

**Clinical trial results:****PHASE I-II CLINICAL TRIAL FOR THE EVALUATION OF THE ROLE OF BRENTUXIMAB VEDOTIN PLUS ETOPOSIDE, SOLUMODERIN, HIGH DOSE ARA-C AND CIS-PLATIN IN THE TRANSPLANT AND POST-TRANSPLANT MANAGEMENT FOR PATIENTS WITH RELAPSED OR REFRACTORY CLASSICAL HODGKIN LYMPHOMA****Summary**

EudraCT number	2014-000835-17
Trial protocol	ES
Global end of trial date	14 January 2019

Results information

Result version number	v1 (current)
This version publication date	16 July 2021
First version publication date	16 July 2021

Trial information**Trial identification**

Sponsor protocol code	BRESHAP-GELTAMO.LH-2013
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02243436
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	GELTAMO
Sponsor organisation address	H. MARQUES DE VALDECILLA SERVICIO DE HEMATOLOGIA, SANTANDER, Spain, 39008
Public contact	GELTAMO, Grupo Español de Linfomas y Trasplante Autólogo de Médula Ósea, 0034 913195780, dm@geltamo.com
Scientific contact	GELTAMO, Grupo Español de Linfomas y Trasplante Autólogo de Médula Ósea, 0034 913195780, sc@geltamo.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	14 January 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	11 January 2019
Global end of trial reached?	Yes
Global end of trial date	14 January 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objectives of the study will be:

1. Search the recommended dose (To determine the Maximum Tolerable Dose of the BV (Brentuximab vedotin) in combination with ESHAP (etoposide, methylprednisolone, high--dose cytarabine, cisplatin) in relapsed/resistant HODGKIN LYMPHOMA patients)
2. To evaluate the global and complete response rate after BV-ESHAP as salvage regimen prior to APBSCT (autologous peripheral blood stem cell transplant)

Protection of trial subjects:

Safety was assessed by the type, frequency and severity (grade) of adverse events reported throughout the study period using the NCIC-CTCAE 4.0 criteria and considering all patients who received at least one dose of the investigational treatment.

reported throughout the study period using the NCIC-CTCAE 4.0 criteria and considering all patients who received at least one dose of the investigational treatment. The

TLDs were assessed in all patients in terms of reported adverse events and their association with treatment

with treatment, according to the dose

Similar criteria were established for Phase II, and all patients who received at least one dose of the investigational treatment were considered.

received at least one dose of the investigational treatment

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	11 November 2014
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: 66
Worldwide total number of subjects	66
EEA total number of subjects	66

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)	66
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

NUMBER OF PATIENTS PLANNED

Phase I: 9-28

Phase II: up to 66

7 NUMBER OF PATIENTS ANALYSED

Phase I: 9

Phase I+II: 66

8 DIAGNOSIS

Classical Hodgkin's lymphoma (cHL), CD30

Pre-assignment

Screening details:

To start the therapy, all the conditions above considered have to be observed. Then the therapy can be started preferably by hospitalizing the patient.

The Screening visit will be done once the patient provides written informed consent to participate in the study

Pre-assignment period milestones

Number of subjects started	66
Number of subjects completed	66

Period 1

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

Arms

Arm title	Experimental: BV-ESHAP
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Arm description:

1) 3 cycles every 21 days:

- Brentuximab Vedotin, on day 1 (BV will be administered at three different doses 0.9mg/kg, 1.2mg/kg, 1.8mg/kg)
- Etoposide 40 mg/m²/day, on days 1 to 4
- Soludomerin (methylprednisolone) 250 mg/day, on days 1 to 4
- Cisplatin 25 mg/m²/day, on days 1 to 4
- Ara C (cytarabine) 2 g/m², on day 5

2) A fourth dose of BV will be given 21 days after the third BV dose during the evaluation of response before the transplant.

3) Autologous peripheral blood stem cell transplant

4) A fifth dose of BV (1.8mg/kg) will be given on between day 28 and 35 post-transplant, followed by two additional doses (1.8mg/kg) every 3 weeks, to complete a total of 7 BV infusions.

Arm type	Experimental
Investigational medicinal product name	Brentuximab Vedotin
Investigational medicinal product code	
Other name	ADCETRIS
Pharmaceutical forms	Powder for concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Brentuximab Vedotin, 0.9mg/kg, 1.2mg/kg, 1.8mg/kg, day 1

Investigational medicinal product name	Etoposide
Investigational medicinal product code	
Other name	

Pharmaceutical forms	Infusion
Routes of administration	Intravenous use
Dosage and administration details:	
Intravenous use, 40mg/m2/day, on days 1 to 4	
Investigational medicinal product name	Soludomerin
Investigational medicinal product code	
Other name	Methylprednisolone
Pharmaceutical forms	Injection/infusion
Routes of administration	Intravenous use
Dosage and administration details:	
Intravenous use, 250mg/day, on days 1 to 4	
Investigational medicinal product name	Cisplatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use
Dosage and administration details:	
Intravenous use, 25mg/m2/day, on days 1 to 4	
Investigational medicinal product name	Ara C
Investigational medicinal product code	
Other name	Cytarabine
Pharmaceutical forms	Injection
Routes of administration	Intravenous use
Dosage and administration details:	
Intravenous use, 2g/m2, day 5	

Number of subjects in period 1	Experimental: BV-ESHAP
Started	66
Completed	66

Baseline characteristics

Reporting groups

Reporting group title	OVERALL TRIAL
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Reporting group description: -

Reporting group values	OVERALL TRIAL	Total	
Number of subjects	66	66	
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)	66	66	
From 65-84 years	0	0	
85 years and over	0	0	
Gender categorical			
Units: Subjects			
Female	35	35	
Male	31	31	

Subject analysis sets

Subject analysis set title	Overall trial
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Subject analysis set type	Full analysis
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Subject analysis set description:

PHASE I: Determine the recommended dose, based on the dose-limiting toxicity (DLT) analysis and safety profile of BV (brentuximab vedotin) in combination with ESHAP (etoposide, solumoderin or methylprednisolone, Ara-C or high-dose cytarabine, cisplatin) in patients with relapsed/refractory classical Hodgkin's lymphoma (cHL).

Hodgkin's lymphoma (cHL) relapsed/refractory.

PHASE II: To assess the complete response (CR) rate after BV-ESHAP as a salvage regimen before autologous peripheral blood transplantation (APBT)

Reporting group values	Overall trial		
Number of subjects	66		
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)	66		
From 65-84 years	0		
85 years and over	0		
Gender categorical			
Units: Subjects			
Female	35		
Male	31		

End points

End points reporting groups

Reporting group title	Experimental: BV-ESHAP
Reporting group description:	
1) 3 cycles every 21 days: - Brentuximab Vedotin, on day 1 (BV will be administered at three different doses 0.9mg/kg, 1.2mg/kg, 1.8mg/kg) - Etoposide 40 mg/m ² /day, on days 1 to 4 - Soludomerin (methylprednisolone) 250 mg/day, on days 1 to 4 - Cisplatin 25 mg/m ² /day, on days 1 to 4 - Ara C (cytarabine) 2 g/m ² , on day 5 2) A fourth dose of BV will be given 21 days after the third BV dose during the evaluation of response before the transplant. 3) Autologous peripheral blood stem cell transplant 4) A fifth dose of BV (1.8mg/kg) will be given on between day 28 and 35 post-transplant, followed by two additional doses (1.8mg/kg) every 3 weeks, to complete a total of 7 BV infusions.	
Subject analysis set title	Overall trial
Subject analysis set type	Full analysis

Subject analysis set description:

PHASE I: Determine the recommended dose, based on the dose-limiting toxicity (DLT) analysis and safety profile of BV (brentuximab vedotin) in combination with ESHAP (etoposide, solumoderin or methylprednisolone, Ara-C or high-dose cytarabine, cisplatin) in patients with relapsed/refractory classical Hodgkin's lymphoma (cHL).

Hodgkin's lymphoma (cHL) relapsed/refractory.

PHASE II: To assess the complete response (CR) rate after BV-ESHAP as a salvage regimen before autologous peripheral blood transplantation (APBT)

Primary: Primary

End point title	Primary
End point description:	
1. Number of TLD in different cohorts. 2. Global response rate and complete response.	
1. we will evaluate three groups of patients with the standardscheme in 3-patient cohorts. It will be based on the assumption of a stable shape of the dose-toxicity curve with no cumulative toxicity for the four plus three doses of BV. Therefore the decision to escalate to the next dose level will be based solely on toxicity results from the first course administration of the current level. 2. Global and Complete response will be evaluated after the fourth dose of Brentuximab Vedotin	
End point type	Primary

End point timeframe:

To determine the MDT is based on an observation period of 21 days, assessing the toxicity results of the administration of the first treatment cycle.

End point values	Experimental: BV-ESHAP	Overall trial		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	66	66		
Units: MTD	66	66		

Statistical analyses

Statistical analysis title	Progression free survival
Comparison groups	Experimental: BV-ESHAP v Overall trial
Number of subjects included in analysis	132
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 50
Method	Logrank
Parameter estimate	TTP

Secondary: Secondary

End point title	Secondary
End point description: As secondary objectives we will also try: <ul style="list-style-type: none">- To determine the toxicity of BV-ESHAP regimen- To assess the stem cell mobilization capacity of the BV-ESHAP regimen- To evaluate the final results of the whole procedure (BV-ESHAP followed by high-dose chemotherapy, APBSCT and three doses of BV): transplant-related mortality (TRM), overall survival (OS), and progression free survival (PFS) (Overall Survival, PFS, Event-Free Survival, Time to HL Progression, Disease-Free Survival, Response Duration, Lymphoma-Specific Survival, and Time to Next Treatment)	
End point type	Secondary
End point timeframe: Visits should be done prior every cycle, the day 14th of the first three cycles, pre and post trasplant visits, Final Protocol Treatment Visit aproximately at day +120; follow-up visits for a minimum of 2 years	

End point values	Experimental: BV-ESHAP	Overall trial		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	66	66		
Units: DLT	66	66		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events will be recorded from the time of informed consent

Report all AEs and SAEs from the time of informed consent up to 30 days after the last study treatment. All SAEs that occur after the 30-day safety reporting period

Assessment type	Systematic
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Dictionary used

Dictionary name	NCI-CTCAE
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Dictionary version	4.0
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Reporting groups

Reporting group title	All patients
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Reporting group description: -

Serious adverse events	All patients		
Total subjects affected by serious adverse events			
subjects affected / exposed	22 / 66 (33.33%)		
number of deaths (all causes)	3		
number of deaths resulting from adverse events	0		
General disorders and administration site conditions			
Neutropenia			
subjects affected / exposed	7 / 66 (10.61%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Thrombocytopenia			
subjects affected / exposed	10 / 66 (15.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Anaemia			
subjects affected / exposed	3 / 66 (4.55%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Renal failure			

subjects affected / exposed	2 / 66 (3.03%)		
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	All patients		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	66 / 66 (100.00%)		
General disorders and administration site conditions			
Vomiting			
subjects affected / exposed	30 / 66 (45.45%)		
occurrences (all)	1		
Mucositis management			
subjects affected / exposed	10 / 66 (15.15%)		
occurrences (all)	1		
Pain			
subjects affected / exposed	30 / 66 (45.45%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
27 August 2014	Any investigator-initiated changes to the protocol (with the exception of changes to eliminate an immediate hazard to a study subject) must be approved by the Sponsor prior to seeking approval from the IRB/IEC/REB, and prior to implementing. The investigator is responsible for enrolling subjects who have met protocol eligibility criteria. Protocol violations must be reported to the Sponsor and the local IRB/IEC/REB in accordance with IRB/IEC/REB policies

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported