octreorida LAR	
Subject analysis set title	Treatment baseline characteristics
Subject analysis set type	Full analysis
Subject analysis set description:	
This is a one arm study. 43 patients of 44 included were analyzed.	

Primary: Supervivencia libre de progresión 12 meses

End point title	Supervivencia libre de progresión 12 meses
End point description:	
La tasa de supervivencia libre de progresión (SLP), variable de resultado principal del estudio, se describirá a partir de los resultados obtenidos en el ensayo tras 12 meses de tratamiento, hasta el registro de una progresión objetiva de la enfermedad o fallecimiento por cualquier causa.	
End point type	Primary
End point timeframe:	
A los 12 meses de tratamiento.	

End point values	Treatment subject disposition	Treatment baseline characteristics		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	1	43		
Units: Progresiones	43	43		

Statistical analyses

Statistical analysis title	Análisis principal
Statistical analysis description:	
Porcentaje de pacientes sin signos de enfermedad progresiva después de 12 meses de tratamiento, incluyendo intervalos de confianza (IC) del 95%. La variable supervivencia libre de progresión (SLP) se analiza con un modelo de supervivencia de Kaplan Meier, estimando la proporción de SLP acumulada a un año con ICs de 95% bilateral.	
Comparison groups	Treatment subject disposition v Treatment baseline characteristics
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	porcentage
Point estimate	62

Confidence interval	
level	95 %
sides	2-sided
lower limit	47
upper limit	76

Secondary: Supervivencia global

End point title	Supervivencia global

End point description:

Porcentage de eventos (muerte) observados desde la fecha de inclusión del paciente en el estudio hasta la fecha de la muerte por cualquier causa. Se describe la sobrevivencia a los 24 meses de iniciado el tratamiento, mediante un modelo de supervivencia de Kaplan-Meier.

End point type	Secondary

End point timeframe:

A los 24 meses de iniciado el tratamiento.

End point values	Treatment subject disposition	Treatment baseline characteristics		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	43	43		
Units: eventos	43	43		

Statistical analyses

Statistical analysis title	Análisis secundario

Statistical analysis description:

Modelo de supervivencia de Kaplan Meier a los 24 meses.

Comparison groups	Treatment subject disposition v Treatment baseline characteristics
Number of subjects included in analysis	86
Analysis specification	Pre-specified
Analysis type	other[1]
Parameter estimate	tiempo (meses)
Point estimate	71
Confidence interval	
level	95 %
sides	2-sided
lower limit	58
upper limit	85

Notes:

[1] - Modelo de supervivencia de Kaplan Meier estimando la mediana y la media. Si se desconoce si un paciente ha fallecido, la supervivencia global será censurada con la fecha del último contacto.

Secondary: Supervivencia libre de progresión 24 meses

End point title	Supervivencia libre de progresión 24 meses

End point description:

Tasa de supervivencia libre de progresión (SLP) observada desde el inicio del tratamiento hasta el registro de una progresión objetiva de la enfermedad o fallecimiento por cualquier causa.

End point type	Secondary

End point timeframe:

24 meses de tratamiento

End point values	Treatment subject disposition	Treatment baseline characteristics		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	43	43		
Units: progresiones	43	43		

Statistical analyses

Statistical analysis title	Supervivencia libre de progresion 24 meses

Statistical analysis description:

Porcentaje de pacientes sin signos de enfermedad progresiva después de 24 meses de tratamiento. Se utiliza un modelo de supervivencia de Kaplan Meier, estimando la proporción de SLP acumulada a un año con ICs de 95% bilateral.

Estudio de un solo brazo. One arm study.

Comparison groups	Treatment subject disposition v Treatment baseline characteristics
Number of subjects included in analysis	86
Analysis specification	Pre-specified
Analysis type	other[2]
Parameter estimate	porcentaje de pacientes
Point estimate	43
Confidence interval	
level	95 %
sides	2-sided
lower limit	28
upper limit	58

Notes:

[2] - Supervivencia de Kaplan Meier

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Hasta los 24 meses de tratamiento del último paciente incluido y hasta 30 días después de la última dosis.

Adverse event reporting additional description:

Se utiliza estadística descriptiva, mediante tablas de frecuencia, de todos los acontecimientos adversos indicando la gravedad valorada según los criterios Common Terminology Criteria for Adverse Events (CTCAE) versión 4.0.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups

Reporting group title	Terapia combinada

Reporting group description:

Brazo de tratamiento

Serious adverse events	Terapia combinada		
Total subjects affected by serious adverse events			
subjects affected / exposed	16 / 44 (36.36%)		
number of deaths (all causes)	11		
number of deaths resulting from adverse events	0		
General disorders and administration site conditions			
Uncontrolled pain			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pericardial effusion	Additional description: Un hombre hipertenso acude a urgencias con fatiga y palpitaciones. Se le realiza un análisis de sangre, una radiografía de tórax y una ecocardiografía y se diagnostica un derrame pericárdico asintomático.		
subjects affected / exposed	1 / 44 (2.27%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Fever (focus unknown)			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			

Vomiting			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Absceso perineal	Additional description: El paciente es hospitalizado y se realiza un drenaje.		
subjects affected / exposed	1 / 44 (2.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Abdominal perforation	Additional description: Posiblemente secundario a una isquemia intestinal relacionada con el tumor. Complicación secundaria a fibrosis extensiva y posible progresión. El paciente muere debido a una perforación secundaria a progresión local de la enfermedad.		
subjects affected / exposed	1 / 44 (2.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Intestinal suboclusion			
subjects affected / exposed	2 / 44 (4.55%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		
Abdominal pain			
subjects affected / exposed	3 / 44 (6.82%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Neumonitis			
subjects affected / exposed	3 / 44 (6.82%)		
occurrences causally related to treatment / all	2 / 3		
deaths causally related to treatment / all	0 / 0		
Dyspnoea			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Insuficiencia renal			

subjects affected / exposed	1 / 44 (2.27%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Cólico nefrítico derecho	Additional description: El paciente es atendido en el hospital, por dolor lumbar derecho. Es diagnosticado un cólico nefrítico derecho.		
subjects affected / exposed	1 / 44 (2.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Endocrine disorders			
Ectopic ACTH syndrome	Additional description: Es diagnosticado de síndrome ACTH ectópico relacionado con progresión de la enfermedad, y es ingresado en el hospital.		
subjects affected / exposed	1 / 44 (2.27%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Bacteremia	Additional description: Due to E.Coli		
subjects affected / exposed	1 / 44 (2.27%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hickman infection	Additional description: La infección se produce tras su manipulación, y se comprueba tras su análisis.		
subjects affected / exposed	1 / 44 (2.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Terapia combinada		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	39 / 44 (88.64%)		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	29 / 44 (65.91%)		
occurrences (all)	82		
Gastrointestinal disorders			
Diarrhoea			

subjects affected / exposed	39 / 44 (88.64%)		
occurrences (all)	100		
Mucositis			
subjects affected / exposed	29 / 44 (65.91%)		
occurrences (all)	60		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
07 October 2015	1/ Modificar el formulario para definir correctamente el final del ensayo. 2/ Comunicar una ampliación del seguimiento de los pacientes. 3/ Incluir un nuevo Manual del investigador versión 14 que sustituye a la versión 13. 4/ Nuevos datos de contacto de la secretaría del promotor.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/29794066